Assessment report

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure No.: EMEA/H/C/001104/II/0028

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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22 September 2011
EMA/858655/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/001104/II/0028

Invented name/name:	Prevenar 13
International non-proprietary name/common name:	pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
Indication summary (as last approved):	prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including sepsis, meningitis, bacteraemia, pneumonia and acute otitis media)
Marketing authorisation holder:	Wyeth Lederle Vaccines S.A.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics, Annex II and Package Leaflet. Extension of indication to include active immunisation for the prevention of **invasive** disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older. To update sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC and corresponding sections of the PL, to include information pertaining to the proposed new indication for use in adults aged 50 years and older based upon the results of the pivotal clinical trials. Update of Annex II.B to remove the RMP version number as per QRD templates. The MAH took the opportunity to update section 6 of the

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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	Package Leaflet, by introducing changes to the local representatives.
Rapporteur:	Tomas Salmonson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2, 4 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	9 December 2010
Start of procedure:	19 December 2010
Rapporteur's assessment report circulated on:	11 February 2011
Request for supplementary information and extension of timetable adopted by the CHMP on :	17 March 2011
MAH's responses submitted to the CHMP on :	20 April 1011
Rapporteur's assessment report on the MAH's responses circulated on:	7 June 2011
Request for supplementary information and extension of timetable adopted by the CHMP on :	23 June 2011
MAH's responses submitted to the CHMP on :	22 July 2011
Rapporteur's assessment report on the MAH's responses circulated on:	2 September 2011
Rapporteur's updated assessment report on the MAH's responses circulated on:	16 September 2011
CHMP opinion:	22 September 2011

3. Scientific discussion

3.1. Introduction

Vaccines against pneumococcal disease have a successful public health impact and the development of safe, effective vaccines that offer broad protection against pneumococcal disease is considered by the WHO as a high priority. Due to the unmet medical need for extended valency vaccines beyond the 7 serotypes in Prevenar, the 13 serotypes in the 13-valent pneumococcal conjugate vaccine (7 Prevenar types + 6 additional serotypes (1, 3, 5, 7F. 6A, 7F, 19A)) have further expanded coverage and in Europe cover 80% or more of IPD cases in children less than 5 years of age, as documented by surveillance studies performed before the introduction of 7-valent Prevenar.

Prevenar 13 is currently indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age.

There is a need for an effective vaccine to prevent pneumococcal disease (PD) in adults beginning at 50 years of age, coincident with the increase in PD seen in the general population starting at this age. The available free-polysaccharide vaccine (PS), 23-valent pneumococcal polysaccharide vaccine (23vPS), has demonstrated efficacy against invasive pneumococcal disease (IPD); albeit the duration of protection is limited and the efficacy of 23vPS against community-acquired pneumonia (CAP) is uncertain. Although the incidence of IPD and related deaths have declined in adults in recent years, because of herd immunity effects resulting from the licensure of Prevenar (7-valent pneumococcal conjugate vaccine, 7vPnC), the IPD death rates in adults over 50 years of age are 10- to 27-fold higher than in children less than 2 years of age.

In contrast, conjugated pneumococcal polysaccharide vaccines (PnCs) have been proven effective against IPD and pneumonia in children in developed and developing countries. In addition, clinical studies in human immunodeficiency virus (HIV)-infected adult populations have provided evidence that conjugated vaccines exhibit noted efficacy against IPD and possibly pneumonia, in circumstances where 23vPS has not afforded such protection to these immune-compromised adults. Findings support the perspective that conjugate vaccine is likely to protect against IPD and pneumococcal pneumonia in the relatively less compromised elderly adult population.
PnCs elicit immune responses that are quantitatively and qualitatively distinct from those elicited by PS. Nonetheless, the best measurable immune response associated with the efficacy of pneumococcal vaccines is antibody-mediated opsonophagocytic activity (OPA).

13vPnC is currently licensed for use in infants and children, and it elicits functional OPA antibodies against 13 pneumococcal serotypes most associated with severe PD in adults.

The clinical development program in adults aged 50 years and older comprised safety and immunogenicity data from eight Prevenar 13 (13vPnC) clinical trials and 1 precursor Prevenar (7vPnC) clinical trial. The clinical program investigated the use of 13vPnC in adults aged 50 years and over and in 2 target groups with the following age stratifications:

1. Individuals naive to 23-valent polysaccharide vaccine (23vPS) aged:
    - ≥65 years
    - 60-64 years
    - 50-59 years
2. Individuals pre-immunized with 23-valent polysaccharide vaccine (23vPS) at least 5 years prior to study enrolment aged:

- ≥70 years

Each trial included healthy adults and immuno-competent subjects with stable underlying conditions known to pre-dispose adults to an increased risk of pneumococcal disease, such as chronic cardiovascular disease, chronic pulmonary disease (including asthma), renal disorders, diabetes mellitus, and chronic liver disease including alcoholic liver disease. Adults who smoked and used alcohol were included in all studies.

The MAH's proposed adult clinical program was conducted in line with the CHMP Follow-up Scientific Advice obtained in 2006 (EMEA/H/SA/690/1/FU/1/2006/II), which stated that a positive outcome based on functional OPA immunogenicity responses would be sufficient for approval of 13vPnC in adults over the age of 50. In accord with Scientific Advice, the 13vPnC data support coverage of the pneumococcal serotypes most responsible for serious adult disease, the potential for reimmunization with 13vPnC to extend protection without blunting of immune response as seen with 23vPS, and the importance of administering 13vPnC as the first pneumococcal vaccine to provide protection.

The MAH initial proposed indication was:

Active immunization for the prevention of disease caused by *Streptococcus pneumoniae* in adults aged 50 years and older.

After two rounds of assessment, including an ad hoc expert meeting to address whether OPA titres are appropriate to bridge efficacy from 23vPS vaccines to 13vPnC, the CHMP concluded that the benefit-risk balance of Prevenar 13 for prevention of invasive disease caused by *S. pneumoniae* is positive.

The evaluation procedure started as a Type II variation to add a new therapeutic indication.

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

*Extension of indication to include active immunisation for the prevention of **invasive** disease caused by Streptococcus pneumoniae in adults aged 50 years and older.*

To update sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC and corresponding sections of the PL, to include information pertaining to the proposed new indication for use in adults aged 50 years and older based upon the results of the pivotal clinical trials. Update of Annex II.B to remove the RMP version number as per QRD templates. The MAH took the opportunity to update section 6 of the Package Leaflet, by introducing changes to the local representatives.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/34/2008) for the following condition(s):

- Pneumococcal disease

On the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed

3.2. Toxico-pharmacological

Since the proposed indication of 13vPnC is intended for use in adults, a reproductive and developmental toxicity study was conducted in rabbits.

Female New Zealand White (NZW) rabbits were immunized with 13vPnC prior to mating and every 2 weeks thereafter through gestation day (GD) 24 to ensure that anti-13vPnC antibodies were present

throughout gestation. Anti-13vPnC antibodies against each of the serotypes was detected in the does on gestation day GD29 confirming that the does responded and anti-13vPnC antibodies were shown to be able to cross the placenta based on the fact that they were also detected in the first filial (F1) fetuses on GD 29 and in the F1 pups on post-partum day (PPD) 21.The results of this study indicate that repeated immunization of female rabbits resulted in the generation of anti-13vPnC antibodies, that the fetuses and F1 pups were exposed to the anti-13vPnC antibodies, and that there were no effects of immunization with 13vPnC on female fertility, or embryo/fetal or post-natal development.
No formal assessment of male fertility was conducted; however, there were no 13vPnC-related effects on male reproductive organs in any of the nonclinical studies conducted in rabbits as well as in other species.

These data support the conclusion that immunization with 13vPnC has no effect on reproduction.

3.3. Clinical aspects

3.3.1. Background

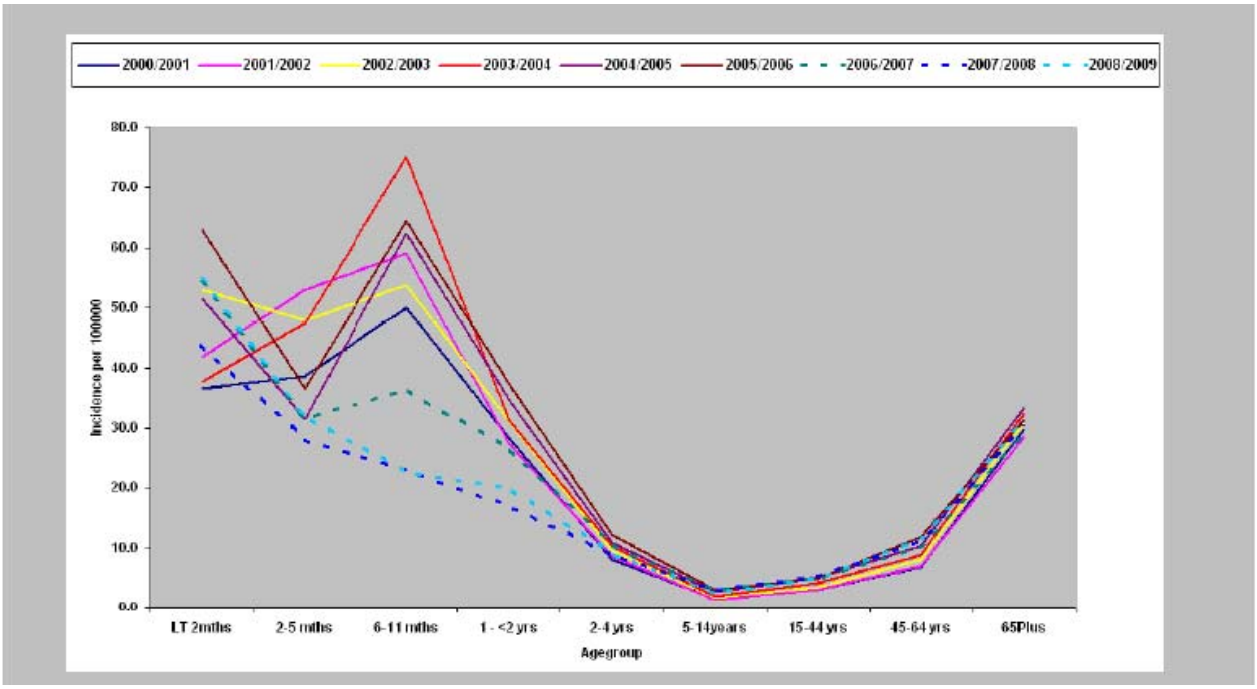
Streptococcus pneumoniae remains a leading cause of morbidity and mortality in adults, particularly in the elderly and in high risk populations. In persons aged 65 years and older, the annual incidence of invasive pneumococcal disease (IPD) in industrialized countries ranges from 24 to 85 cases per 100,000 of the total population. In 2008, approximately 44,000 cases and 4,500 deaths from IPD (bacteremia and meningitis) were estimated to have occurred in the United States and more than half of these cases were in elderly or immunocompromised adults.

Pneumococcal disease can be classified by clinical presentation (invasive or non-invasive) and by risk factors (age, living conditions, and underlying medical conditions). In adults, the clinical presentations of invasive pneumococcal disease (IPD) include meningitis, bacteraemia, and bacteremic pneumonia. IPD is defined by isolation of pneumococcus from a normally sterile site such as cerebrospinal fluid or blood, as well as pleural fluid or peritoneal fluid. Pneumonia without bacteraemia is the most common serious manifestation of non-invasive pneumococcal disease.

Important risk factors for pneumococcal disease include age and underlying medical conditions. In particular, adults older than 65 years (eg, 65 to 75 years, or >75 years) and increasingly, adults between 50 and 65 years (eg, 50 to 59 years, 60 to 64 years) are recognized to be at increased risk. Additional risk factors for serious pneumococcal disease include living circumstances and underlying medical conditions. Living conditions can increase the individual risk of pneumococcal disease, particularly residence in a nursing home or other long-term care facility.

The incidence of IPD is greatest at the extremes of life, creating a classic U-shaped curve of age versus incidence. Figure 1 shows an example from England and Wales, in which an adult 23vPS campaign was initiated in 2003, and 7vPnC was introduced into the national immunization program in 2006.

Figure 1. Invasive Pneumococcal Disease Incidence per 100,000 Population by Age Grouping in England and Wales From 2000 to 2009 (Courtesy of the Health Protection Agency, UK)



The total burden of disease (number of cases) within a population depends both on the size of each age group and on the proportion of individuals within the age group who have a risk factor of disease. In the United Kingdom, for example, for each child below the age of 5 years, there are about 2 adults above the age of 65 years. Nonetheless, for 2009/2010 in England and Wales (Health Protection Agency surveillance), there were about 5 times as many laboratory confirmed cases of IPD in adults older than 65 years as in children aged less than 5 years (respectively, 1,937 and 388 cases). Consequently, the burden of IPD in older adults is much greater than the sizes of the 2 populations (adults >65 years of age compared to young children <5 years of age) would suggest.

In addition to the disease burden in older adults, the case-fatality rate from IPD among hospitalized patients remains important. In spite of advances in medical science over the last decades, the case-fatality rate (12% to 13% in the USA, for instance) has remained constant through the 1950s to the present.

Medical Need for improved Pneumococcal vaccines for adults

As reviewed by Fedson and Musher, Jackson and Neuzil, and Makela and Butler, a number of studies have supported the value of purified free-polysaccharide vaccine (different serotype formulations) in protecting adults against IPD and have estimated the efficacy against IPD caused by vaccine serotypes to be around 50% with an overall effectiveness of around 75%. However, some trials have failed to demonstrate statistically significant efficacy against IPD in elderly adults. Antibody levels and protection against IPD appear to wane over a period of 3 to 5 years. 23vPS efficacy and effectiveness are limited in individuals with co-morbidities or risk factors, as compared to healthy adults.

Introduction of infant and childhood 7vPnC immunization has resulted in a decrease in IPD in infants and toddlers and an indirect decrease in IPD in adults, which is presumed to be due to reduction of vaccine serotype pneumococcal colonization in infants and lower likelihood of transmission to susceptible adults, referred to as indirect (herd) protection. In spite of this indirect protection, the gap in protection of adults in comparison to infants has widened. In 2008, the mortality rate among adults 50 to 64 years of age (2.21/100,000) was more than 2-fold greater than the mortality rate among

infants >1 year of age, and the mortality rate among adults ≥65 years of age (6.35/100,000) was more than 6-fold greater than rates in infants <1 year of age.

In the United States, despite the impact of pediatric 7vPnC in reducing IPD in all age groups by indirect protection, there are 44,000 IPD cases and 4500 deaths each year; approximately 24,000 to 26,000 of the IPD cases and 3600 of the deaths occur annually in adults over 50 years of age.

Data from the Health Protection Agency (HPA) in the UK affords an additional opportunity to evaluate the effect of a comprehensive 23vPS immunization campaign that began in 2003 in older adults, and a 7vPnC infant and childhood national immunization program, which began in 2006. Immunization of adults with 23vPS was encouraged, so that by 2007 rates were 70.1% in 65- to 74-year-olds, 77.3% in 75- to 79-year-olds, and 75.8% in subjects 80 years of age and older. Despite this national comprehensive campaign that more than doubled previous immunization levels, 23vPS did not reduce rates of IPD in adults ≥65 years of age by 2009 (Figure 1).

The efficacy of 23vPS against community-acquired pneumonia (CAP) is uncertain.

Widespread use of 23vPS has not impacted overall CAP pneumonia rates, and by inference from failure to reduce IPD rates, has not reduced pneumococcal CAP. No or limited effectiveness of the 23vPS vaccine has been demonstrated in observational studies. In contrast to indirect reductions of IPD, including bacteremic pneumonia, broad pediatric 7vPnC vaccination has not yet demonstrated convincing evidence of an indirect reduction of cases of CAP (pneumococcal or all cause), particularly in older adults.

Indirect protection from 7vPnC programs

The US Centers for Disease Control and Prevention (CDC) has performed a comprehensive assessment of IPD burden beginning in 1997 prior to the introduction of 7vPnC, through introduction of a 7vPnC paediatric national immunization program (NIP) in 2000 that continues to the present.

Importantly, an indirect (herd) protection effect of childhood 7vPnC immunization has not been universally observed. Rates of adult IPD in some countries, such as Denmark, Germany, or the UK, have remained relatively unchanged over the past 5 years and rates in Spain have decreased, but not yet to the degree seen in the USA.

In contrast to indirect reductions of IPD, including bacteremic pneumonia, broad paediatric 7vPnC vaccination has not yet demonstrated convincing evidence of an indirect reduction of cases of CAP (pneumococcal or all cause), particularly in older adults. No reductions were seen in either outpatient or inpatient settings from these studies.

Serotype coverage of the 13vPnC and 23vPS vaccines

13vPnC Serotypes Responsible for Adult Invasive Pneumococcal Disease

The serotype-specific epidemiology of adult IPD has been studied based on isolates from otherwise sterile sites of patients suffering from pneumococcal diseases such as meningitis, bacteraemia, or bacteremic pneumonia.

In the USA, the distribution of IPD serotypes in adults >65 years of age can be compared, from 1998-1999 (pre-7vPnC) to 2006-2007 (post-7vPnC, Table 1). The 13vPnC coverage fell from 75.5% to 49.9%, which can be attributed to the indirect (herd) effect of the childhood NIP for 7vPnC that began in 2000-2001. The most prevalent serotypes in 2006-2007 (each having a frequency greater than 7%) were 19A, 6A, 3, 7F, and 22F.

Table 1. Serotype Distribution (%) in Invasive Pneumococcal Disease and Coverage of 13vPnC in Adults, USA (Pilishvili et al 2010)

Age	Period	N	13v	23v	Δ
18-64	1998-1999	2983	73.7%	88.0%	18.3%
	2006-2007	2461	52.6%	75.7%	28.7%
>65	1998-1999	1982	75.5%	84.1%	15.1%
	2006-2007	1432	49.9%	64.7%	24.3%

Note: 13v, the 13 serotypes are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
23v, the 23 serotypes are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
Δ, represents the proportion of IPD due to serotypes unique to the PPS23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)

In England and Wales, unpublished surveillance data from the UK HPA reveal the effect of a targeted 23vPS program (2003 to 2006) in elderly adults and the impact of the 7vPnC NIP that began in 2006 (Table 3). In the first period, there was little change in the proportion of isolates covered by 23vPS (from 88.8% in 2002 to 2003 to 87.8% in 2005 to 2006). This absence of impact was equally noted among the 13 serotypes in 13vPnC (from 72.5% in 2002-03 to 74.0% in 2005-06) and the 11 serotypes unique to 23vPS (from 20.4% in 2002-03 to 18.5% in 2005-06). The contrast is striking once 7vPnC was introduced into the NIP in 2006, as there was an important change in the proportion of serotypes associated with 13vPnC (from 74.0% in 2005-06 to 52.6% in 2009-2010), among the most prevalent remaining serotypes being 19A, 3, 22F, and 7F. By contrast, the proportion of serotypes unique to 23vPS rose (from 18.5% in 2005-06 to 29.2% in 2009-2010).

Table 2. Serotype Distribution (%) in Invasive Pneumococcal Disease and Coverage of 13vPnC in Adults, England & Wales (HPA, 2010)

Age	Period	N	13v	23v	Δ
5-64	2002-2003	975	68.7%	92.1%	25.4%
	2003-2004	1159	71.3%	93.1%	24.6%
	2004-2005	1589	71.2%	93.3%	23.9%
	2005-2006	1961	75.0%	94.6%	21.4%
	2006-2007	1839	71.9%	92.4%	23.0%
	2007-2008	2142	67.3%	91.5%	26.9%
	2008-2009	2248	63.2%	90.5%	30.2%
	2009-2010	2053	60.0%	89.2%	30.8%
>65	2002-2003	1258	72.5%	88.8%	20.4%
	2003-2004	1470	73.5%	91.5%	21.5%
	2004-2005	1923	72.4%	90.2%	21.8%
	2005-2006	2024	74.0%	87.8%	18.5%
	2006-2007	1867	73.0%	87.0%	19.4%
	2007-2008	2038	64.9%	84.2%	26.2%
	2008-2009	2238	56.5%	81.5%	30.6%
	2009-2010	1937	52.6%	78.6%	29.2%

Note: 13v, the 13 serotypes are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
23v, the 23 serotypes are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
Δ, represents the proportion of IPD due to serotypes unique to the PPS23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)

In addition to the experience in the USA and the UK (pre-7vPnC and post-7vPnC), there are pre-7vPnC NIP surveillance data from Germany and the Czech Republic. In a report from North-Rhine Westphalia, Germany (2001-2003), 647 invasive isolates of *S pneumoniae* were serotyped, with 9 of the top 10 isolates being represented in the 13vPnC formulation; these 10 isolates in order of prevalence were serotypes 14, 3, 4, 7F, 23F, 1, 9V, 6A, 8, and 19F. Subsequent, nation-wide German surveillance was provided through 2008. Over the period from 2003 to 2008, the 13vPnC serotype coverage (adults >16 years of age) ranged from 71.3% to 77.3%, while the proportion of serotypes unique to 23vPS ranged from 13.3% to 18.4%. In the Czech Republic, over the period from 1997 to 2006, the 13vPnC serotype coverage (adults >65 years of age) was 65.0%, while the proportion of serotypes unique to 23vPS was 25.4%.

In summary, various studies have aimed at ranking the risk for severe disease or death for different pneumococcal serotypes. In most of these studies several of the serotypes associated with high risk for hospitalization or mortality are included in Prevenar 13 vaccine. These strains are also included in the 23vPS vaccine, and do not indicate an advantage of 13vPnC over 23vPS vaccine.

3.3.2. Clinical efficacy

The clinical development program investigated the use of 13vPnC in adults over 50 years of age in 2 target groups with the following age stratifications:

1. Individuals naive to 23-valent polysaccharide vaccine (23vPS) aged:
    - ≥65 years
    - 60-64 years
    - 50-59 years
2. Individuals pre-immunized with 23-valent polysaccharide vaccine (23vPS) at least 5 years prior to study enrolment aged:
    - ≥70 years

The efficacy data include immunogenicity results from seven 13vPnC trials and one precursor 7vPnC trial in adults (see details below).

Main studies: Pivotal Non-inferiority trials (studies 004 and 3005)

The dossier included 2 pivotal non inferiority trials: one in subjects aged 50 to 64 years (study 004) who were naïve to 23vPS, and the other trial in subjects aged 70 years or older who had previously received 1 dose of 23vPS (study 3005) at least 5 years earlier.

Pivotal Non-inferiority Trial in a Naïve Population (Study 004)

Study 004 is the pivotal study to support licensure of 13vPnC in adults aged 50 to 64 years who were naïve to polysaccharide vaccination. This study was conducted at multiple sites in the United States. A primary trial objective was to demonstrate that a single dose of 13vPnC is non-inferior to a single dose of 23vPS in the age cohort of 60 to 64 years, as measured by serotype-specific opsonophagocytic activity (OPA) titers for the 12 serotypes common to both vaccines. A co-primary objective was to demonstrate that the proportion of subjects exhibiting a 4-fold increase in anti-6A OPA titer was statistically significantly greater in subjects receiving 13vPnC than in those receiving 23vPS. A secondary objective was to demonstrate that 13vPnC elicits statistically significantly greater immune responses relative to 23vPS for some serotypes.

In a younger age cohort of 50 to 59 years, subjects received 13vPnC only, and non-inferiority of the immune response in this age group was assessed relative to the immune response in the older cohort.

Pivotal Non-inferiority Trial in a Pre-immunized Population (Study 3005)

Study 3005 is the pivotal non-inferiority trial to support licensure in 23vPS pre-immunized subjects. This study was conducted at multiple sites in Sweden and the United States in subjects aged 70 years or older who had received a dose of 23vPS at least 5 years earlier (ie at the recommended age of 65). Subjects in study 3005 received the first vaccination with either 13vPnC or 23vPS. One year after the initial vaccination both groups received another vaccination with 13vPnC.

The primary objective of this study was to demonstrate that 13vPnC elicits serotype-specific OPA responses that are non-inferior to those induced by 23vPS in pre-immunized subjects. A co-primary objective was to demonstrate that the proportion of subjects exhibiting a 4-fold increase in anti-6A OPA titer was statistically significantly greater in subjects receiving 13vPnC than in those receiving 23vPS. A secondary objective was to show that OPA responses to 13vPnC were statistically significantly greater than responses to 23vPS for some common serotypes.

The study also assessed the immune response of a second dose of 13vPnC. Data from pre-immunized subjects who received 13vPnC one year after 23vPS were evaluated to determine whether 13vPnC would increase immune response following 2 doses of 23vPS.

Subsequent Dose Trial (Study 3010)

Study 3010 was conducted in 23vPS naïve subjects, aged 60 to 64 years, at multiple sites in the United States. The purpose of the study was to assess the ability of subjects to respond to 13vPnC and 23vPS when given a year apart in differing sequential order. The study was also designed to assess response after 2 doses of 13vPnC, each vaccination given a year apart. The primary objective of this study was to assess non inferiority of OPA response to 23vPS administered 1 year after an initial study dose of 13vPnC (i.e. 13vPnC/23vPS) relative to OPA response after an initial study dose of 23vPS for the 12 serotypes common to both 13vPnC and 23vPS. A co-primary objective was to assess non inferiority of immune response to 23vPS administered 1 year after an initial study dose of 13vPnC (ie, 13vPnC/23vPS) relative to OPA response to 13vPnC administered 1 year after an initial study dose of 23vPS (ie, 23vPS/13vPnC) for the 12 common serotypes. Subjects in group 1 received an initial vaccination with 13vPnC followed by either another vaccination with 13vPnC or 23vPS one year later. Subjects in group 2 received an initial vaccination with 23vPS and, 1 year later, another vaccination with 13vPnC.

Trials of 13vPnC Compatibility With Influenza Vaccine (Studies 3001 and 3008)

Most countries in Europe recommend vaccination with seasonal influenza vaccine in adults aged 65 years and older. In the US the influenza vaccine is recommended for adults aged 50 years and older. Clinicians often administer the pneumococcal vaccine at the same time as the influenza vaccine in this population, to limit the number of healthcare visits; administration of both vaccines may also be beneficial because of the high risk of bacterial coinfection in the elderly. For these reasons, the compatibility of 13vPnC given concomitantly with the seasonal influenza vaccine was evaluated.

Studies 3001 and 3008 were conducted at multiple sites in the United States and Europe (Belgium, Germany, Hungary, and the Netherlands), respectively. In study 3001 subjects were aged 50 to 59 years and in study 3008 subjects were aged 65 years or older. In both studies subjects were naïve to 23vPS. One co-primary objective of each study was to evaluate non inferiority of immune response to the influenza antigens contained in TIV after administration of 13vPnC + TIV relative to that after TIV alone (ie, 13vPnC+TIV versus placebo+TIV), as measured by the standard hemagglutination inhibition assay (HAI) for the A/H1, A/H3, and B vaccine strains. Another co-primary objective of each study was to evaluate the non inferiority of pneumococcal serotype-specific IgG response to the combined administration of 13vPnC and TIV relative to that of 13vPnC alone (ie, 13vPnC+TIV versus 13vPnC), as measured by serotype-specific immunoglobulin G (IgG) concentrations.

Over 1000 subjects were enrolled in each study and randomly assigned to 2 groups: one group received 13vPnC and TIV (Fluarix™), followed by placebo (13vPnC+TIV/placebo); the other group received placebo and TIV followed by 13vPnC (placebo+TIV/13vPnC) one month later. The data from both studies demonstrate compatibility of the two vaccines.

Study 3001 has a 5-year follow up with yearly bleeds and revaccination with 13vPnC at year 5; these data were not included in the dossier.

Supportive Studies (Studies 500 and 3009)

Two trials included in the dossier did not use the final commercial formulation of13vPnC; these were study 500 and study 3009, a follow up trial to study 500. Both studies are considered supportive studies.

Formulation Choice and Non inferiority Trial (Study 500)

Study 500 was conducted at multiple sites in South Africa in subjects aged 65 years and older who were naïve to previous 23vPS. The study was designed as a formulation choice trial and as a non inferiority study. Subjects were randomly assigned to 1 of 3 vaccine groups: group 1 received 13vPnC with aluminium phosphate (13vPnC+AlPO4); group 2 received 13vPnC without AlPO4 (13vPnC-AlPO4); and group 3 received 23vPS. A year after the initial vaccination subjects who received the selected 13vPnC formulation were to receive either a subsequent dose of 23vPSor a second dose of the selected 13vPnC formulation.

Formulation choice: The formulation of Prevenar includes aluminium phosphate (AlPO4), which evidence suggests may enhance immune response in infants. Thus, AlPO4 is also a component of the 13vPnC formulation licensed for use in infants. To determine whether AlPO4 should be included in the final 13vPnC formulation for use in adults, study 500 evaluated the non inferiority of IgG response induced by 13vPnC with AlPO4 (13vPnC+AlPO4) relative to 13vPnC without AlPO4 (13vPnC-AlPO4), ie, the first co-primary objective. Based on the results of an interim analysis and logistical considerations to supply the same vaccine for infants and adults, the 13vPnC formulation with AlPO4 was selected for use in the 13vPnC adult program.

Non-inferiority: To address the other co-primary objective, the study assessed non-inferiority of immune response to the selected 13vPnC formulation relative to 23vPS, which is licensed for use in adults aged 65 years and older and in high risk groups. This analysis was based on serotype-specific OPA responses in subjects who received a single dose of 13vPnC or 23vPS.

The study was also designed to assess the immune responses of subsequent doses of 13vPnC or 23vPS given 1 year after an initial dose of 13vPnC.

South African Follow up Trial (Study 3009)

Study 3009 was a continuation of study 500 and used the selected 13vPnC formulation from study 500. Subjects who received 13vPnC as an initial vaccination and 23vPS one year later (ie, 13vPnC/23vPS) in study 500 were included in study 3009; these subjects received another dose of 13vPnC one year after the 23vPS dose in study 500. The primary objective of this study was to compare immune response after receipt of the subsequent 13vPnC dose in study 3009 relative to that after 13vPnC given as a first dose in study 500 (ie, 13vPnC/23vPS/13vPnC versus 13vPnC). This study was of interest because previous experience showed that when 23vPS is given as the initial vaccine, the immune response to a subsequent dose of pneumococcal vaccine may be diminished.

Study 3009 was conducted to determine whether priming with 13vPnC before 23vPS (ie, 13vPnC/23vPS in study 500) overcomes the potential decline of antibodies caused by 23vPS to a subsequent dose of 13vPnC (ie [13vPnC/23vPS]/13vPnC in study 3009).

3.3.3. Statistical Methods

Studies 004, 500, 3005, and, 3010 had non-inferiority objectives and were powered to assess non-inferiority of immune response to pneumococcal serotypes. In addition, studies 3001 and 3008 were also powered to assess non-inferiority of immune response to the pneumococcal serotypes and to the influenza strains in TIV, when 13vPnC was given with the concomitant influenza vaccine.

Immunogenicity data were based on results of assays performed using blood samples obtained at protocol-specified time points.

Assay values were reported in the database as provided by the testing laboratories. Missing values were excluded from the immunogenicity analyses; no imputation or estimation of missing values was performed.

Analysis Populations

In each study, an evaluable immunogenicity population and an all-available immunogenicity population were defined for the analyses. In all studies, the primary analysis population was the evaluable immunogenicity population. Within these broad categories, additional analysis populations have been created for the evaluation of vaccination 1 or vaccination 2.

Comparisons of Interest and Endpoints

The primary immunogenicity endpoint for pneumococcal response was the serotype-specific OPA titers measured 1 month after each vaccination. The immunologic comparisons for pneumococcal response varied according to the individual study. In the non-inferiority studies (studies 004, 3005, and 500) a primary comparison of interest was OPA response to 13vPnC relative to 23vPS. In studies with primary objectives that required assessment of sequential use (studies 3010, 3009) OPA titers elicited by 1 vaccine sequence or dose relative to another were compared.

In the concomitant influenza vaccine studies the primary pneumococcal endpoint was the serotype-specific anticapsular IgG concentrations, and the primary influenza endpoints was the proportions of subjects (responders) who achieved at least a 4-fold increase (ie, seroconverters) in HAI titers elicited by the 3 strains in TIV (A/H1N1, A/H3N2, and B). The comparisons of interest in these 2 studies were the serotype-specific pneumococcal IgG geometric mean concentrations (GMCs) after 13vPnC + TIV relative to 13vPnC and the proportions of responders to the 3 strains in TIV in subjects receiving 13vPnC + TIV relative to TIV + placebo.

Pneumococcal Antibody Titers and Concentrations

Geometric Means

Within each vaccine group and for each serotype, OPA geometric mean titers (GMTs) or IgG GMCs were calculated. Each titer or concentration was logarithmically transformed for analysis. Two (2)-sided 95% confidence intervals (CIs) were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. Fold rises in antibody concentrations from before to after each vaccination, or from vaccination 1 to vaccination 2 (for purposes of comparing vaccination 2 to vaccination 1 within a vaccine sequence) were summarized by geometric means and 95% CIs, and were also computed using the logarithmically transformed assay results; for within-group comparisons each subject was their own control.

To assess differences between the 2 vaccine groups, 2-sided 95% CIs for the ratio of OPA GMTs or IgG GMCs (test to reference) were constructed. In studies 004 and 3005 and 500, non-inferiority of 13vPnC relative to 23vPS (and of cohort 2 relative to cohort 1 in study 004), or non-inferiority of 1 vaccine sequence or dose to another (3010, 3005, 500), was declared if the lower limit of the CI for the ratio was greater than 0.5 (2-fold criterion).

Statistical significance was defined for OPA GMT or IgG GMC comparisons as a lower limit of the 95% CI for the ratio (test to reference) of >1 (statistically significantly higher) or the upper limit of the 95% CI for the ratio of <1 (statistically significantly lower).

Comparisons involving serotype 6A were the topic of specific regulatory consultation, as serotype 6A is not included in 23vPS. In the pivotal non-inferiority studies 004 and 3005, statistically significantly greater response to 13vPnC was demonstrated for serotype 6A if the lower limit of the 95% CI for the geometric mean ratio (13vPnC GMT/ 23vPS GMT) was >2.0.

Rationale for Non-inferiority Criterion for Comparison of OPA GMTs

The non-inferiority criterion for application in the adult 13vPnC program was chosen after regulatory consultation and was based upon relevant publications at the time of study design.

Additional justification is provided as follows:

Study 6097A1-508 evaluated administration of 7vPnC compared to 23vPS in pneumococcal vaccine-naive adults ≥70 years of age. Based on observed GMT OPA data in study 6097A1-508, it was found that, the conservative estimate (lower 95% bound) for the 23vPS treatment effect relative to placebo (estimated using baseline data from all treatment groups) is in the range 4.08 to 30.38 across the serotypes studied (Table 3). It is assumed that placebo would behave similarly to the observed baseline data.

Table 3. GMR of 23vPS in Study 6097A1-508

	23vPS	**Baseline**	**Lower bound of 95% CI for the GMR (23vPS:Baseline)**
Serotype	**GMT**	**GMT**	
1	142	25	4.08
4	663	15	30.38
5	248	21	8.35
6B	809	59	8.24
9V	985	144	4.34
14	1011	92	6.30
18C	465	45	6.94
19F	203	14	9.73
23F	302	45	4.16

Table 4. displays what non-inferiority margin is recommended by preserving increasing percentages of the conservative estimate of the 23vPS treatment effect

Preserved 23vPS Effect	Non Inferiority margin	
	Conservative 23vPS Effect= 4.08	Conservative 23vPS Effect= 30.38
50%	2.0	15.2
60%	1.6	12.2
70%	1.2	9.1
80%	0.8	6.1
88%	0.5	3.6
90%	0.4	3.0
98.5%	0.1	0.5

From these findings, it may be inferred that the non-inferiority bound (0.5), applied in the 13vPnC adult program non-inferiority studies for 13vPnC testing to 23vPS, preserves between 88% to 99% of the control effect and therefore is conservative for non-inferiority trials.

Proportion of Subjects Achieving Defined Levels

The proportion of subjects achieving or exceeding an OPA titer prespecified as the lower limit of quantitation (LLOQ) for each serotype in each vaccine group (ie, responders) was assessed in studies 004, 3005, and 500 (and as ad hoc comparisons in studies 3010 and 3005). In addition, exact, unconditional, 2-sided, 95% CIs on the proportion were calculated using Clopper and Pearson.

To assess vaccine differences, exact, unconditional, 2-sided 95% CIs for the difference in proportions of responders between vaccine groups were calculated. The CIs for the difference in proportions were computed by the non-inferiority procedure of Chan and Zhang. Non-inferiority was declared if the difference in proportion of responders (test – reference) at the lower limit of the 95% CI was greater than -10%. The rationale for use of this criterion is provided in Horne et al.

The same method was used to compare the proportion of responders achieving a 4-fold rise in antibody titer or an OPA titer of 1:8.

Statistical significance was defined for comparison of the proportion of responders as a lower limit of the 95% CI for the difference (test - reference) of >0 (statistically significantly higher) or the upper limit of the 95% CI for the difference of <0 (statistically significantly lower).

Antigens in the Concomitant Vaccine TIV

The primary endpoint for the TIV comparisons in study 3001 and 3008 was the proportion of subjects who achieved at least a 4-fold increase in the HAI titer, ie, the definition of seroconversion, for each influenza strain (A/H1N1, A/H3N2, and B) 1 month after vaccination with TIV. The same statistical methods as used in pneumococcal non-inferiority analyses for calculating exact, unconditional, 2-sided 95% CIs for the proportion of responders and for the difference in proportions (13vPnC + TIV – placebo + TIV) were used for the TIV antigens. For each antigen, non-inferiority was declared if the lower bound of the 2-sided 95% CI for the difference in the proportion of responders was greater than -0.10.

Geometric Means

Within each vaccine group and for each antigen separately, the geometric means of the TIV antibody titers measured 1 month after vaccine administration were calculated. The same statistical methods for computing GMTs and corresponding 95% CIs as those described for the pneumococcal serotypes were used for the TIV antigens, although these studies were not designed to show non-inferiorty of TIV + 13vPnC relative to TIV + placebo based on GMTs.

Reverse Cumulative Distribution Curves

The empirical reverse cumulative distribution curves (RCDCs) were presented graphically for serotype-specific OPA titers, and IgG concentrations when assessed. These graphs show (not included herein) the distribution of OPA or IgG responses 1 month after each vaccination.

Analyses in High-Risk Groups

Various categories of high risk were identified across the studies in the filing, and OPA GMTs or IgG GMCs in these subgroups were computed. (Immunocompetent high-risk subjects with stable disease were not excluded from participating in the study.) No statistical comparisons between vaccine groups were presented; only descriptive analyses of immunogenicity results were provided. Subjects may have had more than 1 condition identified as high risk and thus may have been included in more than 1 high-risk group.

Measurements of Immune Response

Description of the Modified OPA Assay Used in the Serological Analysis of 13vPnC Adult Program

The OPA assay measures functional antibodies to *Streptococcus pneumoniae*. OPA assays have been used to measure the functional antibody activity elicited by 13vPnC in the infant program, and results were central to licensure of the 13vPnC paediatric indications. These assays used the "traditional" method of manually dribbling the final assay samples onto growth medium for viable bacterial colony formation and enumeration. The assays are labor-intensive and limited in their ability to handle the high throughput clinical testing required in support of the 13vPnC phase 3 trials in adults. Hence, the assay was modified by simplification of some of the assay steps and by introduction of automation. This modified assay, termed microcolony OPA (mcOPA), has been developed to increase throughput and robustness in order to be able to analyze the large number of serological samples. The microcolony, or "mc" designation, refers to the use of bacterial microcolonies for the enumeration of viable bacterial cells. However, the mcOPA assay uses the same killing endpoint of 50% as the dOPA assay. As part of the assessment of the mcOPA assay, samples from the infant phase 3 study 6096A1-006 were tested using the assay and a statistical assessment of mcOPA and dOPA assay results was performed. This assessment found significant concordance between the findings of both assays, supporting the perspective that the use of the mcOPA will not confound statistical inference in future studies of pneumococcal vaccines.

The serotype-specific OPA assays do not use an external reference standard, and therefore OPA titers cannot be compared across serotypes. An OPA titer is defined as the interpolated reciprocal serum dilution that results in complement mediated killing of 50% of the bacteria in each OPA assay. The lowest titer that can be determined in OPA assays is a titer of 1:8 (limit of detection, LOD) and is the same for each serotype-specific OPA assay. However, to quantify functional antibodies in the OPA assays with appropriate precision and accuracy, the lower limit of quantitation (LLOQ) was determined for each serotype-specific OPA assay during assay validation. The LLOQ for each serotype-specific OPA assay was used as a cut-off to determine serum response for the immunogenicity subjects. Previously, an OPA serum response was determined using an OPA titer cut-off of 1:8 as was done for the 13vPnC assessments in support of the infant/young children indication. However, additional more stringent qualification and validation of the improved mcOPA assays did not support a universal LLOQ of 1:8 for

the quantitation of a serum response and thus the following cut-offs (LLOQs) were used for the mcOPA: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype l4, 1:35; serotype 18, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13.

Given the range of LLOQs, the individual LLOQs are used for each of the serotypes as "serotype specific cut-offs" rather than the previously proposed cut-off of 1:8.

It should also be noted that because of the changes to the assay LLOQs, the study endpoints for clinical trials 6115A1-004, 6115A1-500, and 6115A1-3005 required modification because they originally involved determining the proportion of vaccinated subject exhibiting an OPA titer of ≥1:8. Endpoints that involve use of an OPA titer of ≥ 1:8 were changed to endpoints that describe use of an OPA titer ≥ LLOQ. Both studies 6115A1-004 and 6115A1-3005 were conducted in the United States and therefore the protocol amendments were filed to the investigational new drug application (IND). None of the remaining study protocols required a protocol amendment because they did not originally describe an OPA titer of ≥1:8 as a study objective.

The OPA assay is considered an appropriate method for determination of immune responses following vaccination as it measures functional antibodies. In children the OPA titres have been shown to correlate to protection, and the ELISA IgG levels have been shown to correlate to OPA results after vaccination with conjugate vaccines. No such correlate of protection has been established for adults. Therefore, the OPA titres, representing functional immune responses is considered more likely to reflect protection than IgG levels measured by ELISA. Thus, the CHMP endorsed the choice of OPA as primary assay instead of ELISA for the adult development program.

The OPA assay was used in the paediatric studies, but has now been modified for high-throughput clinical testing. The assay is considered validated, and the LLOQ have been justified.

Justification for Use of OPA Comparisons as Immunologic Basis for Licensure

In infants, serotype-specific capsular antipolysaccharide binding antibody of 0.35 µg/ mL accompanied by functional opsonophagocytic activity (OPA) and elicited after administration of CRM197 conjugate pneumococcal vaccine has been established as a correlate of protection against IPD. In infants, the presence of IgG binding antibody is a necessary but insufficient condition for this protection. This is best evidenced by the ability of 7vPnC to protect against all serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) but the failure of 7vPnC to protect against serotype 19A. For each of the serotypes contained in 7vPnC, IgG responses have been shown to correlate with OPA response. In contrast, serotype 19F elicits IgG serotype-specific antipolysaccharide binding antibody to 19A, but without an accompanying OPA response. This deficiency in OPA response is likely responsible for the failure of 7vPnC to protect against 19A. (13vPnC contains 19A, elicits an IgG response correlated with OPA response, and is expected to confer protection against this serotype in infants.) Therefore, when the anti-polysaccharide IgG response as measured by ELISA is correlated with a serotype-specific OPA response, protection is afforded by the CRM197 conjugate vaccine.

In contrast to the experience in infants, there is no established correlate of protection against pneumococcal disease after either 23vPS or pneumococcal conjugate vaccine in adults. However, both elicit OPA responses to serotypes contained in the respective vaccines. Also, 7vPnC or 9vPnC in adults induces OPA titers that are concordant (by serotype) with those achieved after effective vaccination in children; consequently, in adults, similar OPA responses elicited by 13vPnC are likely to be associated with protection against pneumococcal disease. Given that 23vPS provides limited protection against IPD but not VT-CAP, that opsonophagocytic antibody response is fundamental to protection, and that OPA has been demonstrated to be associated with this protection against IPD and pneumonia in

children, it is appropriate to compare OPA responses in adults after 13vPnC to those after 23vPS, for serotypes in common, as a basis for adult indications.

3.3.4. Efficacy Study Results

Pivotal Non inferiority Trial (Study 004)

Study 004 was a phase 3, randomized, modified double-blind, active-controlled, multicenter trial conducted in the United States in subjects naïve to previous 23vPS. Results from subjects aged 60-64 years (cohort 1) and 50-59 years (cohort 2) are provided in this summary. The primary objectives of this study were: to demonstrate that immune response to 13vPnC was non inferior to that of 23vPS for the 12 serotypes common to both vaccines, as measured by serotype-specific OPA titers; and to demonstrate that the proportion of subjects with a 4-fold increase in anti-6A OPA titer was statistically significantly greater in the 13vPnC group than in the 23vPS group. Subjects (planned: 370 in each group; actual: 418 in the 13vPnC group and 417 in the 23vPS group) in cohort 1 were randomly assigned to either 13vPnC or 23vPS in a 1:1 ratio; 417 subjects in the 13vPnC group and 414 subjects in the 23vPS group were vaccinated. Of the 406 subjects in cohort 2 assigned to open label 13vPnC, 404 subjects were vaccinated. An overview of study details is provided in below.

Study 004 schema

Study 6115A1-004			
Age	**Cohort**	**Year 1**	**Year 2**
60-64y naive	1.1	13vPS	Bleed
	1.2	23vPS	Bleed
50-59y naive	2	13vPS	Bleed

The immunogenicity analyses were based on results of OPA and IgG ELISA measurements of antibody levels in blood samples taken at protocol specified time points. All subjects provided blood samples for OPA analysis at baseline (on day 1 before vaccine administration) and approximately 1 month after vaccination. Blood samples for OPA analysis at 1 year after vaccination were obtained from a subset of 100 subjects.

Blood samples for all IgG ELISA analyses were obtained from a subset of 100 subjects; these blood samples were obtained at baseline (on day 1 before vaccine administration), approximately 1 month after vaccination, and approximately 12 months after vaccination.

The evaluable immunogenicity population of cohort 1 included 411 (98.3%) subjects in the 13vPnC group and 407 (97.6%) subjects in the 23vPS group. The demographic results and baseline characteristics were comparable in subjects randomly assigned to each vaccine group with respect to race, and age. However, a disparity in proportion of males to females was noted, particularly in the 23vPS group (ie, 61.2% female, 38.8% male) when compared with the 13vPnC group (ie, 53.5% female, 46.5% male). This disparity was addressed in an ad hoc analysis of immune response by sex.

The evaluable immunogenicity population for cohort 2 included 388 (95.6%) subjects and the all available immunogenicity population included 403 (99.3%) subjects (Table 5). All subjects received open-label 13vPnC. The primary analysis population was the evaluable immunogenicity population for each cohort.

Table 5. All-Available and Evaluable Immunogenicity Populations for Subjects Aged 60-64 Years (Cohort 1) and 50-59 Years (Cohort 2)

	Vaccine Group (as Randomized) Cohort 1				Vaccine Group (as Assigned) Cohort 2			
	13vPnC		23vPS		13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%
Randomized/assigned	418	100.0	417	100.0	406	100.0	1241	100.0
All-available immunogenicity population	417	99.8	414	99.3	403	99.3	1234	99.4
Subjects excluded from the all-available immunogenicity population	1	0.2	3	0.7	3	0.7	7	0.6
No prevaccination or postvaccination assay result for any serotype/antibody	1	0.2	3	0.7	3	0.7	7	0.6
Evaluable immunogenicity population	411	98.3	407	97.6	388	95.6	1206	97.2
Subjects excluded from the evaluable immunogenicity population	7	1.7	10	2.4	18	4.4	35	2.8
Not in all-available immunogenicity population	1	0.2	3	0.7	3	0.7	7	0.6
Not eligible for the study	2	0.5	0	0.0	2	0.5	4	0.3
Prevaccination sample not within 15 days prior to vaccination and day 1	0	0.0	0	0.0	1	0.2	1	0.1
Had no postvaccination blood draw in prescribed time window	3	0.7	6	1.4	11	2.7	20	1.6
Postvaccination blood drawn <28 days after vaccination[b]	2	0.5	3	0.7	1	0.2	6	0.5
Postvaccination blood drawn >57 days after vaccination[b]	0	0.0	1	0.2	4	1.0	5	0.4
Received prohibited vaccines	1	0.2	1	0.2	5	1.2	7	0.6
Other protocol violation	2	0.5	0	0.0	0	0.0	2	0.2

a. n = Number of subjects with specified characteristic.
b. Prespecified time frame for purposes of analysis (specified in SAP).
Program ID: Study 6115A1-004/CP IMM_POPNS.SAS. Runtime ID: 22JUN2010 01:56
Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/004/Reports, Tables, and Figures/Immunogenicity/Immunogenicity_Final.ZIP/ immunogenicity_population_c12.htm

Cohort 1 - OPA Response

OPA GMTs

To assess non-inferiority of OPA response to 13vPnC relative to 23vPS, a 2-fold non-inferiority criterion of a lower limit of the 95% CI for the ratio of > 0.5 was applied. Results showed that OPA GMTs after 13vPnC were non-inferior to those after 23vPS for all 12 serotypes common to both vaccines (Table 6). OPA GMT ratios (13vPnC to 23vPS) ranged from 0.9 (serotype 14) to 5.2 (serotype 23F) and values at the lower limits of the 95% CIs for the ratios were ≥ 0.64 for all serotypes. For 8 of the 12 common serotypes, the 95% CI lower limit for the ratio was > 1.0, indicating that OPA GMTs were statistically significantly greater in the 13vPnC group than in the 23vPS group (secondary objective).

Table 6. Comparison of Pneumococcal OPA GMTs 1 Month After Vaccination With 13vPnC and 23vPS in Subjects Aged 60-64 Years (Cohort 1) - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)				Vaccine Comparison	
	13vPnC		23vPS			
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	404	146	402	104	1.4	(1.10, 1.78)
3	394	93	401	85	1.1	(0.90, 1.32)
4	359	2062	367	1295	1.6	(1.19, 2.13)
5	392	199	393	162	1.2	(0.93, 1.62)
6B	371	1984	371	788	2.5	(1.82, 3.48)
7F	394	1120	396	405	2.8	(1.98, 3.87)
9V	367	1164	368	407	2.9	(2.00, 4.08)
14	375	612	378	692	0.9	(0.64, 1.21)
18C	379	1726	381	925	1.9	(1.39, 2.51)
19A	392	682	388	352	1.9	(1.56, 2.41)
19F	377	517	370	539	1.0	(0.72, 1.28)
23F	375	375	375	72	5.2	(3.67, 7.33)
6A	401	2593	392	213	12.1	(8.63, 17.08)

a. n = Number of subjects with a determinate OPA titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all evaluable subjects with available data for the specified blood draw.
c. Ratio of GMTs 13vPnC to 23vPS is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – 23vPS).

Program ID: Study 6115A1-004/CP IMM_PNEUM_COMP_C1.SAS. Runtime ID: 22JUN2010 01:52
Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/004/ Reports, Tables, and Figures/Immunogenicity/Immunogenicity_Final.ZIP/imm_pneum_comp_opa_c1_ev1.htm (modified)

At 1 year after vaccination, OPA titers were higher in the 13vPnC group than in the 23vPS group for 7 of 12 common serotypes (all except serotypes 5, 14, 19A, and 19F). At the 1 year post-vaccination time point, OPA titers remained higher than pre-vaccination levels, but were lower than levels observed at 1 month after vaccination (Table 7).

Table 7. Pneumococcal OPA GMTs in Subjects Aged 60-64 Years (Cohort 1) and 50-59 Years (Cohort 2) – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized) Cohort 1						Vaccine Group (as Assigned) Cohort 2		
		13vPnC			23vPS			13vPnC		
Serotype	Time Point[a]	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])
1	Before vaccination	411	5	(4.9, 5.7)	407	6	(5.5, 6.6)	384	5	(4.8, 5.6)
	1 month after vaccination	404	146	(124.0, 172.9)	402	104	(87.7, 124.4)	382	200	(170.3, 236.0)
	1 year after vaccination	99	38	(27.2, 53.1)	98	28	(19.7, 38.7)	95	54	(37.9, 77.2)
3	Before vaccination	400	7	(6.1, 7.6)	401	8	(6.7, 8.5)	380	7	(6.2, 7.9)
	1 month after vaccination	394	93	(81.1, 106.6)	401	85	(74.2, 98.3)	379	91	(79.9, 104.7)
	1 year after vaccination	97	19	(13.9, 25.3)	94	17	(12.2, 23.2)	93	20	(15.0, 27.2)
4	Before vaccination	354	15	(11.5, 19.9)	331	16	(12.0, 20.5)	318	16	(12.2, 21.2)
	1 month after vaccination	359	2062	(1693.6, 2510.5)	367	1295	(1045.9, 1603.0)	350	2833	(2412.1, 3327.4)
	1 year after vaccination	90	248	(148.9, 414.4)	86	192	(107.2, 345.4)	83	863	(541.8, 1376.1)
5	Before vaccination	405	6	(5.3, 6.4)	402	6	(5.5, 6.8)	382	6	(5.2, 6.3)
	1 month after vaccination	392	199	(164.0, 242.3)	393	162	(133.6, 197.5)	373	269	(218.1, 332.5)
	1 year after vaccination	100	35	(23.0, 52.1)	96	41	(26.6, 62.2)	93	79	(51.9, 121.4)
6A	Before vaccination	383	14	(11.0, 17.1)	391	17	(13.2, 21.3)	364	19	(15.1, 24.7)
	1 month after vaccination	401	2593	(2146.7, 3131.1)	392	213	(160.3, 284.3)	384	4328	(3658.1, 5121.5)
	1 year after vaccination	95	733	(480.0, 1120.3)	93	89	(50.4, 156.1)	92	1147	(798.1, 1648.8)
6B	Before vaccination	354	37	(27.4, 49.6)	360	29	(21.6, 38.3)	335	40	(29.3, 53.9)
	1 month after vaccination	371	1984	(1604.0, 2453.6)	371	788	(615.9, 1008.5)	361	3212	(2728.6, 3781.4)
	1 year after vaccination	98	445	(267.5, 739.4)	89	216	(119.8, 389.7)	92	1234	(863.3, 1764.4)
7F	Before vaccination	399	7	(6.2, 8.6)	386	7	(5.9, 8.2)	369	7	(6.0, 8.5)
	1 month after vaccination	394	1120	(907.6, 1382.9)	396	405	(311.9, 524.7)	378	1520	(1274.5, 1812.1)
	1 year after vaccination	98	125	(72.6, 216.9)	99	72	(40.9, 126.6)	92	296	(183.4, 479.2)
9V	Before vaccination	356	22	(16.4, 28.3)	343	20	(14.9, 25.9)	326	27	(20.0, 36.2)
	1 month after vaccination	367	1164	(934.8, 1448.3)	368	407	(307.2, 539.8)	364	1726	(1428.5, 2086.2)
	1 year after vaccination	93	193	(109.0, 340.5)	88	176	(94.4, 330.0)	92	763	(486.7, 1196.2)
14	Before vaccination	372	28	(21.6, 36.0)	379	27	(20.8, 34.2)	355	45	(34.3, 59.5)
	1 month after vaccination	375	612	(489.6, 764.2)	378	692	(553.3, 866.2)	373	957	(779.6, 1174.5)
	1 year after vaccination	99	240	(149.7, 385.0)	96	338	(198.1, 575.6)	91	706	(456.3, 1093.3)
18C	Before vaccination	393	25	(19.5, 31.5)	383	25	(20.0, 32.2)	365	22	(17.1, 27.7)
	1 month after vaccination	379	1726	(1429.7, 2082.9)	381	925	(735.3, 1162.9)	373	1939	(1599.2, 2350.2)
	1 year after vaccination	93	477	(304.4, 748.5)	95	303	(182.5, 502.7)	93	652	(440.1, 965.4)
19A	Before vaccination	385	21	(17.9, 25.4)	384	23	(19.6, 27.8)	376	30	(24.5, 35.6)
	1 month after vaccination	392	682	(596.5, 779.9)	388	352	(297.0, 416.1)	377	956	(837.6, 1090.7)
	1 year after vaccination	92	138	(101.1, 189.7)	91	150	(106.8, 210.4)	94	303	(233.8, 392.9)
19F	Before vaccination	383	17	(13.7, 20.7)	379	16	(12.7, 19.0)	365	18	(14.2, 21.8)
	1 month after vaccination	377	517	(420.8, 635.3)	370	539	(442.1, 658.2)	367	599	(491.0, 731.0)
	1 year after vaccination	94	102	(67.2, 153.6)	92	173	(113.1, 263.3)	87	171	(107.5, 272.7)
23F	Before vaccination	382	8	(7.2, 9.9)	386	8	(6.4, 8.8)	359	8	(7.1, 10.0)
	1 month after vaccination	375	375	(297.2, 472.6)	375	72	(55.9, 93.4)	368	494	(386.8, 630.7)
	1 year after vaccination	94	79	(47.7, 132.2)	93	40	(24.7, 63.6)	94	143	(86.0, 237.8)

Note: OPA titers were obtained for a subset of subjects at 1 year after vaccination.

a. SAP-specified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

Proportion of Subjects Achieving OPA Titers ≥ LLOQ

Non-inferiority of response to 13vPnC relative to that of 23vPS was also assessed for the proportion of subjects achieving OPA titers ≥ LLOQ (ie, proportion of responders); the noninferiority criterion was achieved if the difference [13vPnC – 23vPS] at the lower limit of the 95% CI was > -10% for each serotype.

The non-inferiority criterion for proportion of responders to 13vPnC relative to 23vPS was met for all serotypes (Table 8). Differences ranged from -1.2% (serotype 19F) to 23.2% (serotype 23F) and differences at the lower limits of the 95% CIs were ≥ -5.6% for all serotypes (secondary objective).

The analyses of proportion of subjects achieving an OPA titer ≥ 1:8 supported these findings.

Table 8. Comparison of Subjects Aged 60-64 Years (Cohort 1) Achieving an OPA Titer of ≥LLOQ 1 Month After Vaccination With 13vPnC and 23vPS – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				23vPS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	404	365	90.3	(87.0, 93.0)	402	337	83.8	(79.9, 87.3)	6.5	(1.9, 11.2)
3	394	363	92.1	(89.0, 94.6)	401	354	88.3	(84.7, 91.3)	3.9	(-0.3, 8.1)
4	359	341	95.0	(92.2, 97.0)	367	336	91.6	(88.2, 94.2)	3.4	(-0.2, 7.2)
5	392	341	87.0	(83.3, 90.2)	393	333	84.7	(80.8, 88.1)	2.3	(-2.6, 7.2)
6B	371	347	93.5	(90.5, 95.8)	371	319	86.0	(82.0, 89.4)	7.5	(3.2, 12.0)
7F	394	356	90.4	(87.0, 93.1)	396	309	78.0	(73.6, 82.0)	12.3	(7.3, 17.4)
9V	367	330	89.9	(86.4, 92.8)	368	279	75.8	(71.1, 80.1)	14.1	(8.7, 19.5)
14	375	329	87.7	(84.0, 90.9)	378	335	88.6	(85.0, 91.6)	-0.9	(-5.6, 3.8)
18C	379	362	95.5	(92.9, 97.4)	381	339	89.0	(85.4, 91.9)	6.5	(2.6, 10.5)
19A	392	386	98.5	(96.7, 99.4)	388	366	94.3	(91.5, 96.4)	4.1	(1.2, 7.1)
19F	377	338	89.7	(86.1, 92.5)	370	336	90.8	(87.4, 93.6)	-1.2	(-5.5, 3.2)
23F	375	317	84.5	(80.5, 88.0)	375	230	61.3	(56.2, 66.3)	23.2	(17.0, 29.3)
6A	401	384	95.8	(93.3, 97.5)	392	271	69.1	(64.3, 73.7)	26.6	(21.7, 31.7)

Abbreviation: LLOQ = Lower limit of quantitation.

a. N = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference (13vPnC – 23vPS) in proportions, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan and Zhang) for the difference in proportions, 13vPnC – 23vPS, expressed as a percentage.

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Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/004/ Reports, Tables, and Figures/Immunogenicity/Immunogenicity_Final_LLOQ_1_8.ZIP/imm_opa_resp_c1_ev1.htm (modified)

OPA Responses to Serotype 6A

Proportion of responders at prespecified anti-6A OPA levels: A co-primary immunogenicity objective in cohort 1 was to demonstrate that the proportion of subjects achieving a 4-fold increase in anti-6A OPA titer was statistically significantly greater in the 13vPnC group than in the 23vPS group; the criterion for achieving this objective was a lower limit of the 95% CI for the difference in proportions (13vPnC – 23vPS) of >0.

Results showed that this criterion was met. The proportion of subjects achieving a 4-fold increase in anti-6A OPA titer was statistically significantly higher in the 13vPnC group (88.5%, 95% CI: 84.8; 91.6) than in the 23vPS group (49.3%, 95% CI: 44.2; 54.5). The difference in proportions between groups (13vPnC – 23vPS) was 39.2% and the difference at the lower limit of the 95% CI was 33.0% (ie, well above the threshold of >0).

The proportion of subjects achieving an anti-6A OPA titer ≥LLOQ was assessed to address a secondary objective. This objective was achieved if the lower limit of the 95% CI for proportion of responders to 13vPnC was ≥85%. Results showed that the proportion of responders to serotype 6A in 13vPnC was 95.8%, with a lower limit of the 95% CI of 93.3%, thus exceeding the criterion. In addition, the proportion of subjects achieving an OPA titer ≥LLOQ was statistically significantly higher in the 13vPnC group than in the 23vPS group (ie, the lower limit of the 95% CI for the difference in proportions [13vPnC – 23vPS] was >0). The difference in proportion of responders was 26.6% and the difference at the lower limit of the 95% CI was 21.7%.

The analyses of proportion of subjects achieving an OPA titer ≥ 1:8 supported these findings.

Anti-6A OPA GMTs: To address a secondary objective, anti-6A OPA GMTs in the 2 vaccine groups were compared. For serotype 6A, statistical significance was demonstrated if the lower limit of the 2-sided, 95% CI for the geometric mean ratio (GMR, 13vPnC GMT/23vPS GMT) was >2.0. Results showed that responses were statistically significantly higher in the 13vPnC group (GMT: 2593) than in the 23vPS group (GMT: 213). The ratio (13vPnC GMT/ 23vPS GMT) was 12.1 and the ratio at the lower limit of the 95% CI was 8.63.

IgG Response

IgG GMCs were also compared in the 13vPnC group relative to the 23vPS group in a subset of approximately 100 subjects per group (Table 9-7). The same 2-fold noninferiority criterion used for the OPA evaluation was used for the IgG analysis (ie, a lower limit of the 95% CI for the ratio of > 0.5). The noninferiority of 13vPnC relative to 23vPS was demonstrated for 11 of 12 common serotypes (exception, serotype 14). Ratios among the 11 serotypes ranged from 0.86 (serotype 5) to 2.05 (serotype 18C), and the lower limits of the 95% CIs were ≥ 0.58. The ratio for serotype 14 was 0.73 and the ratio at the lower limit of the 95% CI was 0.46 (Table 9).

Table 9. Comparison of Pneumococcal IgG GMCs (µg/mL) 1 Month After Vaccination With 13vPnC and 23vPS in a Subset of Subjects Aged 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	13vPnC		23vPS		Vaccine Comparison	
Serotype	n[a]	GMC[b]	n[a]	GMC[b]	Ratio[c]	(95% CI[d])
1	99	4.42	98	2.95	1.50	(1.00, 2.26)
3	98	1.65	96	1.55	1.06	(0.75, 1.50)
4	98	2.64	97	1.42	1.86	(1.26, 2.76)
5	99	6.04	96	7.03	0.86	(0.58, 1.27)
6B	98	7.87	97	6.20	1.27	(0.89, 1.81)
7F	99	10.07	97	6.60	1.53	(1.03, 2.26)
9V	98	6.32	97	4.83	1.31	(0.94, 1.82)
14	99	7.09	98	9.71	0.73	(0.46, 1.16)
18C	97	12.04	98	5.89	2.05	(1.34, 3.12)
19A	99	12.30	98	10.16	1.21	(0.87, 1.68)
19F	99	4.57	95	4.29	1.07	(0.70, 1.61)
23F	98	6.98	97	4.44	1.57	(1.07, 2.30)
6A	99	7.16	97	3.86	1.86	(1.38, 2.49)

a. n = Number of subjects with a determinate IgG concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMCs 13vPnC to 23vPS is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – 23vPS).

Furthermore, IgG GMCs were statistically significantly higher (ie, a lower limit of the 95% CI for the ratio of > 1.0) in the 13vPnC group relative to the 23vPS group for 4 of 12 common serotypes (serotypes 4, 7F, 18C, 23F).

At 1 year after vaccination, IgG GMCs remained higher than pre-vaccination levels in all vaccine groups (Table 10).

Table 10. Pneumococcal IgG Antibody GMCs (µg/mL) in a Subset of Subjects Aged 60-64 Years (Cohort 1) and 50-59 Years (Cohort 2) - Evaluable Immunogenicity Population

		Vaccine Group (as Randomized) Cohort 1						Vaccine Group (as Assigned) Cohort 2		
		13vPnC			23vPS			13vPnC		
Serotype	Time Point[a]	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])
1	Before vaccination	93	0.39	(0.30, 0.50)	91	0.32	(0.24, 0.43)	92	0.48	(0.36, 0.64)
	1 month after vaccination	99	4.42	(3.24, 6.02)	98	2.95	(2.25, 3.86)	96	6.59	(4.76, 9.13)
	1 year after vaccination	100	2.08	(1.57, 2.77)	97	1.86	(1.40, 2.46)	96	2.88	(2.13, 3.91)
3	Before vaccination	97	0.40	(0.31, 0.52)	95	0.50	(0.38, 0.65)	92	0.61	(0.49, 0.77)
	1 month after vaccination	98	1.65	(1.28, 2.12)	96	1.55	(1.22, 1.96)	95	1.79	(1.52, 2.11)
	1 year after vaccination	100	0.74	(0.57, 0.96)	98	0.94	(0.75, 1.19)	94	0.89	(0.72, 1.09)
4	Before vaccination	96	0.21	(0.16, 0.28)	93	0.28	(0.22, 0.37)	90	0.34	(0.26, 0.43)
	1 month after vaccination	98	2.64	(1.95, 3.58)	97	1.42	(1.10, 1.82)	96	4.03	(3.16, 5.15)
	1 year after vaccination	100	1.12	(0.83, 1.50)	96	0.94	(0.73, 1.21)	96	1.59	(1.23, 2.06)
5	Before vaccination	97	1.80	(1.51, 2.14)	96	1.79	(1.50, 2.13)	95	2.37	(1.97, 2.85)
	1 month after vaccination	99	6.04	(4.54, 8.05)	96	7.03	(5.39, 9.15)	96	10.02	(7.68, 13.07)
	1 year after vaccination	100	3.23	(2.55, 4.11)	97	4.26	(3.39, 5.35)	96	4.90	(3.88, 6.18)
6A	Before vaccination	97	1.72	(1.45, 2.04)	97	1.89	(1.56, 2.28)	96	2.55	(2.14, 3.03)
	1 month after vaccination	99	7.16	(5.80, 8.84)	97	3.86	(3.14, 4.75)	95	11.92	(9.15, 15.51)
	1 year after vaccination	100	3.95	(3.20, 4.87)	96	2.74	(2.21, 3.39)	96	6.14	(4.91, 7.69)
6B	Before vaccination	96	1.80	(1.47, 2.21)	96	1.92	(1.57, 2.36)	96	2.81	(2.27, 3.48)
	1 month after vaccination	98	7.87	(6.06, 10.21)	97	6.20	(4.86, 7.91)	96	18.05	(13.61, 23.93)
	1 year after vaccination	100	4.13	(3.27, 5.23)	97	4.09	(3.20, 5.21)	96	8.30	(6.39, 10.79)
7F	Before vaccination	96	0.78	(0.62, 0.99)	97	0.71	(0.58, 0.87)	96	0.96	(0.77, 1.21)
	1 month after vaccination	99	10.07	(7.59, 13.35)	97	6.60	(4.99, 8.72)	96	14.64	(11.48, 18.66)
	1 year after vaccination	100	3.71	(2.82, 4.88)	97	4.11	(3.08, 5.51)	95	5.08	(4.07, 6.33)
9V	Before vaccination	97	0.95	(0.79, 1.14)	97	1.08	(0.90, 1.31)	96	1.33	(1.12, 1.58)
	1 month after vaccination	98	6.32	(5.00, 7.99)	97	4.83	(3.81, 6.11)	96	6.90	(5.47, 8.69)
	1 year after vaccination	100	2.80	(2.27, 3.47)	98	3.25	(2.61, 4.04)	96	3.06	(2.50, 3.75)
14	Before vaccination	96	1.68	(1.25, 2.26)	97	1.72	(1.26, 2.34)	96	1.80	(1.37, 2.37)
	1 month after vaccination	99	7.09	(5.24, 9.59)	98	9.71	(6.80, 13.86)	96	15.76	(11.52, 21.56)
	1 year after vaccination	100	4.48	(3.40, 5.89)	97	6.95	(4.85, 9.95)	96	7.94	(5.94, 10.61)
18C	Before vaccination	95	0.89	(0.71, 1.13)	96	0.82	(0.62, 1.09)	95	0.85	(0.65, 1.11)
	1 month after vaccination	97	12.04	(8.91, 16.28)	98	5.89	(4.35, 7.96)	96	14.74	(10.95, 19.86)
	1 year after vaccination	99	4.90	(3.73, 6.45)	97	3.65	(2.74, 4.85)	96	5.21	(3.94, 6.89)
19A	Before vaccination	96	2.77	(2.29, 3.35)	97	2.90	(2.43, 3.47)	96	4.07	(3.39, 4.89)
	1 month after vaccination	99	12.30	(9.93, 15.22)	98	10.16	(7.90, 13.06)	96	21.52	(17.08, 27.12)
	1 year after vaccination	100	6.02	(4.88, 7.44)	98	7.01	(5.52, 8.91)	96	8.85	(7.10, 11.04)
19F	Before vaccination	94	1.17	(0.95, 1.45)	94	1.19	(0.94, 1.51)	91	1.75	(1.37, 2.23)
	1 month after vaccination	99	4.57	(3.44, 6.06)	95	4.29	(3.15, 5.83)	96	10.46	(7.63, 14.35)
	1 year after vaccination	100	2.48	(1.96, 3.13)	97	2.58	(1.92, 3.47)	96	4.21	(3.20, 5.52)
23F	Before vaccination	94	1.05	(0.82, 1.33)	96	1.21	(1.00, 1.46)	95	1.47	(1.18, 1.82)
	1 month after vaccination	98	6.98	(5.19, 9.39)	97	4.44	(3.48, 5.66)	95	10.04	(7.48, 13.49)
	1 year after vaccination	100	2.80	(2.14, 3.67)	97	2.88	(2.28, 3.64)	95	4.02	(3.08, 5.24)

a. SAP-specified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. Geometric mean concentrations (GMCs) were calculated using all evaluable subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

Response Curves

Antibody response curves of OPA titers and IgG concentrations from baseline (prevaccination) to 1 month after vaccination, and 1 year after vaccination showed increased OPA and IgG antibody levels from baseline to 1 month after vaccination. These levels decreased from 1 month to 1 year after vaccination. OPA and GMC curves for all serotypes were higher at 1 year after vaccination than before vaccination for all serotypes in both vaccine groups. In general, the decline in serum concentrations from 1 month after vaccination to 1 year after vaccination was similar in the 13vPnC and 23vPS groups.

Cohort 2

OPA Response

OPA GMTs: Comparison of OPA GMTs in subjects 50 to 59 years old in cohort 2 relative to those of subjects 60 to 64 years old in cohort 1 showed that responses were similar or higher in the younger cohort (Table 11). All serotypes met the 2-fold noninferiority criterion (ie, a lower limit of the 95% CI for the ratio of > 0.5) and OPA GMTs for 8 of 13 serotypes were statistically significantly higher (ie, a lower limit of the 95% CI for the ratio of > 1.0) in cohort 2 relative to cohort 1. Ratios (cohort 2 to cohort 1) ranged from 1.0 (serotype 3) to 1.7 (serotype 6A), and values at the lower limits of the 95% CIs for the ratios ranged from 0.81 (serotype 3) to 1.30 (serotype 6A).

Table 11. Comparison of Pneumococcal OPA Titer GMTs 1 Month After Vaccination With 13vPnC in Subjects Aged 50-59 Years Old (Cohort 2) and 60-64 Years Old (Cohort 1) - Evaluable Immunogenicity Population

	50-59 Years Old (Cohort 2)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 2/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	382	200	404	146	1.4	(1.08, 1.73)
3	379	91	394	93	1.0	(0.81, 1.19)
4	350	2833	359	2062	1.4	(1.07, 1.77)
5	373	269	392	199	1.4	(1.01, 1.80)
6A	384	4328	401	2593	1.7	(1.30, 2.15)
6B	361	3212	371	1984	1.6	(1.24, 2.12)
7F	378	1520	394	1120	1.4	(1.03, 1.79)
9V	364	1726	367	1164	1.5	(1.11, 1.98)
14	373	957	375	612	1.6	(1.16, 2.12)
18C	373	1939	379	1726	1.1	(0.86, 1.47)
19A	377	956	392	682	1.4	(1.16, 1.69)
19F	367	599	377	517	1.2	(0.87, 1.54)
23F	368	494	375	375	1.3	(0.94, 1.84)

a. n = Number of subjects with a determinate OPA titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all evaluable subjects with available data for the specified blood draw.
c. Ratio of GMTs, cohort 2 to cohort 1 is calculated by back transforming the mean difference between vaccine cohorts on the logarithmic scale.
d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (cohort 2 – cohort 1).

At 1 year after vaccination, OPA GMTs remained higher in cohort 2 than in cohort 1 for all serotypes. In both groups OPA levels at 1 year after vaccination remained higher than prevaccination levels (Table 7).

Proportion of Subjects Achieving OPA Titers ≥ LLOQ: The proportion of subjects achieving an OPA titer ≥ LLOQ after 13vPnC were non-inferior in cohort 2 relative to cohort 1 for all 13vPnC serotypes (Table 9-9). (The noninferiority criterion was defined as a lower limit of the 95% CI for the difference in proportions [cohort 2 – cohort 1] of >-10%). Differences ranged from -0.9% (serotype 5) to 4.4% (serotype 7F) and differences at the lower limits of the 95% CIs ranged from -5.8% (serotype 5) to 0.8% (serotype 6B).

The analyses of proportion of subjects achieving an OPA titer ≥ 1:8 supported these findings.

Trial in a Population Preimmunized With 23vPS (Study 3005)

Study 3005 was a phase 3, randomized, modified double-blind, active-control, multicenter trial to assess the immunogenicity, safety and tolerability of 13vPnC in healthy subjects aged ≥70 years who had received a previous vaccination with 23vPS at least 5 years before study enrolment (see study

schema). The primary objectives of the study were: 1) to demonstrate that OPA response to 13vPnC is non-inferior to that of 23vPS when measured 1 month after the initial vaccination; and 2) to demonstrate that the proportion of subjects achieving a 4-fold rise in anti- 6A OPA titer is statistically significantly greater in the 13vPnC group than in the 23vPS group, when measured 1 month after vaccination 1. The study was designed as a parallel group study in which 938 subjects were randomly assigned in a 1:1 ratio to one of 2 vaccine groups: 13vPnC (n = 464) or 23vPS (n=474). All subjects received a dose of 13vPnC 1 year after the initial dose.

Study 3005 schema

Study 6115A1-3005				
Subjects	Group	N	Year 0	Year 1
Prior PS ≥ 5	1	462	13vPnC	13vPnC
	2	462	23vPS	13vPnC

The immunogenicity analyses were based on serotype-specific OPA responses measured in blood samples obtained on the day of each vaccination (before vaccine administration) and approximately 1 month after each vaccination.

The evaluable immunogenicity population for vaccination 1 included 879 (93.7%).subjects and for vaccination 2 included 745 (79.4%) subjects. The all available immunogenicity population for vaccination 1 included 936 (99.8%) subjects and for vaccination 2 included 797 (85.0%) subjects (Table 12 and Table 13). The 2 vaccine groups were similar with respect to sex, race, and age at vaccination. In the 13vPnC and 23vPS groups, respectively, there was an even distribution by sex (52.3% male and 47.7% female, 50.3% male and 49.7% female), and the majority of subjects (95.9% and 96.0%) were characterized as white. The mean age at vaccination was 76.7 years for both the 13vPnC and 23vPS groups.

Table 12. All available immunogenicity populations for vaccination 1 – year 0

	Vaccine Group (as Randomized)					
	13vPnC		23vPS		Total	
	n[a]	%	n[a]	%	n[a]	%
Randomized	464	100.0	474	100.0	938	100.0
Vaccination 1 all-available immunogenicity population	463	99.8	473	99.8	936	99.8
Subjects excluded from the vaccination 1 all-available immunogenicity population	1	0.2	1	0.2	2	0.2
No prevaccination 1 or postvaccination 1 assay result for any serotype/antibody	1	0.2	1	0.2	2	0.2
Vaccination 1 evaluable immunogenicity population	431	92.9	448	94.5	879	93.7
Subjects excluded from the evaluable immunogenicity population[b]	33	7.1	26	5.5	59	6.3
Other protocol violation	17	3.7	12	2.5	29	3.1
Received prohibited vaccine after vaccination 1 and prior to vaccination 1 postvaccination blood draw	8	1.7	12	2.5	20	2.1
Not eligible for the study	10	2.2	8	1.7	18	1.9
No postvaccination 1 blood drawn	4	0.9	0	0.0	4	0.4
Postvaccination 1 sample <28 days after vaccination 1	2	0.4	1	0.2	3	0.3
Not in vaccination 1 all-available immunogenicity population	1	0.2	1	0.2	2	0.2
Postvaccination 1 sample >57 days after vaccination 1	2	0.4	0	0.0	2	0.2

a. n = Number of subjects with the specified characteristic.
b. Subjects may have been excluded for more than 1 reason.

Table 13. All available immunogenicity populations for vaccination 2 – year 1

	Vaccine Sequence (as Randomized)					
	13vPnC/13vPnC		23vPS/13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%
Randomized	464	100.0	474	100.0	938	100.0
Vaccination 2 all-available immunogenicity population	394	84.9	403	85.0	797	85.0
Subjects excluded from the vaccination 2 all-available immunogenicity population	70	15.1	71	15.0	141	15.0
No prevaccination 2 or postvaccination 2 assay result for any serotype/antibody	70	15.1	71	15.0	141	15.0
Vaccination 2 evaluable immunogenicity population	372	80.2	373	78.7	745	79.4
Subjects excluded from the vaccination 2 evaluable immunogenicity population[b]	92	19.8	101	21.3	193	20.6
Not in vaccination 2 all-available immunogenicity population	70	15.1	71	15.0	141	15.0
Other protocol violation	11	2.4	9	1.9	20	2.1
Received prohibited vaccines after vaccination 2 and prior to vaccination 2 postvaccination blood drawn	4	0.9	11	2.3	15	1.6
Not eligible for the study	5	1.1	3	0.6	8	0.9
Did not receive 13vPnC at vaccination 2	4	0.9	2	0.4	6	0.6
No postvaccination 2 blood drawn	3	0.6	2	0.4	5	0.5
Postvaccination 2 blood draw <28 days after vaccination 2	0	0.0	5	1.1	5	0.5
Postvaccination 2 blood draw >57 days after vaccination 2	1	0.2	2	0.4	3	0.3
Prevaccination 2 blood draw not 15 days prior to vaccination 2 or the same day as vaccination 2	1	0.2	0	0.0	1	0.1

a. n = Number of subjects with the specified characteristic.
b. Subjects may have been excluded for more than 1 reason.

The primary immunologic comparison was the serotype-specific pneumococcal response to each of the 13 serotypes in 13vPnC in the 13vPnC group relative to those in the 23vPS group, as measured by OPA assay in blood samples taken 1 month after vaccination. The primary endpoint was the OPA GMT for each serotype in each vaccination group. To address the primary objective, non inferiority of response to 13vPnC relative to 23vPS was assessed. The non inferiority criterion for OPA GMTs was a lower limit of the 95% CI for the geometric mean ratio of >0.5. Non inferiority of the proportion of subjects achieving prespecified levels was also assessed; the non inferiority criterion was a lower limit of the 95% CI for the difference in proportions (test – reference) of >-10%.

Vaccination 1

OPA Response to Common Serotypes

OPA GMTs: To address the primary objective, OPA GMTs in the 13vPnC group were compared to those in the 23vPS group (Table 14). Results showed that OPA response to 13vPnC was non inferior to that of 23vPS in preimmunised subjects for all common serotypes. The GMT ratios ranged from 1.1 (serotype 14) to 3.7 for (serotype 23F). The lower limits of the 95% CIs for the ratios were all >0.5, thus meeting the 2-fold non inferiority criterion. In addition OPA GMTs were statistically significantly higher (ie, a lower limit of the 95% CI for the ratio of >1) in the 13vPnC group for 10 of 12 common serotypes (all except serotypes 3 and 14, secondary objective).

Table 14. Comparison of Pneumococcal OPA GTMs, 13vPnC relative to 23vPS (year 0) Vaccination 1 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			23vPS			Vaccine Comparison	
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	426	81	(68.4, 95.9)	445	55	(46.2, 64.8)	1.5	(1.17 , 1.88)
3	405	55	(47.7, 62.9)	424	49	(42.9, 56.9)	1.1	(0.91 , 1.35)
4	400	545	(441.9, 672.3)	395	203	(157.1, 262.2)	2.7	(1.93 , 3.74)
5	422	72	(59.7, 86.6)	442	36	(29.5, 43.1)	2.0	(1.55 , 2.63)
6B	411	1261	(1024.7, 1552.6)	411	417	(330.5, 526.7)	3.0	(2.21 , 4.13)
7F	420	245	(191.9, 312.4)	431	160	(123.5, 207.9)	1.5	(1.07 , 2.18)
9V	402	181	(138.0, 237.0)	402	90	(67.8, 119.7)	2.0	(1.36 , 2.97)
14	411	280	(227.5, 345.5)	410	285	(228.9, 354.3)	1.0	(0.73 , 1.33)
18C	411	907	(761.9, 1080.1)	416	481	(385.1, 600.7)	1.9	(1.42 , 2.50)
19A	420	354	(307.7, 408.4)	442	200	(170.0, 234.4)	1.8	(1.43 , 2.20)
19F	414	333	(273.2, 404.8)	417	214	(174.3, 262.8)	1.6	(1.17 , 2.06)
23F	403	158	(126.0, 198.6)	417	43	(34.2, 53.5)	3.7	(2.69 , 5.09)
6A	421	903	(726.7, 1121.3)	433	94	(74.1, 118.5)	9.6	(7.00 , 13.26)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for both the specified blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMT (13vPnC to 23vPS), is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – 23vPS).

Proportion of responders: The proportion of subjects achieving an OPA titer ≥LLOQ (ie, responders) 1 month after vaccination with 13vPnC was non inferior to the proportion of responders after 23vPS for each serotype (Table 15). Furthermore, the proportion of responders was statistically significantly higher after 13vPnC than after 23vPS for 9 of 12 common serotypes (ie, the lower limits of the 95% CIs for the differences were > 0). Differences (13vPnC -23vPS) ranged from 1.0% (serotype 14) to 21.3% (serotype 23F) and the lower limits of the 95% CIs for the difference in proportions were >-10%.

The analyses using the cut-off criterion of ≥1:8 also showed non inferiority of 13vPnC relative to 23vPS for all 12 common serotypes.

Table 15. Comparison of Subjects Achieving OPA Titer > LLOQ, 13vPnC Relative to 23vPS (Year 0) – Vaccination 1 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				23vPS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	426	356	83.6	(79.7, 87.0)	445	341	76.6	(72.4, 80.5)	6.9	(1.6, 12.3)
3	405	338	83.5	(79.5, 86.9)	424	343	80.9	(76.8, 84.5)	2.6	(-2.7, 7.9)
4	400	351	87.8	(84.1, 90.8)	395	289	73.2	(68.5, 77.5)	14.6	(9.1, 20.1)
5	422	315	74.6	(70.2, 78.7)	442	260	58.8	(54.1, 63.5)	15.8	(9.6, 22.1)
6B	411	377	91.7	(88.6, 94.2)	411	337	82.0	(77.9, 85.6)	9.7	(5.1, 14.4)
7F	420	314	74.8	(70.3, 78.8)	431	286	66.4	(61.7, 70.8)	8.4	(2.3, 14.5)
9V	402	270	67.2	(62.3, 71.7)	402	221	55.0	(50.0, 59.9)	12.2	(5.4, 18.9)
14	411	345	83.9	(80.0, 87.4)	410	340	82.9	(78.9, 86.4)	1.0	(-4.1, 6.1)
18C	411	390	94.9	(92.3, 96.8)	416	362	87.0	(83.4, 90.1)	7.9	(4.0, 11.9)
19A	420	403	96.0	(93.6, 97.6)	442	400	90.5	(87.4, 93.1)	5.5	(2.0, 8.9)
19F	414	359	86.7	(83.1, 89.8)	417	342	82.0	(78.0, 85.6)	4.7	(-0.3, 9.7)
23F	403	310	76.9	(72.5, 80.9)	417	232	55.6	(50.7, 60.5)	21.3	(14.9, 27.6)
6A	421	378	89.8	(86.5, 92.5)	433	282	65.1	(60.4, 69.6)	24.7	(19.3, 30.1)

Abbreviation: LLOQ = lower limit of quantitation.

a. N = number of subjects with a determinate antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
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 (based on Chan & Zhang) for the difference in proportions, 13vPnC – 23vPS, expressed as a percentage.

OPA Response to Serotype 6A

Proportion of responders: The proportion of subjects with a 4-fold increase in OPA titer for serotype 6A was statistically significantly greater 1 month after 13vPnC (71.1%) than after 23vPS (27.3%); ie, the difference (13vPnC -23vPS) was 43.8% and the lower limit of the 95% CI for the difference (13vPnC – 23vPS) in proportions was >0 (ie, 37.4% co-primary objective).

Table 16. Comparison of Subjects Achieving a 4 fold Increase in Titer for Serotype 6A, 13vPnC relative to 23vPS (year 0) – Vaccination 1 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC N[a]=408			23vPS N[a]=411				
Serotype	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
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 antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
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 (based on Chan & Zhang) for the difference in proportions, 13vPnC – 23vPS, expressed as a percentage.

The proportion of responders was significantly higher in the 13vPnC group than in the 23vPS group (ie, the lower limit of the 95% CI for the difference in proportions [13vPnC – 23vPS] was >0). The difference in proportions was 24.7% and the lower limit of the 95% CI for the difference was 19.3% (Table 15). The results for the analyses of the proportion of subjects achieving an OPA titer of ≥1:8 supported this finding (data not shown in this AR).

Anti-6A OPA GMT: The anti-6A OPA GMT was statistically significantly higher after 13vPnC (GMT: 903) than after 23vPS (GMT: 94. The ratio was 9.6 and the lower limit of the 95% CI for the ratio was 7.00, thus meeting the 6A criterion for statistical significance (Table 14).

Vaccination 2 and Vaccination 1

13vPnC/13vPnC relative to 13vPnC:

When OPA GMTs after 2 doses of 13vPnC (ie, 13vPnC/13vPnC) were compared to those after a single dose of 13vPnC, the lower limits of the 95% CIs for the Geometric Mean Fold Rises (GMFRs) were > 0.5 for all serotypes (Table 17). However, OPA GMTs were statistically significantly lower (ie, a upper limit of the 95% CI for the GMFR of < 1.0) after 13vPnC/13vPnC than after 13vPnC alone for 2 of 13 serotypes (serotypes 4 and 5). For 3 of the 13 serotypes (serotypes 6A, 6B, and 23F), the lower limits of the 95% CIs for the GMFRs exceeded 1.0, indicating that the OPA response was statistically significantly greater after 13vPnC/13vPnC than after 13vPnC for these serotypes.

Table 17. Comparison of Pneumococcal OPA GMTs and GMFRs, 13vPnC/13vPnC (Year 1) Relative to 13vPnC (Year 0) - Evaluable Immunogenicity Population

	13vPnC/13vPnC (as Randomized)								
	Vaccination 1 (Year 0)			Vaccination 2 (Year 1)			Fold Rise		
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
1	361	79	(65.3, 94.6)	361	76	(64.8, 89.7)	361	1.0	(0.85, 1.10)
3	337	55	(47.2, 64.0)	337	55	(48.4, 63.1)	337	1.0	(0.91, 1.11)
4	324	614	(489.8, 768.8)	324	487	(393.9, 603.3)	324	0.8	(0.68, 0.92)
5	355	69	(56.2, 84.2)	355	57	(46.9, 68.5)	355	0.8	(0.73, 0.94)
6A	354	971	(771.0, 1222.1)	354	1169	(974.0, 1403.0)	354	1.2	(1.03, 1.40)
6B	339	1358	(1085.4, 1700.2)	339	1590	(1316.9, 1919.8)	339	1.2	(1.02, 1.35)
7F	351	222	(170.2, 290.2)	351	180	(138.1, 233.8)	351	0.8	(0.65, 1.01)
9V	331	187	(139.3, 250.4)	331	166	(124.2, 220.8)	331	0.9	(0.69, 1.15)
14	348	265	(209.9, 333.6)	348	241	(194.4, 299.1)	348	0.9	(0.79, 1.05)
18C	342	918	(763.4, 1104.3)	342	1003	(850.2, 1182.1)	342	1.1	(0.97, 1.23)
19A	349	349	(299.7, 405.5)	349	341	(297.2, 390.5)	349	1.0	(0.89, 1.07)
19F	340	329	(265.6, 408.6)	340	322	(266.3, 389.6)	340	1.0	(0.83, 1.15)
23F	335	167	(130.9, 213.0)	335	309	(251.6, 380.1)	335	1.9	(1.60, 2.14)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype at both the postvaccination 1 and postvaccination 2 blood draws.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Geometric mean fold rises (GMFRs) [(13vPnC/13vPnC) / (13vPnC)] were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.

One of the exploratory objectives of the study was a comparison of the proportion of subjects achieving an OPA titer ≥LLOQ after 13vPnC/13vPnC was non inferior to that after a single dose of 13vPnC for all serotypes, using the non inferiority criterion applied in the pivotal non inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/13vPnC - 13vPnC] of > -10%). In addition proportions were statistically significantly higher after 13vPnC/13vPnC than after 13vPnC alone for 5 of the 13 serotypes (3, 6A, 6B, 18C, 23F). Differences ranged from -2.0% (serotype 7F) to 10.1% (serotype 23F) and lower limits of the 95% CIs for the difference were ≥ -6.2% (Table 18).

Table 18. Comparison of Subjects Achieving an OPA Titer ≥ LLOQ, 13vPnC (Year 0) Relative to 13vPnC/13vPnC (Year 1) - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)						Treatment Comparison	
	13vPnC			13vPnC/13vPnC				
Serotype	N[a]	n[b]	%	N[a]	n[b]	%	Difference[c]	(95% CI[d])
1	361	299	82.8	361	305	84.5	1.7	(-2.1, 5.4)
3	337	282	83.7	337	294	87.2	3.6	(0.4, 6.6)
4	324	288	88.9	324	288	88.9	-0.0	(-2.8, 2.8)
5	355	263	74.1	355	258	72.7	-1.4	(-5.2, 2.4)
6A	354	322	91.0	354	336	94.9	4.0	(1.4, 6.4)
6B	339	313	92.3	339	323	95.3	2.9	(0.9, 5.0)
7F	351	259	73.8	351	252	71.8	-2.0	(-6.2, 2.2)
9V	331	226	68.3	331	223	67.4	-0.9	(-5.8, 4.0)
14	348	289	83.0	348	294	84.5	1.4	(-1.5, 4.4)
18C	342	327	95.6	342	334	97.7	2.0	(0.2, 3.8)
19A	349	336	96.3	349	337	96.6	0.3	(-1.1, 1.7)
19F	340	295	86.8	340	305	89.7	2.9	(-0.4, 6.2)
23F	335	263	78.5	335	297	88.7	10.1	(6.8, 13.4)

Abbreviation: LLOQ = lower limit of quantitation.

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number with an OPA titer ≥ LLOQ for the given serotype.
c. Difference in proportions, expressed as a percentage.
d. Adjusted Wald 2-sided confidence interval for the difference in dependent proportions, [(13vPnC/13vPnC) – 13vPnC], expressed as a percentage.

13vPnC/13vPnC relative to 23vPS:

OPA responses for all common serotypes met the non-inferiority criterion after 13vPnC/13vPnC when compared with those after 23vPS (ie, a lower limit of the 95% CI for the ratio [13vPnC/13vPnC - 23vPS] of >0.5, secondary objective, Table 9-7). In addition, 9 of 12 common serotypes elicited responses that were statistically significantly greater after 13vPnC/13vPnC than after 23vPS (all except serotypes 3, 7F, 14). The ratios ranged from 0.8 (serotype 14) to 7.3 (serotype 23F), and the lower limits of the 95% CIs for the ratio were ≥ 0.62.

OPA response to serotype 6A after 13vPnC/13vPnC (GMT: 1134) was statistically significantly greater than after 23vPS (GMT: 94). Statistical significance was demonstrated if the lower limit of the 2-sided, 95% CI for the ratio was >2 (secondary objective). The ratio for serotype 6A was 12.1 and the lower limit of the 95% CI for the ratio was 8.92 (Table 19).

Table 19. Comparison of Pneumococcal OPA GMTs, 13vPnC/13vPnC (Year 1) Relative to 23vPS (Year 0) - Evaluable Immunogenicity Population

	Vaccine Sequence (as Randomized)							
	13vPnC/13vPnC			23vPS			Vaccine Comparison	
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	370	76	(64.9, 89.5)	445	55	(46.2, 64.8)	1.4	(1.10 , 1.76)
3	362	55	(47.9, 62.0)	424	49	(42.9, 56.9)	1.1	(0.91 , 1.34)
4	347	472	(383.5, 580.2)	395	203	(157.1, 262.2)	2.3	(1.66 , 3.25)
5	365	56	(46.6, 67.7)	442	36	(29.5, 43.1)	1.6	(1.21 , 2.06)
6B	356	1565	(1306.1, 1875.9)	411	417	(330.5, 526.7)	3.8	(2.78 , 5.07)
7F	365	185	(142.9, 239.7)	431	160	(123.5, 207.9)	1.2	(0.80 , 1.67)
9V	356	158	(119.5, 209.5)	402	90	(67.8, 119.7)	1.8	(1.18 , 2.62)
14	366	238	(192.3, 293.8)	410	285	(228.9, 354.3)	0.8	(0.62 , 1.13)
18C	361	975	(829.0, 1147.3)	416	481	(385.1, 600.7)	2.0	(1.53 , 2.69)
19A	362	339	(296.4, 386.9)	442	200	(170.0, 234.4)	1.7	(1.37 , 2.10)
19F	354	311	(257.1, 375.9)	417	214	(174.3, 262.8)	1.5	(1.09 , 1.93)
23F	360	310	(254.1, 378.0)	417	43	(34.2, 53.5)	7.3	(5.36 , 9.82)
6A	366	1134	(943.6, 1363.7)	433	94	(74.1, 118.5)	12.1	(8.92 , 16.44)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for both the specified blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMT (13vPnC/13vPnC to 23vPS), is calculated by back transforming the mean difference between vaccine group/sequence on the logarithmic scale.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [(13vPnC/13vPnC) – (23vPS)].

13vPnC/13vPnC relative to 23vPS/13vPnC:

For 12 of 13 serotypes, OPA GMTs were statistically significantly greater after 13vPnC/13vPnC than after 23vPS/13vPnC. Ratios ranged from 1.2 (serotype 14) to 3.6 (serotype 23F); the lower limits of the 95% CIs for the ratio were ≥1 for all serotypes, except for serotype 14 (0.89).

In an ad hoc analysis, the proportion of responders ≥LLOQ after 13vPnC/13vPnC met the non inferiority criterion applied in the pivotal non inferiority study for all serotypes (ie, a lower limit of the 95% CI for the difference [13vPnC/13vPnC – 23vPS/13vPnC] of > -10%). In addition proportions were statistically significantly higher after 13vPnC/13vPnC than after 23vPS/13vPnC for 11 of the 13 serotypes (all except serotypes 14 and 19A). Differences among serotypes ranged from 2.8% (serotype 19A) to 23.0% (serotype 23F) and lower limits of the 95% CIs for the difference were ≥ -1.2% (Table 20).

Table 20. Comparison of Subjects Achieving an OPA Titer ≥ LLOQ, 13vPnC/13vPnC Relative to 23vPS/13vPnC (Year 1) - Vaccination 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC/13vPnC				23vPS/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	370	312	84.3	(80.2, 87.9)	367	245	66.8	(61.7, 71.6)	17.6	(11.4, 23.7)
3	362	315	87.0	(83.1, 90.3)	362	268	74.0	(69.2, 78.5)	13.0	(7.2, 18.7)
4	347	308	88.8	(85.0, 91.9)	338	275	81.4	(76.8, 85.4)	7.4	(2.1, 12.8)
5	365	265	72.6	(67.7, 77.1)	362	228	63.0	(57.8, 68.0)	9.6	(2.8, 16.4)
6A	366	346	94.5	(91.7, 96.6)	352	309	87.8	(83.9, 91.0)	6.8	(2.5, 11.1)
6B	356	340	95.5	(92.8, 97.4)	352	306	86.9	(83.0, 90.3)	8.6	(4.4, 12.9)
7F	365	263	72.1	(67.1, 76.6)	357	228	63.9	(58.6, 68.9)	8.2	(1.4, 15.0)
9V	356	236	66.3	(61.1, 71.2)	349	182	52.1	(46.8, 57.5)	14.1	(6.8, 21.3)
14	366	308	84.2	(80.0, 87.7)	361	288	79.8	(75.3, 83.8)	4.4	(-1.2, 10.0)
18C	361	352	97.5	(95.3, 98.9)	360	323	89.7	(86.1, 92.7)	7.8	(4.1, 11.6)
19A	362	350	96.7	(94.3, 98.3)	362	340	93.9	(90.9, 96.2)	2.8	(-0.3, 6.1)
19F	354	315	89.0	(85.2, 92.0)	358	291	81.3	(76.9, 85.2)	7.7	(2.5, 13.0)
23F	360	319	88.6	(84.9, 91.7)	349	229	65.6	(60.4, 70.6)	23.0	(17.0, 29.0)

Abbreviation: LLOQ = lower limit of quantitation.

a. N = number of subjects with a determinate antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference in proportions, [(13vPnC/13vPnC) – (23vPS/13vPnC)], expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, [(13vPnC/13vPnC) – (23vPS/13vPnC)], expressed as a percentage.

23vPS/13vPnC relative to 13vPnC:

OPA GMTs after 23vPS/13vPnC were statistically significantly lower than after 13vPnC alone for all serotypes (Table 21). Ratios (23vPS/13vPnC to 13vPnC) ranged from 0.4 (serotypes 3, 9V) to 0.7 (serotypes 14, 19A), and the upper limits of the 95% CIs were all <1. The lower limit of the 95% CI for the ratio was >0.5 for 2 serotypes (serotypes 19A, 14).

Table 21. Comparison of Pneumococcal OPA GMTs, 23vPS/13vPnC (Year 1) Relative to 13vPnC (Year 0) -Evaluable Immunogenicity Population

	Vaccine Sequence (as Randomized)						Vaccine Comparison	
	23vPS/13vPnC			13vPnC				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	367	34	(28.7, 41.3)	426	81	(68.4, 95.9)	0.4	(0.33 , 0.54)
3	362	33	(28.1, 38.4)	405	55	(47.7, 62.9)	0.6	(0.49 , 0.74)
4	338	267	(209.9, 340.0)	400	545	(441.9, 672.3)	0.5	(0.36 , 0.67)
5	362	42	(33.8, 51.0)	422	72	(59.7, 86.6)	0.6	(0.44 , 0.76)
6B	352	721	(565.6, 918.6)	411	1261	(1024.7, 1552.6)	0.6	(0.42 , 0.78)
7F	357	120	(91.2, 158.8)	420	245	(191.9, 312.4)	0.5	(0.34 , 0.71)
9V	349	72	(53.2, 96.4)	402	181	(138.0, 237.0)	0.4	(0.27 , 0.59)
14	361	194	(153.9, 245.2)	411	280	(227.5, 345.5)	0.7	(0.51 , 0.95)
18C	360	513	(412.5, 636.8)	411	907	(761.9, 1080.1)	0.6	(0.43 , 0.74)
19A	362	248	(211.0, 290.6)	420	354	(307.7, 408.4)	0.7	(0.56 , 0.86)
19F	358	180	(145.1, 223.5)	414	333	(273.2, 404.8)	0.5	(0.40 , 0.72)
23F	349	87	(67.2, 112.9)	403	158	(126.0, 198.6)	0.6	(0.39 , 0.78)
6A	352	549	(436.5, 690.3)	421	903	(726.7, 1121.3)	0.6	(0.44 , 0.83)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for both the specified blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMT (23vPS/13vPnC to 13vPnC) is calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student tdistribution for the mean difference of the logarithms of the measures [(23vPS/13vPnC) – (13vPnC)].

Antibody Response Curves

OPA responses increased from the day of vaccination 1 before administration of 13vPnC or 23vPS to the blood draw approximately 1 month after vaccination 1. For all serotypes, OPA GMTs showed a decline over the year, from 1 month after vaccination 1 to the day of vaccination 2 (before vaccination). At the prevaccination 2 time point, all levels remained higher than baseline levels observed before vaccination 1 for each group. In each vaccine group, GMTs rose from before vaccination 2 to 1 month after vaccination 2. OPA GMTs after vaccination 2 exceeded values noted after vaccination 1 for several serotypes in each vaccine group: serotypes 6A, 6B, 18C and 23F for 13vPnC/13vPnC and serotypes 4, 6A, 6B, 18C, and 23F for 23vPS/13vPnC. From the day of vaccination 1 to 1 month after vaccination 2, the curves for 23vPS/13vPnC were lower, to varying degrees, than those for 13vPnC/13vPnC for most serotypes.

Trial with sequential use of 13vPnC and 23vPS (Study 3010)

Study 3010 was a phase 3, parallel-group, randomised, active-controlled, modified double-blind multicenter trial (Figure 2-2). The study was conducted to assess the immunogenicity, tolerability, and safety of the sequential use of 2 doses of 13vPnC or 13vPnC followed, or proceeded, by 23vPS when administered to adults aged 60 to 64 years who were naïve to 13vPnC.

The primary objectives of the study were: to demonstrate non-inferiority of OPA response to 23vPS administered 1 year after an initial dose of 13vPnC (ie, 13vPnC/23vPS) relative to a dose of 23vPS alone; and to demonstrate non-inferiority of OPA response to 23vPS administered 1 year after an initial dose of 13vPnC (ie, 13vPnC/23vPS) relative to 13vPnC administered 1 year after an initial dose of 23vPS (23vPS/13vPnC). A total of 720 subjects were randomly assigned in a 3:5:4 ratio to 1 of 3 groups (Figure 2-2). Group 1.1 (180 subjects) received 13vPnC at year 0 and 13vPnC at year 1 (ie, 13vPnC/13vPnC). Group 1.2 (302 subjects) received 13vPnC at year 0 and 23vPS at year 1 (ie, 13vPnC/23vPS). Group 2 (238 subjects) received 23vPS at year 0 and a subsequent dose of 13vPnC at year 1 (ie, 23vPS/ 13vPnC). An overview of the details of the study is provided below.

Study 3010 schema

Study 6115A1-3010			
Group	**N**	**Year 1**	**Year 2**
1	480	13vPS	13vPS
			23vPS
2	240	23vPS	13vPS

The immunogenicity analyses were based on results of OPA assays performed on blood samples obtained on the day of each vaccination (before vaccine administration) and approximately 1 month after each vaccination.

The vaccination 1 and 2 all-available and evaluable immunogenicity population are summarised in Table 22 and Table 23 respectively. The vaccine groups were similar with respect to sex, race, and age at vaccination. In the vaccination 1 safety population, approximately 58% of the subjects were women and 42% of the subjects were men. Most subjects (95.4%) were characterized as being white. The mean age at vaccination was 61.7 years in both vaccine groups.

Table 22. All-Available and Evaluable Immunogenicity Populations for Vaccination 1 (Year 0)

	Vaccine Sequence (as Randomized)							
	13vPnC/13vPnC		13vPnC/23vPS		23vPS/13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%
Randomized	180	100.0	302	100.0	238	100.0	720	100.0
Vaccination 1 all-available immunogenicity population	178	98.9	301	99.7	237	99.6	716	99.4
Subjects excluded from the vaccination 1 all-available immunogenicity population	2	1.1	1	0.3	1	0.4	4	0.6
No prevaccination or postvaccination assay result for any serotype	2	1.1	1	0.3	1	0.4	4	0.6
Vaccination 1 evaluable immunogenicity population	176	97.8	294	97.4	236	99.2	706	98.1
Subjects excluded from the vaccination 1 evaluable immunogenicity population[b]	4	2.2	8	2.6	2	0.8	14	1.9
No valid or determinate vaccination 1 assay result for any serotype	1	0.6	3	1.0	0	0.0	4	0.6
Not in vaccination 1 all-available immunogenicity population	2	1.1	1	0.3	1	0.4	4	0.6
Postvaccination 1 sample <28 days after vaccination 1	1	0.6	3	1.0	0	0.0	4	0.6
Age <60 years on day of first vaccination	0	0.0	1	0.3	0	0.0	1	0.1
Not eligible for the study	0	0.0	1	0.3	0	0.0	1	0.1
Postvaccination 1 sample >57 days after vaccination 1	0	0.0	0	0.0	1	0.4	1	0.1
Prevaccination 1 sample not within 15 days prior to vaccination 1	1	0.6	0	0.0	0	0.0	1	0.1
Received previous 23vPS before vaccination 1	0	0.0	1	0.3	0	0.0	1	0.1

a. n = Number of subjects with the specified characteristic.
b. Subjects may have been excluded for more than 1 reason.

Table 23. All-Available and Evaluable Immunogenicity Populations for Vaccination 2 (Year 1)

	Vaccine Sequence (as Randomized)							
	13vPnC/13vPnC		13vPnC/23vPS		23vPS/13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%
Randomized	180	100.0	302	100.0	238	100.0	720	100.0
Vaccination 2 all-available immunogenicity population	163	90.6	266	88.1	223	93.7	652	90.6
Subjects excluded from the vaccination 2 all-available immunogenicity population	17	9.4	36	11.9	15	6.3	68	9.4
No prevaccination or postvaccination assay result for any serotype	17	9.4	36	11.9	15	6.3	68	9.4
Vaccination 2 evaluable immunogenicity population	133	73.9	237	78.5	199	83.6	569	79.0
Subjects excluded from the vaccination 2 evaluable immunogenicity population[b]	47	26.1	65	21.5	39	16.4	151	21.0
Not in vaccination 2 all-available immunogenicity population	17	9.4	36	11.9	15	6.3	68	9.4
Received vaccination 2 <351 or >379 days after vaccination 1	19	10.6	24	7.9	19	8.0	62	8.6
Received prohibited vaccine	2	1.1	4	1.3	3	1.3	9	1.3
Not eligible to receive vaccination 2	1	0.6	2	0.7	1	0.4	4	0.6
Postvaccination 2 sample <28 days after vaccination 2	2	1.1	1	0.3	1	0.4	4	0.6
No valid or determinate pair of vaccination 2 assay results for any serotype	3	1.7	0	0.0	0	0.0	3	0.4
Postvaccination 2 sample >57 days after vaccination 2	2	1.1	0	0.0	1	0.4	3	0.4
Received diphtheria vaccine prior to blood collection (between visit 4 and 5)	1	0.6	0	0.0	1	0.4	2	0.3
Age <60 years on day of first vaccination	0	0.0	1	0.3	0	0.0	1	0.1
Received previous 23vPS between visit 5 and 6	1	0.6	0	0.0	0	0.0	1	0.1
Received systemic steroids prior to vaccination 2	0	0.0	1	0.3	0	0.0	1	0.1
Received vaccine other than randomized at vaccination 2	1	0.6	0	0.0	0	0.0	1	0.1

a. n = Number of subjects with the specified characteristic.
b. Subjects may have been excluded for more than 1 reason.

The primary endpoint for the immunogenicity analyses was the serotype-specific OPA GMTs measured before and after each vaccination. Comparisons were made using ratios of the GMTs (test to reference). Geometric fold rises (GMFRs) from vaccination 1 to vaccination 2 in subjects randomly assigned to the sequence 13vPnC/13vPnC or the sequence 13vPnC/23vPS were also calculated. The 2-fold noninferiority criterion was achieved if the lower limit of the 95% CI for the geometric mean ratio (test/ reference) was greater than 0.5. Ad hoc analyses were performed for the proportion of subjects achieving an OPA titer of ≥ LLOQ. Although not prespecified for the ad hoc analyses, the same noninferiority criterion used in the pivotal noninferiority study was applied, i.e., a lower limit of the 95% CI for the difference in proportions (test – reference) of >-10%.

OPA GMTs and Proportion of Responders

13vPnC/23vPS relative to 23vPS:

When OPA GMTs after dose 2 of 13vPnC/23vPS were compared with those after 23vPS alone (primary objective), the non-inferiority criterion was met for the 12 common serotypes. In addition, responses were statistically significantly greater (ie, a lower limit of the 95% CI for the ratio of >1) after 13vPnC/23vPS than after 23vPS for 6 of 12 serotypes. For serotypes 3, 5, 6B, 7F, 19F, and 23F the 95% CI lower bound for the ratio was > 1.0. Geometric mean ratios ranged from 0.8 (serotype 14) to 2.8 (serotype 23F) and the lower bounds of the 95% CIs for the ratios were ≥ 0.58 (Table 24).

Table 24. Comparison of Pneumococcal OPA GMTs for the 12 Common Serotypes, 13vPnC/23vPS (Year 1) Relative to 23vPS (Year 0) - Evaluable Immunogenicity Populations

Vaccine Sequence (as randomised)								
Serotype	13vPC/23vPS			23vPS			Vaccine comparison	
	N[a]	GTM[b]	(95% CI[c])	N[a]	GTM[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	231	148	(123.7 176.5)	227	148	(117.9 185.9)	1.0	(0.75 1.33)
3	228	125	(108.6 143.4)	229	80	(67.5 95.7)	1.6	(1.24 1.94)
4	232	1385	(1171.2 1632.7)	220	1357	(1023.0 1799.0)	1.0	(0.74 1.41)
5	218	199	(161.4 246.2)	224	140	(107.0 183.5)	1.4	(1.01 2.00)
6B	231	1215	(965.4 1528.3)	219	706	(522.1 954.0)	1.7	(1.18 2.51)
7F	227	537	(422.4 682.6)	219	331	(233.5 469.1)	1.6	(1.07 2.47)
9V	229	373	(268.4 517.6)	215	288	(198.0 419.1)	1.3	(0.79 2.12)
14	231	622	(495.7 796.4)	218	734	(543.6 990.1)	0.8	(0.58 1.25)
18C	226	1062	(863.2 1307.6)	224	789	(586.2 1062.2)	1.3	(0.94 1.93)
19A	216	467	(403.5 541.0)	218	376	(302.8 465.7)	1.2	(0.96 1.61)
19F	222	774	(642.0 933.6)	217	509	(385.5 672.9)	1.5	(1.09 2.12)
23F	233	198	(151.2 259.4)	214	70	(49.9 97.3)	2.8	(1.86 4.35)

[a]. n = Number of subjects with a determinate OPA antibody titer to the given serotype.
[b]. Geometric mean titers (GMTs) were calculated using all evaluable subjects with data for the specified blood draw.
[c]. Confidence intervals (CIs) for the GMTs are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
[d]. Ratios for GMTs of 13vPnC/23vPS to 23vPS (GMTRs) are calculated by back transformation of the mean difference between vaccine groups on the logarithmic scale.

[e]. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ([13vPnC/23vPS] – [23vPS]).

In the ad hoc analysis, for all serotypes the proportion of subjects achieving OPA titers ≥ LLOQ after 13vPnC/23vPS met the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/23vPS - 23vPS] of >-10%) when compared with 23vPS alone. Proportions of responders were statistically significantly higher after 13vPnC/23vPS than after 23vPS for 9 of 12 common serotypes (Table 25).

Table 25. Comparisons for Subjects Achieving a Pneumococcal OPA Titer ≥ LLOQ, 23vPS (Vaccination 1) Versus 13vPnC/23vPS (Vaccination 2) - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	23vPS			13vPnC/23vPS			Vaccine Comparison	
Serotype	N[a]	n[b]	%	N[a]	n[b]	%	Difference[c]	(95% CI[d])
1	227	203	89.4	231	218	94.4	4.9	(-0.2, 10.2)
3	229	208	90.8	228	219	96.1	5.2	(0.5, 10.1)
4	220	202	91.8	232	228	98.3	6.5	(2.2, 11.0)
5	224	182	81.3	218	201	92.2	11.0	(4.5, 17.4)
6A	228	172	75.4	225	214	95.1	19.7	(13.3, 26.2)
6B	219	191	87.2	231	217	93.9	6.7	(1.2, 12.4)
7F	219	167	76.3	227	204	89.9	13.6	(6.6, 20.6)
9V	215	155	72.1	229	179	78.2	6.1	(-2.0, 14.2)
14	218	193	88.5	231	210	90.9	2.4	(-3.3, 8.2)
18C	224	200	89.3	226	218	96.5	7.2	(2.1, 12.3)
19A	218	208	95.4	216	214	99.1	3.7	(0.5, 7.4)
19F	217	192	88.5	222	215	96.8	8.4	(2.9, 13.6)
23F	214	131	61.2	233	191	82.0	20.8	(12.4, 28.9)

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number with an OPA titer ≥ LLOQ for the given serotype.
c. Difference in proportions, expressed as a percentage.
d. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions.

13vPnC/23vPS relative to 23vPS/13vPnC:

Comparison of vaccination 2 results showed that OPA GMTs after 13vPnC/23vPS were non-inferior to those after 23vPS/13vPnC for the 12 common serotypes (co-primary objective); ie, the lower limits of the 95% CIs for the ratio were all greater than 0.5. In addition, for 11 of the 12 common serotypes, 13vPnC/23vPS elicited statistically significantly greater responses than 23vPS/13vPnC (The exception was serotype 14, with a lower limit of the 95% CI for the ratio of 0.98, ie, not > 1.00) (Table 26). Ratios ranged from 1.4 (serotype 14) to 4.3 (serotype 7F). The lower limits of the 95% CIs for the ratios ranged from 0.98 (serotype 14) to 2.76 (serotype 7F) (Table 9-4).

Table 26. Comparison of Pneumococcal OPA GMTs for the 12 Common Serotypes, 13vPnC/23vPS Relative to 23vPS/13vPnC (Year 1) - Evaluable Immunogenicity Population

	Vaccine Sequence (as Randomized)							
	13vPnC/23vPS			23vPS/13vPnC			Vaccine Comparison	
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	231	148	(123.7, 176.5)	196	77	(60.7, 98.1)	1.9	(1.43, 2.57)
3	228	125	(108.6, 143.4)	190	50	(40.9, 61.7)	2.5	(1.95, 3.16)
4	232	1385	(1171.2, 1638.7)	192	935	(739.9, 1182.4)	1.5	(1.12, 1.96)
5	218	199	(161.4, 246.2)	180	85	(64.2, 112.0)	2.4	(1.67, 3.31)
6B	231	1215	(965.4, 1528.3)	191	710	(529.1, 953.2)	1.7	(1.19, 2.47)
7F	227	537	(422.4, 682.6)	189	126	(85.6, 184.6)	4.3	(2.76, 6.61)
9V	229	373	(268.4, 517.6)	187	114	(76.5, 169.3)	3.3	(1.97, 5.45)
14	231	622	(485.7, 796.4)	193	435	(323.0, 585.7)	1.4	(0.98, 2.10)
18C	226	1062	(863.2, 1307.6)	192	564	(418.2, 761.7)	1.9	(1.32, 2.69)
19A	216	467	(403.5, 541.0)	184	289	(235.7, 353.9)	1.6	(1.27, 2.07)
19F	222	774	(642.0, 933.6)	187	286	(217.3, 376.7)	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. n = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all evaluable subjects with data for the specified blood draw.
c. Confidence intervals (CIs) for the GMTs are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratios of GMTs 13vPnC/23vPS to 23vPS/13vPnC (GMTRs) are calculated by back transformation of the mean difference between vaccine groups on the logarithmic scale.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ([13vPnC/23vPS] – [23vPS/13vPnC]).

The ad hoc analysis showed that for all common serotypes the proportions of subjects achieving OPA titers ≥ LLOQ after 13vPnC/23vPS met the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/23vPS - 23vPS/ 13vPnC] of > -10%). Proportions were statistically significantly higher after 13vPnC/23vPS than after 23vPS/ 13vPnC for 10 of 12 common serotypes (Table 27).

Table 27. Comparisons for Subjects Achieving a Pneumococcal OPA Titer ≥ LLOQ, 13vPnC/23vPS Versus 23vPS/13vPnC (Vaccination 2) - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	23vPS/13vPnC			13vPnC/23vPS			Vaccine Comparison	
Serotype	N[a]	n[b]	%	N[a]	n[b]	%	Difference[c]	(95% CI[d])
1	196	163	83.2	231	218	94.4	11.2	(4.8, 17.6)
3	190	157	82.6	228	219	96.1	13.4	(7.5, 19.8)
Serotype	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**Difference[c]**	**(95% CI[d])**
4	192	181	94.3	232	228	98.3	4.0	(0.4, 8.4)
5	180	141	78.3	218	201	92.2	13.9	(6.7, 21.2)
6A	186	178	95.7	225	214	95.1	-0.6	(-4.9, 3.9)
6B	191	173	90.6	231	217	93.9	3.4	(-1.8, 8.9)
7F	189	121	64.0	227	204	89.9	25.8	(17.8, 33.8)
9V	187	114	61.0	229	179	78.2	17.2	(8.1, 26.0)
14	193	171	88.6	231	210	90.9	2.3	(-3.6, 8.5)
18C	192	172	89.6	226	218	96.5	6.9	(1.8, 12.3)
19A	184	176	95.7	216	214	99.1	3.4	(0.3, 7.5)
19F	187	163	87.2	222	215	96.8	9.7	(4.2, 15.5)
23F	192	138	71.9	233	191	82.0	10.1	(2.0, 18.3)

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number with an OPA titer ≥ LLOQ for the given serotype.
c. Difference in proportions, expressed as a percentage.
d. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, [(13vPnC/23vPS) – (23vPS/13vPnC)], expressed as a percentage.

13vPnC/13vPnC relative to 13vPnC:

OPA GMTs after vaccination 2 were compared to those after vaccination 1 of the sequence 13vPnC/13vPnC (Table 28). For 9 of the 13 serotypes (1, 3, 6A, 6B, 14, 18C, 19A, 19F, and 23F), the lower limits of the 95% CIs for the GMFRs (ie, vaccination 2/ vaccination 1) exceeded 0.5 (secondary objective). However, the responses after 13vPnC/13vPnC were statistically significantly lower (ie, an upper limit of the 95% CI for the GMFR of < 1.0) than responses after 13vPnC alone for 7 of 13 serotypes (all except serotypes 3, 6A, 6B, 14, 19F, 23F). The OPA GMT was statistically significantly greater after 13vPnC/13vPnC than after 13vPnC for serotype 23F.

Table 28. Comparison of Pneumococcal OPA GMTs and GMFRs, 13vPnC (Year 0) and 13vPnC/13vPnC (Year 1) - Evaluable Immunogenicity Populations

	Vaccine Sequence (as Randomized)							
	Vaccination 1 (Year 0)			Vaccination 2 (Year 1)			Fold Rise	
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	GMFR[d]	(95% CI[c])
1	123	215	(163.9, 282.4)	123	142	(112.2, 180.4)	0.7	(0.54, 0.82)
3	117	73	(57.2, 94.1)	117	89	(75.2, 105.4)	1.2	(0.99, 1.49)
4	126	2255	(1625.2, 3128.6)	126	1214	(931.8, 1582.1)	0.5	(0.43, 0.68)
5	115	170	(112.1, 258.6)	115	98	(69.6, 136.6)	0.6	(0.43, 0.77)
6A	126	2682	(1969.5, 3652.1)	126	2281	(1747.1, 2978.5)	0.9	(0.67, 1.08)
6B	118	2112	(1508.0, 2958.2)	118	1882	(1429.7, 2477.9)	0.9	(0.71, 1.12)
7F	125	930	(602.1, 1437.1)	125	323	(215.8, 482.8)	0.3	(0.24, 0.49)
9V	116	919	(619.1, 1364.0)	116	335	(214.6, 522.6)	0.4	(0.26, 0.51)
14	120	492	(312.7, 774.5)	120	384	(262.4, 561.2)	0.8	(0.60, 1.02)
18C	120	1440	(1015.3, 2043.5)	120	986	(730.8, 1330.2)	0.7	(0.54, 0.87)
19A	102	583	(426.6, 796.8)	102	385	(308.2, 481.6)	0.7	(0.53, 0.82)
19F	115	566	(385.7, 829.2)	115	502	(381.3, 662.1)	0.9	(0.69, 1.15)
23F	127	291	(187.7, 452.2)	127	456	(322.4, 644.7)	1.6	(1.15, 2.13)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype at both blood draws.
b. Geometric mean titers (GMTs) were calculated using data from all evaluable subjects who had determinate assay values at both the postvaccination 1 (13vPnC; year 0) and postvaccination 2 (13vPnC/13vPnC; year 1) time points.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, or mean fold rises.
d. Geometric mean fold rises (GMFRs) were calculated using all evaluable subjects with data from both the postvaccination 1 (13vPnC; year 0) and postvaccination 2 (13vPnC/13vPnC; year 1) blood draws.

For 11 of 13 serotypes in the ad hoc analysis, the proportions of subjects achieving OPA titres ≥LLOQ after 13vPnC/13vPnC met the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/13vPnC – 13vPnC] of >-10%).The proportions of responders were statistically significantly higher after 13vPnC/13vPnC than after 13vPnC for serotypes 3, 19F, and 23F.

<u>13vPnC/23vPS relative to 13vPnC:</u>

OPA GMTs after vaccination 2 were compared with those after vaccination 1 in subjects randomly assigned to the vaccine sequence 13vPnC/23vPS. For 8 of the 12 common serotypes, the lower limits of the 95% CIs for the GMFRs (vaccination 2/ vaccination 1) were >0.5 (serotypes 1, 3, 5, 6B, 14, 18C, 19A, and 19F). However, OPA GMTs after 13vPnC/23vPS were statistically significantly lower (ie, an upper limit of the 95% CI for the GMFR of < 1.0) than after 13vPnC alone for 8 of 12 common serotypes (all except serotypes 3, 5, 14, 19F). Responses were statistically significantly greater for 13vPnC/23vPS relative to 13vPnC for serotype 3, with a GMFR of 1.7 and a value at the lower limit of the 95% CI of 1.5.

For 12 of 13 serotypes in the ad hoc analysis, the proportions of responders at OPA titres ≥ LLOQ after 13vPnC/23vPS met the non-inferiority criterion applied in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/23vPS – 13vPnC] of > -10%). Proportions were statistically significantly higher after 13vPnC/23vPS than after 13vPnC alone for serotypes 3 and 14.

<u>13vPnC relative to 23vPS/13vPnC:</u>

When OPA GMTs after dose 1 with 13vPnC were compared with those after dose 2 of 23vPS/13vPnC, results showed that 13vPnC elicited statistically significantly greater OPA responses than did 23vPS/13vPnC. The lower limits of the 95% CIs for the ratios were greater than 1.0 for all 12 common serotypes.

In the ad hoc analysis, for all serotypes, the proportions of subjects achieving OPA titers ≥ LLOQ after 13vPnC met the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC – 23vPS/ 13vPnC] of > -10%).

Proportions were statistically significantly higher after 13vPnC than after 23vPS/ 13vPnC for 10 of 13 serotypes.

13vPnC relative to 23vPS:

Although not a prespecified objective, an ad hoc analysis showed that OPA GMTs were statistically significantly higher (ie, a lower limit of the 95% CI for the ratio [13vPnC to 23vPS] of >1) after 13vPnC than after 23vPS for 10 of 12 common serotypes; the exceptions were serotypes 3 and 14, for which values were non-inferior (ie, the lower limits of the 95% CIs for the ratio [13vPnC to 23vPS] were >0.5) after 13vPnC relative to 23vPS.

An additional ad hoc analysis showed that for all serotypes the proportions of responders at OPA titers ≥ LLOQ in the 13vPnC group met the non-inferiority criterion used in the pivotal non-inferiority study 004 (ie, a lower limit of the 95% CI for the difference [13vPnC – 23vPS] of > -10%). The proportions of responders were statistically significantly higher after 13vPnC than after 23vPS for 7 of 12 common serotypes.

13vPnC/13vPnC relative to 23vPS:

An ad hoc comparison of OPA GMTs showed that the non-inferiority criterion was met after 13vPnC/13vPnC relative to 23vPS for 10 of 12 common serotypes. The lower limits of the 95% CIs were > 0.5 for all serotypes, except for serotype 5 (ie, 0.44) and serotype 14 (ie, 0.33). OPA GMTs were statistically higher after 13vPnC/13vPnC than after 23vPS for serotype 6B and serotype 23F.

An additional ad hoc analysis showed that, for all serotypes, the proportions of responders at OPA titers ≥ LLOQ after 13vPnC/13vPnC relative to 23vPS met the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/13vPnC – 23vPS] of > -10%). Proportions were statistically significantly higher after 13vPnC/13vPnC for serotypes 3, 6B, 18C, 19F, and 23F.

13vPnC/13vPnC relative to 23vPS/ 13vPnC:

An ad hoc analysis showed that OPA GMTs were statistically significantly higher after 13vPnC/13vPnC than after 23vPS/ 13vPnC for 10 of 13 serotypes (all except serotypes 4, 5, 14); ie, for these 10 serotypes, the lower limits of the 95% CIs for the ratio [13vPnC/13vPnC to 23vPS/13vPnC] were >1. In addition, the non-inferiority criterion used in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the GMT ratio [13vPnC/13vPnC to 23vPS/13vPnC] of > 0.5) was met for all serotypes after 13vPnC/13vPnC relative to 23vPS/13vPnC. Ratios ranged from 0.9 (serotype 14) to 3.8 (serotype 23F) and the lower limits of the 95% CIs for the ratios were ≥0.56.

For 12 of 13 serotypes in another ad hoc analysis, the proportions of responders at OPA titers ≥ LLOQ after 13vPnC/13vPnC met the non-inferiority criterion applied in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [13vPnC/13vPnC – 23vPS/ 13vPnC] of > -10%). Proportions were statistically significantly higher after 13vPnC/13vPnC for 8 of 13 serotypes.

23vPS/13vPnC relative to 23vPS:

In an ad hoc analysis, OPA GMTs were statistically significantly lower (ie, upper limits of the 95% CIs for the GMFRs [vaccination 2/ vaccination 1] of < 1) after 23vPS/13vPnC relative to 23vPS for 10 of 12 common serotypes (all except serotypes 6B and 23F). For serotype 23F, OPA GMTs were statistically significantly higher (ie, lower limit of the 95% CI for the GMFR [vaccination 2/ vaccination 1] of >1) after 23vPS/13vPnC than after 23vPS alone, and for serotype 6B OPA GMTs were similar for the 2 groups.

For 8 of 12 common serotypes the ad hoc analysis showed that the proportion of responders at OPA titers ≥ LLOQ after 23vPS/13vPnC met the non-inferiority criterion applied in the pivotal non-inferiority study (ie, a lower limit of the 95% CI for the difference [23vPS/13vPnC – 23vPS] of > -10%). Proportions were statistically significantly lower after 23vPS /13vPnC than after 23vPS alone for

serotypes 1, 3, 7F, and 9V and were statistically significantly higher after 23vPS /13vPnC for serotype 23F.

Response to Serotype 6A:

Evaluation of response to serotype 6A (the serotype that is not included in 23vPS) showed that the anti-6A OPA GMT point estimate was higher after 13vPnC/23vPS (GMT: 1268) than after a single dose of 23vPS (275) or after 23vPS/13vPnC (GMT: 1133). Response to serotype 6A was also higher after a single dose of 13vPnC (2766) relative to the sequence 23vPS/13vPnC (GMT: 1133) In addition, the point estimate for the OPA GMT after a single dose of 13vPnC (GMT: 2682) was higher than that after 2 doses of 13vPnC (GMT: 2281), in subjects who received both doses. Furthermore in subjects receiving each vaccination of the sequence 13vPnC/23vPS, OPA response after 13vPnC/23vPS (GMT: 1302) was statistically significantly lower than after 13vPnC alone (GMT: 3068).

Antibody Response Curves

For the 13 serotypes, OPA responses rose substantially from the day of vaccination 1 to the blood draw approximately 1 month after vaccination 1 with either 13vPnC or 23vPS. For all serotypes, OPA GMTs showed a decline over the year, from 1 month after vaccination 1 to the day of vaccination 2 (before vaccination). However, at the prevaccination 2 time point all levels remained substantially higher than baseline levels observed before vaccination 1 for each group

In each vaccine group, GMTs rose from before vaccination 2 to 1 month after vaccination 2. OPA GMTs after vaccination 2 exceeded values noted after vaccination 1 for a few serotypes in each vaccine group: serotypes 3 and 23F for 13vPnC/13vPnC; serotypes 3 and 19F for 13vPnC/23vPS; and serotypes 6A and 23F for 23vPS/13vPnC. For most serotypes, the antibody response curves for 23vPS/13vPnC were lower than those for 13vPnC/13vPnC and 13vPnC/23vPS, except for serotypes 3, 5, and 14.

Concomitant Use of Trivalent Inactivated Influenza Vaccine (Studies 3001 and 3008)

Study 3001

Study 3001 was a phase 3, parallel-group, randomized, double-blind, multicenter trial to evaluate the immunogenicity, safety, and tolerability of 13vPnC when administered concomitantly with TIV (Fluarix) (13vPnC+TIV) in healthy adults aged 50 to 59 years who were naïve to 23vPS (see study schema). The primary objectives of the study were: 1) to demonstrate that immune responses induced by the licensed influenza vaccine TIV when given concomitantly with 13vPnC were noninferior to immune responses elicited by TIV alone (ie, TIV given with placebo); and 2) to demonstrate that the serotype-specific IgG responses to 13vPnC when given concomitantly with TIV are noninferior to IgG responses elicited by 13vPnC alone when given 1 month after administration of TIV. A total of 1116 subjects were randomly assigned in a 1:1 ratio to 2 treatment groups: group 1 received 13vPnC with concomitant TIV followed 1 month later by placebo (13vPnC + TIV/placebo, n = 554); group 2 received placebo with TIV followed 1 month later by 13vPnC (placebo + TIV/13vPnC, n = 562).

Study schema 6115A1 -3001

		Pre-licensure		Post-licensure	
Group	N	Year 0	1 Month	Year 1-4	Year 5
1	550	TIV + 13vPnC	Placebo	Annual	13vPnC
2	550	TIV + Placebo	13vPnC	Bleeds	13vPnC

The immunogenicity analyses were based on results of assays performed on blood samples taken on the day of each vaccination (before vaccine administration) and approximately 1 month after the second vaccination. To assess immune response to TIV, the standard hemagglutination inhibition assays (HAIs) were used to measure antibody response to the A/H1N1, A/H3N2, and B vaccine strains selected for the 2007/ 2008 influenza season. IgG ELISA was used to measure serotype-specific response to 13vPnC. The evaluable immunogenicity population included a total of 1063 subjects (95.3%): 531 subjects (95.8%) in the 13vPnC + TIV/placebo group and 532 subjects (94.7%) in the placebo+ TIV/13vPnC group. The demographic and baseline characteristics in the evaluable immunogenicity population were similar in subjects randomly assigned to each vaccine sequence with respect to sex, race, and age.

Response to TIV

The primary endpoint for the comparison of TIV + 13vPnC versus TIV + placebo was the proportion of subjects who achieved at least a 4-fold increase in the HAI titer (ie, proportion who seroconverted) elicited by each influenza strain included in the vaccine. The noninferiority criterion for proportion of responders was a lower limit of the 95% CI for the difference (13vPnC + TIV – placebo + TIV) in proportion of responders of greater than -10%.

The non-inferiority criterion for the proportion of subjects achieving a ≥4-fold rise in HAI titer was met for all 3 strains of TIV after dose 1 (Table 29).

Table 29. Comparison of Subjects Achieving a ≥4-Fold Increase in Titer for Concomitant Vaccine (TIV) Antigens After Dose 1 (Year 0) – Evaluable Immunogenicity Population

	Vaccine Sequence (as Randomized)							
	Group 1 13vPnC+TIV/Placebo N[a]=530			Group 2 Placebo+TIV/13vPnC N[a]=531				
Concomitant Vaccine	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
TIV: HAIs								
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 prespecified level for the given antigen.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, expressed as a percentage.
e. Exact 2-sided confidence interval (based on the methodology by Chan and Zhang) for the difference in proportions, 13vPnC+TIV/Placebo – Placebo+TIV/13vPnC, expressed as a percentage.

At baseline before dose 1, GMTs were higher for A/H3N2 (43.44 before 13vPnC+TIV and 49.45 before placebo+TIV) than for the other vaccine strains, which elicited GMTs ranging across vaccine groups from 14.00 to 26.02. The higher baseline GMTs for A/H3N2 may have been due to exposure to this strain in the previous influenza season. After vaccination, the A/H3N2 GMTs increased approximately 10-fold.

Response to 13vPnC

Pneumococcal responses were assessed approximately 1 month after vaccination in a subset of 605 subjects. The primary endpoint for the pneumococcal analysis was the GMCs for each serotype. Non-inferiority of IgG response to 13vPnC + TIV relative to 13vPnC alone was assessed based on the GMR and the 2-fold non-inferiority criterion (ie, a lower limit of the 2 sided 95% CI for the GMR of greater than 0.5).

The non-inferiority criterion was met for all serotypes. IgG GMCs ranged from 1.15 µg/mL (serotype 3) to 16.80 µg/mL (serotype 19A) in 13vPnC + TIV recipients and from 1.46 µg/mL (serotype 3) to 18.84 µg/mL (serotype 19A) in 13vPnC recipients. The geometric mean ratios ranged from 0.69 (serotype 4) to 0.89 (serotype 19A), and ratios at the lower limits of the 95% CIs ranged from 0.55 (serotype 4) to 0.74 (serotype 19A).

GMFRs from baseline (before dose 1) to 1 month after each dose were also assessed for each serotype in the 2 groups. GMFRs from before to after dose 1 with 13vPnC+TIV ranged from 2.60 (serotype 3) to 11.95 (serotype 18C). GMFRs from before dose 1 to 1 month after dose 2 with 13vPnC alone ranged from 2.71 (serotype 3) to 14.72 (serotype 4). GMFRs at the lower limits of the 95% CIs ranged from 2.33 (serotype 3) to 10.20 (serotype 18C) after 13vPnC+TIV and from 2.42 (serotype 3) to 12.41 (serotype 4) after 13vPnC.

Reverse Cumulative Distribution Curves (RCDCs) showed the distribution of IgG responses in both groups by serotype. In general the curves were slightly lower for the 13vPnC+TIV group compared with the 13vPnC group; however at antibody concentrations of 1.0 µg/mL or less, the curves for most serotypes overlapped.

Study 3008

Study 3008 was a phase 3, parallel-group, randomized, double-blind, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC when administered concomitantly with TIV (13vPnC+TIV) in healthy adults aged 65 years or older who were naïve to 23vPS (Figure 2-4). The primary objectives of the study were: 1) to demonstrate that immune responses induced by the licensed influenza vaccine TIV when given concomitantly with 13vPnC (13vPnC+TIV) were noninferior to immune responses elicited by TIV given with placebo (ie, TIV + placebo), as measured by the standard HAI for the A/H1N1, A/H3N2, and B vaccine strains; and 2) to demonstrate that the serotype-specific IgG responses to 13vPnC when given concomitantly with TIV are noninferior to IgG responses elicited by 13vPnC alone when given 1 month after administration of TIV.

1160 subjects were randomly assigned in a 1:1 ratio to 2 treatment groups: group 1 received 13vPnC + TIV followed 1 month later by placebo (13vPnC+TIV/placebo, 580 subjects); group 2 received placebo with TIV followed 1 month later by 13vPnC (placebo+TIV/13vPnC, 580 subjects).

Study schema 6115A1 -3008

Group	N	Year 0	Month 1
1	550	TIV + 13vPnC	Placebo
2	550	TIV + Placebo	13vPnC

The immunogenicity analyses were based on results of assays performed on blood samples taken on the day of each vaccination (before vaccine administration) and approximately 1 month after the second dose. To assess immune response to TIV, the standard HAI was used to measure antibody response to the A/H1N1, A/H3N2, and B vaccine strains selected for the 2007/ 2008 influenza season. IgG ELISA was used to measure serotype-specific IgG response to 13vPnC.

The evaluable immunogenicity population included a total of 1096 subjects (94.5%); of these, 549 evaluable subjects (94.7%) were assigned to the 13vPnC+TIV/placebo group and 547 subjects (94.3%) were assigned to the placebo+TIV/13vPnC group. The demographic and baseline

characteristics in the evaluable immunogenicity population were similar in subjects randomly assigned to each vaccine sequence with respect to sex, race and age.

Response to TIV

The primary endpoint for the comparison of 13vPnC+TIV versus placebo+TIV was the proportion of subjects (ie, responders) achieving at least a 4-fold increase in HAI titer elicited by each influenza strain in TIV (A/H1N1, A/H3N2, and B vaccine strains) approximately 1 month after vaccination.

The non-inferiority criterion for the proportion of subjects achieving a ≥4-fold increase in HAI titer (ie, proportion who seroconverted) was met for the A/H1N1 and B vaccine strains, but was missed by a very small margin for A/H3N2 (ie, missing the predefined non-inferiority criterion by 0.4%) (Table 30). Differences between the 2 vaccine groups for A/H1NI, A/H3N2, and B were 1.7%, -4.6%, and -1.8%, respectively, and lower limits of the 95%CIs for the differences were -3.1%, -10.4% and -7.8%, respectively. Thus, the value for A/H3/N2 was slightly lower than the predefined non-inferiority criterion of >-10% (Table 30).

Table 30. Comparison of Subjects Achieving a ≥4-Fold Increase in Titer for Concomitant Vaccine Antigens After Dose 1 - Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC+TIV/Placebo				Placebo+TIV/13vPnC					
Concomitant Vaccine	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
TIV: HAIs										
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 for the given concomitant vaccine antigen.
b. n = Number of subjects with an antibody titer that met the prespecified level.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC+TIV/Placebo - Placebo+TIV/13vPnC, expressed as a percentage.

The proportion of seroconversions of greater than 30% (as per EMA guidance) was exceeded for all 3 strains. The proportions of responders after dose 1 in the 13vPnC+TIV group and placebo+TIV group, respectively, were: A/H1N1, 80.3% and 78.6%; A/H3N2, 58.0% and 62.6%; and B, 52.2% and 54.0%.

The GMFRs for each strain in each vaccine group surpassed the value for a geometric mean increase after vaccination of greater than 2.0.

In contrast to the other 2 influenza strains, the prevaccination 1 HAI titers for A/H3N2 were quite high, ie, 62.9 in 13vPnC+TIV recipients and 65.3 in placebo + TIV recipients. This result perhaps reflects the pressure due to A/H3N2 epidemics that have been observed over several years before the study. In the region where the study was conducted, H3N2 predominated over H1N1 and B in the 2006–2007 season and in 4 of the 5 prior influenza seasons. Higher prevaccination titers may limit the likelihood of demonstrating a ≥ 4-fold increase in HAI responses, and the lower frequency of response would be expected to impact the ability to demonstrate non-inferiority.

An additional endpoint was the proportion of subjects achieving HAI titers ≥40 (ie, responders). The proportion of responders was similar in the 2 vaccine groups and exceeded the value of 60% for each vaccine strain.

Response to 13vPnC

Pneumococcal responses were assessed before dose 1 and approximately 1 month after each dose in a subset of 605 subjects. The primary pneumococcal comparison was evaluation if immune response in

subjects receiving 13vPnC+TIV at dose 1 versus 13vPnC at dose 2. The primary endpoints were the serotype-specific pneumococcal IgG concentrations in the 13vPnC+TIV group and in the 13vPnC group.

Non-inferiority of IgG response to 13vPnC + TIV relative to 13vPnC alone was assessed based on the GMR and the 2-fold non-inferiority criterion (ie, a lower limit of the 2-sided 95% CI for the GMR of >0.5).

All serotypes met the non-inferiority criterion, except for serotype 19F. GMRs (ie, 13vPnC+TIV to 13vPnC) ranged from 0.65 (serotype 19F) to 0.97 (serotype 6B) and the lower limits of the 95% CIs for the GMRs ranged from 0.49 (serotype 19F) to 0.78 (serotype 3).

GMFRs from baseline (before dose 1) to 1 month after each dose were also assessed for each serotype. GMFRs from before to after dose 1 with 13vPnC+TIV ranged from 2.47 (serotype 5) to 10.77 (serotype 4). GMFRs from before dose 1 to after dose 2 with 13vPnC alone ranged from 2.98 (serotype 3) to 18.06 (serotype 4). GMFRs at the lower limits of the 95% CIs ranged from 2.16 (serotype 5) to 9.03 (serotype 4) after 13vPnC+TIV and from 2.64 (serotype 3) to 14.82 (serotype 4) after 13vPnC.

RCDCs showed the range of IgG responses in subjects receiving 13vPnC+TIV versus those receiving 13vPnC alone. Curves were similar in both groups, although, for most serotypes, the curves were slightly lower in 13vPnC+TIV recipients, particularly at higher antibody concentrations (Data not shown in this AR).

Supportive studies

Study 500

Study 500 was a randomized, open-label, active-control, phase 2 multicenter trial to evaluate the safety, tolerability, and immunogenicity of 2 different 13vPnC formulations, ie, 13vPnC given with aluminium phosphate (13vPnC + AlP04) versus 13vPnC given without aluminium phosphate (13vPnC - AlP04). The patient population included subjects aged 65 years and older who were naïve to previous immunization with 23vPS. A total of 915 subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 vaccine groups: group 1 received 13vPnC+AlPO4; group 2 received 13vPnC-AlPO4; and, group 3 received 23vPS (Figure 2-6).

Study schema 6115A1- 500

Group	N	Year 0		Year 1
1	300	13vPnC + $AlPO_4$	**Formula choice**	13vPnC
				23vPS
2	300	13vPnC - $AlPO_4$		23vPS
3	300	23vPS		-

The evaluable immunogenicity population for the formulation decision analysis (vaccination 1 only) included a total of 893 (97.6%) subjects, ie, 300 (97.1%) in the 13vPnC + ALPO4 group and 298 (97.7%) in the 13vPnC - ALPO4 group, and 295 (98.0%) in the 23vPS group.

The primary endpoint for the **formulation decision** analysis was the serotype-specific IgG response to the two 13vPnC formulations. Another endpoint was the proportion of subjects achieving a ≥ 4-fold rise in pneumococcal IgG antibody concentration.

The non-inferiority of IgG response after 13vPnC-AlPO4 relative to 13vPnC+AlPO4 was assessed using the 2-fold criterion and 95% CIs; non-inferiority was declared if the lower limit of the 95% CI for the ratio (13vPnC-AlPO4 to 13vPnC+AlPO4) was > 0.5. The non-inferiority criterion for the proportion of responders at prespecified levels was a lower limit of the 95% CI for the difference in proportions (13vPnC-AlPO4 - 13vPnC+AlPO4) of >-10%.

IgG GMCs: IgG GMCs in the 13vPnC-AlPO4 group were non-inferior to values in the 13vPnC+AlPO4 group for all 13 serotypes. Ratios ranged from 0.8 (23F) to 1.5 (serotype 7F), and the lower limits of the 95% CIs for the ratios ranged from 0.6 (23F) to 1.2 (serotype 7F). IgG GMCs were similar when adjusted for age, sex, current smoking status, and prevaccination 1 value. The non-inferiority criterion was met for all serotypes.

Formulation decision: The data indicated that the immunogenicity of 13vPnC in adults older than 65 years, as measured by IgG GMCs, did not differ when formulated with or without AlPO4.

The local reactions of erythema, induration, and pain were observed significantly more frequently in the group that received the 13vPnC+AlPO4 formulation compared with the other groups. However, these reactions were predominantly mild and considered to have little direct impact on the subject's functional status. Other local and systemic reactions of importance did not differ between study groups. The logistical considerations on maintaining two different formulations of Prevenar13 were in favour of the 13vPnC+AlPO4 formulation, which was chosen as the final formulation.

Final Analysis:

OPA GMTs (Vaccination 1): Comparisons of OPA GMTs after 13vPnC+$AlPO_4$ and after 23vPS at vaccination 1 showed that responses to 10 of 12 common serotypes were statistically significantly greater after 13vPnC than after 23vPS (exceptions serotypes 7F and 14), and the non-inferiority criterion was met for 11 of 12 common serotypes (exception 7F). Among these 11 serotypes, OPA GMT ratios (13vPnC+AlPO4 to 23vPS) ranged from 0.88 (serotype 14) to 3.36 (serotype 9V) and the lower limits of the 95% CIs for the ratios ranged from 0.63 (serotype 14) to 2.30 (serotype 5). The ratio for serotype 7F was 0.65 and the lower limit of the 95% CI for the ratio was 0.46. For serotype 6A (serotype not contained in 23vPS), the ratio of 13vPnC+$AlPO_4$ to 23vPS was 7.14, with a ratio at the lower limit of the 95% CI of 5.00. Results were similar when adjusted for age, sex, current smoking status, and prevaccination 1 value.

Proportion of Subjects Achieving Prespecified OPA Antibody Levels (Vaccination 1): Results showed that the proportion of responders at an antibody titer ≥LLOQ in the 13vPnC+$AlPO_4$ group was non-inferior to that of the 23vPS group for all 12 common serotypes; responses were statistically significantly higher in the 13vPnC +$AlPO_4$ group for 6 of 12 common serotypes.

Vaccination 1 and Vaccination 2: 13vPnC+$AlPO_4$/13vPnC+$AlPO_4$ relative to 13vPnC+$AlPO_4$: OPA GMTs were similar or lower after 13vPnC+$AlPO_4$/13vPnC+$AlPO_4$ than after 13vPnC+$AlPO_4$ alone for all serotypes except 23F. OPA GMTs were statistically significantly lower after 13vPnC+$AlPO_4$/13vPnC+$AlPO_4$ for 8 of 13 serotypes, with an upper limit of the 95% CI for the GMFR of < 1.0 (all except serotypes 6A, 6B, 7F, 19F, 23F). However, for serotype 23F, the OPA response was statistically significantly higher after 13vPnC+$AlPO_4$/13vPnC+$AlPO_4$ than after 13vPnC+AlPO4 alone.

Study 3009

Study 3009 was an open label, single arm, multicenter trial in subjects who had previously been enrolled in study 500 a year earlier. Subjects who were enrolled in study 3009 had previously received

13vPnC +$AlPO_4$ (selected formulation) at vaccination 1 and 23vPS a year later at vaccination 2 (13vPnC +$AlPO_4$/23vPS) in study 500.

One hundred and five (105) subjects were given a single dose of 13vPnC in study 3009 (see study schema). The primary objective of the study was to compare serotype-specific OPA responses to 13vPnC given in study 3009 (ie, vaccination 3 of the sequence 13vPnC/23vPS/13vPnC) with OPA responses elicited by 13vPnC given as the first dose in study 500 (ie, 13vPnC/23vPS/13vPnC versus 13vPnC) . The study was conducted to determine whether a dose of 13vPnC (vaccination 1 in study 500) administered before 23vPS (vaccination 2 in study 500) could protect against the reduction of OPA responses to a subsequent 13vPnC vaccination (vaccination 3 in study 3009). The study also compared IgG responses after vaccination 3 and after vaccination 1. In addition, serotype-specific OPA and IgG responses after vaccination 3 were compared with those after vaccination 2 of the vaccine sequence 13vPnC/23vPS/13vPnC. Vaccination in study 3009 was administered approximately 1 year after the second vaccination in study 500.

Study schema 6115A1 – 3009

Group	Year 0	Year 1	**N**	**Year 2**
1	13vPnC	23vPS	**100**	**13vPnC**

OPA GMTs

Vaccination 3 vs vaccination 1: Point estimates for OPA GMTs for all serotypes tended to be lower after vaccination 3 relative to vaccination 1, and for 10 of 13 serotypes (all serotypes except 3, 6B, 23F) responses were statistically significantly lower (ie, upper limit of the 95% CI for the GMFR of <1.0) after vaccination 3. For serotypes 3, 6B, and 23F, the lower limits of the 95% CIs for the GMFRs were >0.5; for all other serotypes the lower limits of the 95% CIs for the GMFRs were <0.5. These results reflect the notable decrease in immune response after the vaccine sequence 13vPnC/23vPS/13vPnC relative to a single dose of 13vPnC. Hence, a dose of 13vPnC given before 23vPS does not protect against reduced immune response to subsequent 13vPnC in this 3-dose vaccine sequence.

The OPA GMTs and IgG GMCs were plotted at each time point before and after each of the 3 vaccinations in the sequence 13vPnC/23vPS/13vPnC For the 13 serotypes, OPA GMTs and IgG GMCs increased substantially from before the first dose of 13vPnC (vaccination 1) to the blood draw approximately 1 month after vaccination 1.

For all serotypes, OPA GMTs and IgG GMCs decreased over the year, from 1 month after vaccination 1 to before vaccination 2. However, at the pre–vaccination 2 time point, all levels remained substantially higher than baseline levels observed before vaccination 1. OPA GMTs and IgG GMCs increased from before vaccination 2 to 1 month after vaccination 2. Following vaccination 3 in the vaccine sequence 13vPnC/23vPS/13vPnC, GMTs and GMCs increased for all serotypes from before to after vaccination. For the majority of serotypes, there was a trend for postvaccination responses to be either similar or somewhat less after each subsequent vaccination in the vaccine sequence 13vPnC/23vPS/13vPnC, with prevaccination levels of all subsequent vaccines still well above the baseline values.

3.3.5. Additional data provided by the MAH during the procedure

During the procedure the MAH has finalised a summary report of an extension to study 6115A1-004. The present extension of study 6115A1-004 assessed the safety, tolerability, and immunogenicity of 13vPnC or 23vPS when administered 3 to 4 years after an initial vaccination with 13vPnC, as well as the safety, tolerability and immunogenicity of 23vPS when administered 3 to 4 years after an additional vaccine with 23vPS in adults 60 to 64 years of age (cohort 1). Also, the safety, tolerability

and immunogenicity of 13vPnC was assessed when administered 3 to 4 years after an initial vaccination with 13vPnC in adults 50 to 59 years of age (cohort 2). Therefore, subjects in cohort 1 received 1 of 3 vaccine sequences: 13vPnC/13vPnC, 13vPnC/23vPS, or 23vPS/23vPS. All subjects in cohort 2 received the vaccine sequence of 13vPnC/13vPnC.

A brief summary of the relevant data is provided below:

Study 6115A1-004

Objectives of Primary Interest

- To evaluate the antibody responses to 23vPS administered 3 to 4 years after an initial dose of 13vPnC compared to an initial dose of 23vPS in the 60 to 64 year old age group as measured by serotype-specific OPA geometric mean titers (GMTs) (13vPnC/23vPS versus 23vPS).
- To evaluate the antibody responses to 23vPS administered 3 to 4 years after an initial dose of 13vPnC compared to 23vPS administered 3 to 4 years after an initial dose of 23vPS in the 60 to 64 year old age group as measured by serotype-specific OPA GMTs (13vPnC/23vPS versus 23vPS/23vPS).

Objectives of Secondary Interest

- The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 13vPnC/23vPS vaccine sequence: 13vPnC/23vPS versus 13vPnC for subjects in cohort 1
- The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 23vPS/23vPS vaccine sequence: 23vPS/23vPS versus 23vPS for subjects in cohort 1,
- The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 13vPnC/13vPnC vaccine sequence in both cohorts 1 and 2: 13vPnC/13vPnC versus 13vPnC,
- The between-group comparison of cohort 1 and cohort 2 in the 13vPnC/13vPnC vaccine sequence,
- The vaccination 2 responses of subjects in vaccine sequence 13vPnC/13vPnC versus subjects in vaccine sequence 13vPnC/23vPS for subjects in cohort 1,
- The vaccination 2 responses of subjects in vaccine sequence 13vPnC/13vPnC versus subjects in vaccine sequence 23vPS/23vPS for subjects in cohort 1.

Results

A primary immunogenicity objective of the study was to assess whether responses to 23vPS administered 3 to 4 years after an initial dose of 13vPnC (13vPnC/23vPS) was as immunogenic as 23vPS given alone in cohort 1. As shown in Table 31, the noninferiority criterion (lower limit of the 95% CI for the GMR greater than 0.5) was met for all 12 common serotypes. The lower limit of the 95% CI for the GMRs exceeded 1.0, indicating that the OPA response was statistically significantly greater after 13vPnC/23vPS than after 23vPS, for 9 of the 12 common serotypes: 1, 3, 5, 6B, 7F, 18C, 19A, 19F, and 23F. The GMRs were greater than 1 for all serotypes, ranging from 1.3 (serotype 4) to 4.7 (serotype 7F).

In summary, the results indicate that antibody responses were similar, and for the majority of serotypes, statistically significantly greater for 13vPnC/23vPS compared to 23vPS alone.

Table 31. Comparison of Pneumococcal OPA GMTs (Titer) 1 Month After Vaccination With 13vPnC/23vPS (Year 3 to 4) and 23vPS (Year 0) in Subjects Aged 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	Vaccine Sequence (As Randomized)							
	13vPnC/23vPS			23vPS			Vaccine Comparison	
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	105	398	(306.2, 516.3)	184	116	(89.4, 149.6)	3.4	(2.32, 5.09)
3	107	164	(129.0, 207.5)	184	105	(85.3, 128.7)	1.6	(1.13, 2.16)
4	107	1875	(1488.8, 2360.7)	174	1420	(1066.2, 1890.5)	1.3	(0.88, 1.98)
5	106	476	(356.2, 636.1)	181	149	(111.1, 201.2)	3.2	(2.04, 4.97)
6B	104	2670	(2012.9, 3540.6)	174	1088	(774.7, 1528.1)	2.5	(1.50, 4.00)
7F	105	1895	(1471.0, 2441.1)	181	403	(276.3, 588.9)	4.7	(2.76, 7.99)
9V	107	1089	(699.2, 1695.0)	167	654	(452.5, 944.9)	1.7	(0.93, 2.97)
14	105	1268	(951.8, 1690.0)	173	824	(612.9, 1107.8)	1.5	(0.99, 2.39)
18C	103	2489	(1941.1, 3192.7)	174	1135	(815.7, 1578.6)	2.2	(1.37, 3.50)
19A	106	966	(763.2, 1223.6)	182	377	(296.1, 479.6)	2.6	(1.78, 3.68)
19F	99	1653	(1302.2, 2099.5)	170	621	(468.6, 821.7)	2.7	(1.77, 4.01)
23F	105	299	(203.9, 437.5)	173	86	(58.8, 124.5)	3.5	(1.99, 6.13)

a. n = Number of subjects with a determinate OPA titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titer.
d. Ratio of GMTs 13vPnC/23vPS to 23vPS is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC/23vPS-23vPS).

The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 13vPnC/23vPS vaccine sequence (13vPnC/23vPS versus 13vPnC) is summarized in Table 32. The lower limit of the 95% CI for the GMFR was greater than 0.5 for all but 2 serotypes (6A and 9V). The lower limit of the 95% CI for the GMFRs exceeded 1.0, indicating that the OPA response was statistically significantly greater after 13vPnC/23vPS than after 13vPnC, for 7 of the 12 common serotypes: 1, 3, 5, 7F, 14, 19A, and 19F. The upper limit of the 95% CI for the GMFRs were less than 1.0, indicating the OPA response was statistically significantly lower after 13vPnC/23vPS than after 13vPnC for 2 of the 12 common serotypes (4 and 9V) and serotype 6A. The serotype-specific GMFRs ranged from 0.3 (serotype 6A) to 2.5 (serotype 19F) with 9 of the 12 common serotypes greater than 1.

Table 32. Comparison of Pneumococcal OPA GMTs (Titer) and GMFRs, 13vPnC/23vPS (Year 3 to 4) Relative to 13vPnC (Year 0) in Subjects Aged 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	13vPnC/23vPS (as Randomized)								
	Postvaccination 1 (Year 0)			Postvaccination 2 (Year 3 to 4)			Fold Rise (Postvaccination 2/Postvaccination 1)		
Serotype	n[a]	GMT[b]	95% CI[c]	n[a]	GMT[b]	95% CI[c]	n[a]	GMFR[d]	95% CI[c]
1	100	172	(122.5, 240.4)	100	377	(288.0, 492.3)	100	2.2	(1.64, 2.94)
3	96	102	(76.7, 136.1)	96	162	(124.1, 210.2)	96	1.6	(1.23, 2.03)
4	90	2894	(2008.5, 4169.7)	90	1997	(1622.3, 2458.6)	90	0.7	(0.51, 0.94)
5	97	239	(166.3, 343.3)	97	445	(330.6, 600.2)	97	1.9	(1.37, 2.53)
6A	100	2884	(1978.6, 4204.1)	100	812	(529.7, 1244.0)	100	0.3	(0.21, 0.37)
6B	93	2664	(1835.8, 3866.8)	93	2707	(1995.7, 3673.0)	93	1.0	(0.79, 1.31)
7F	100	971	(598.0, 1576.8)	100	1818	(1397.8, 2363.9)	100	1.9	(1.25, 2.80)
9V	90	1474	(993.1, 2187.6)	90	909	(548.1, 1506.5)	90	0.6	(0.42, 0.91)
14	88	655	(408.8, 1048.0)	88	1367	(1017.4, 1836.3)	88	2.1	(1.43, 3.04)
18C	96	2136	(1500.5, 3042.0)	96	2503	(1932.2, 3243.7)	96	1.2	(0.92, 1.49)
19A	99	765	(589.7, 992.9)	99	976	(761.1, 1251.8)	99	1.3	(1.05, 1.55)
19F	93	675	(452.4, 1007.1)	93	1670	(1303.3, 2138.7)	93	2.5	(1.69, 3.61)
23F	94	432	(271.8, 685.3)	94	333	(224.6, 494.9)	94	0.8	(0.56, 1.07)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype at both the postvaccination 1 and postvaccination 2 blood draws.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) [(13vPnC/23vPS) / (13vPnC)] were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.

The within-group comparison of the vaccination 2 response versus the vaccination 1 response for subjects in the 23vPS/23vPS vaccine sequence (23vPS/23vPS versus 23vPS) is summarised in Table 33. The lower limit of the 95% CI for the GMFR was greater than 0.5 for 7 of the 12 common serotypes: 1, 6B, 7F, 14, 18C, 19A, and 19F. The upper limit of the 95% CI for the GMFRs was less than 1.0, indicating that the OPA response was statistically significantly lower after 23vPS/23vPS than after 23vPS for 8 of the 12 common serotypes: 3, 4, 5, 9V, 14, 18C, 19F, and 23F and serotype 6A. The serotype-specific GMFRs ranged from 0.3 (serotype 9V) to 1.1 (serotype 7F) with only 1 serotype greater than 1 (serotype 7F). In summary, these results indicate a statistically significantly diminished antibody response after the second dose of 23vPS compared to the initial dose.

Table 33. Comparison of Pneumococcal OPA GMTs (Titer) and GMFRs, 23vPS/23vPS (Year 3 to 4) Relative to 23vPS (Year 0) in Subjects Aged 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	23vPS/23vPS (as Randomized)								
	Postvaccination 1 (Year 0)			Postvaccination 2 (Year 3 to 4)			Fold Rise (Postvaccination 2/Postvaccination 1)		
Serotype	n[a]	GMT[b]	95% CI[c]	n[a]	GMT[b]	95% CI[c]	n[a]	GMFR[d]	95% CI[c]
1	181	115	(88.4, 149.0)	181	95	(74.5, 122.0)	181	0.8	(0.68, 1.02)
3	177	103	(83.6, 127.9)	177	53	(42.7, 64.8)	177	0.5	(0.44, 0.59)
4	162	1437	(1068.5, 1933.3)	162	725	(542.9, 968.4)	162	0.5	(0.40, 0.64)
5	173	152	(111.6, 206.2)	173	71	(51.5, 96.5)	173	0.5	(0.39, 0.56)
6A	167	286	(183.7, 446.4)	167	133	(89.4, 198.1)	167	0.5	(0.35, 0.62)
6B	168	1133	(803.5, 1598.9)	168	915	(658.8, 1272.1)	168	0.8	(0.62, 1.04)
7F	174	440	(301.7, 642.7)	174	466	(336.0, 645.0)	174	1.1	(0.81, 1.37)
9V	157	669	(458.1, 978.2)	157	181	(118.3, 276.6)	157	0.3	(0.18, 0.41)
14	165	823	(608.1, 1112.8)	165	619	(473.8, 808.8)	165	0.8	(0.60, 0.95)
18C	165	1096	(777.8, 1544.4)	165	822	(601.7, 1123.6)	165	0.8	(0.60, 0.94)
19A	177	374	(292.3, 478.0)	177	361	(287.2, 453.7)	177	1.0	(0.83, 1.12)
19F	158	596	(446.8, 794.9)	158	405	(307.0, 533.1)	158	0.7	(0.57, 0.81)
23F	165	91	(61.9, 133.6)	165	56	(38.8, 80.7)	165	0.6	(0.50, 0.76)

a. n = Number of subjects with a determinate OPA antibody titer to the given serotype at both the postvaccination 1 and postvaccination 2 blood draws.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) [(23vPS/23vPS) / (23vPS)] were calculated using all subjects with available data from both the postvaccination 1 and postvaccination 2 blood draws.

3.3.6. Efficacy Conclusions

The immunogenicity data from study 004 indicate that 13vPnC elicited OPA and IgG responses 1 month after vaccination that were non-inferior to those induced by 23vPS for all common serotypes. For 8 of 12 common serotypes, OPA GMTs were statistically significantly greater after 13vPnC than after 23vPS. In addition, the proportion of subjects achieving a 4-fold rise in anti-6A titers and the proportion achieving the LLOQ for serotype 6A were statistically significantly higher after 13vPnC than after 23vPS; the anti-6A OPA GMT was also statistically significantly higher after 13vPnC than after 23vPS. At 1 year after vaccination OPA titres remained above prevaccination levels for all serotypes.

Comparisons between age groups showed that OPA and IgG responses to 13vPnC in subjects aged 50 to 59 years (cohort 2) were noninferior to those aged 60-64 years (cohort 1). For each comparison within or between cohorts, the IgG evaluations supported the OPA analyses.

In conclusion, the 13vPnC vaccine elicited non-inferior responses compared to the 23vPS vaccine in a naïve population. As expected, responses in younger subjects, 50-59 years, were generally higher than the responses in older subjects. The IgG responses generally support the OPA results, with the exception on duration of antibody responses.

Overall, results of study 3005 showed that in adults aged ≥ 70 years who were preimmunized with 23vPS at least 5 years before study enrolment, 13vPnC elicited statistically significantly higher OPA responses than those elicited by 23vPS. In addition, OPA responses after 1 and 2 doses of 13vPnC were similar for most serotypes in this preimmunized population. When 13vPnC was given alone or administered as a two dose sequence given a year apart (ie, 13vPnC/13vPnC) OPA responses were generally statistically significantly higher than those after 23vPS alone or after 23vPS/13vPnC.

In study 3010, OPA responses after 13vPnC/23vPS were non-inferior to those after 23vPS for all 12 common serotypes (primary objective) and were statistically significantly greater for 6 of 12 serotypes (secondary objective). In addition, OPA responses after 13vPnC/23vPS were non-inferior to those after 23vPS/13vPnC (primary objective) and were statistically greater for 11 of the 12 common serotypes (exception serotype 14). Furthermore, OPA responses were statistically significantly greater after 13vPnC compared with 23vPS/13vPnC for all serotypes. Parallel ad hoc analyses of the proportion of subjects achieving an OPA titer ≥LLOQ supported these results, which suggest that if both vaccines are to be given sequentially, then 13vPnC should preferably be given first.

Furthermore, under the stringent conditions of 1 year dosing, comparison of responses after 13vPnC/13vPnC to those after 13vPnC alone revealed that the lower limit of the 95% CI of the GMFR (vaccination 2/ vaccination 1) was >0.5 for 9 of 13 serotypes; however, OPA GMTs for 7 of 13 serotypes were statistically significantly lower after 13vPnC/13vPnC than after 13vPnC alone. Nevertheless, an ad hoc comparison showed that the proportion of subjects achieving LLOQ was non-inferior after 13vPnC/13vPnC relative to 13vPnC alone for 11 of 13 serotypes. Similar results were observed for the comparison of 13vPnC/23vPS relative to a single dose of 13vPnC.

In conclusion, the 13vPnC vaccine elicits higher OPA responses than the 23vPS vaccine alone. Vaccination with 23vPS vaccine results in lower responses to the subsequent 13vPnC vaccine compared to vaccination with 13vPnC only. The responses to a second dose of 13vPnC are generally expected to be higher than the response to a first dose. This was not the case in this study, and therefore the possibility of hyporesponsiveness could not be entirely ruled out. The negative effect of a first dose of 23vPS vaccine is clearly more pronounced than the effect of the 13vPnC vaccine.
The results of study 3010 using repeated vaccinations in a naive population generally confirm what was demonstrated in the pivotal studies 004 and 3005. This study also confirms what was seen in study 3005, that vaccination with 23vPS vaccine followed by 13vPnC one year later results in lower responses than 13vPnC vaccine alone. However, the GMTs after the second dose were generally lower than after the first dose, regardless of what vaccine was used for first vaccination.

13vPnC and licensed TIV are immunologically compatible when administered together. The responses to the TIV were very similar between the two groups, and the responses were considered adequate, i.e the CHMP criteria for seasonal TIV were fulfilled.

Overall, the 3008 study results showed that 13vPnC may be given with the influenza vaccine, without adversely affecting pneumococcal serotype-specific IgG responses to 13vPnC or HAI responses to the antigens in the influenza vaccine. The results showed that the predefined non-inferiority criteria were fulfilled for all serotypes except 19F.

Based on the study 500 results a formulation without $AlPO_4$ may have been more appropriate, but the general safety profile of the vaccine, taking all clinical data together is not causing concern.

In cases requiring administration of both 13vPnC and 23vPS, 13vPnC should be given first. However, it should be noted that antibody levels to a subsequent dose of 13vPnC given after 13vPnC/23vPS may be impaired by the apparent negative immunologic effect of 23vPS when administered at a 1-year interval.

3.3.7. Clinical safety

Safety database

Safety data were obtained from more than 5600 adults who received at least 1 dose of 13vPnC. The same 13vPnC formulation licensed and marketed for infants was used in all 6 phase 3 adult studies.

Safety data were submitted to support the extension of the indication to include the use of 13vPnC in adults 50 years of age and older. Six primary phase 3 studies have been completed in the adult clinical development program, of which 4 studies conducted in adults not previously vaccinated (naive subjects) with the licensed 23-valent pneumococcal polysaccharide vaccine (23vPS) and 2 studies in adults who had previously received 23vPS (pre-immunized subjects).

Safety data from the 2 supportive studies (studies 6115A1-500 and 6115A1-3009) were also submitted. The 6 primary studies were conducted in the United States and in various countries in Europe. In the 6 studies, the safety populations comprise a total of 6198 (100%) subjects, of which 4213 (68.0%) were naive to 23vPS and 1985 (32.0%) were pre-immunized (Table 34)

Table 34. Number (%) of Subjects Who Received at Least 1 Dose of Study Vaccine

Study (Age per Protocol)[a] Vaccine Group (as Randomized)	Number (%) of Subjects
TOTAL[b]	6198 (100.0)
Naive Subjects	4213 (68.0)
3001 (50-59 y)	1111 (17.9)
13vPnC+TIV/placebo	551 (8.9)
Placebo+TIV/13vPnC	560 (9.0)
004	1235 (19.9)
13vPnC (50-59 y)	404 (6.5)
13vPnC (60-64 y)	417 (6.7)
23vPS (60-64 y)	414 (6.7)
3010 (60-64 y)	715 (11.5)
13vPnC/13vPnC	177 (2.9)
13vPnC/23vPS	301 (4.9)
23vPS/13vPnC	237 (3.8)
3008 (≥65 y)	1152 (18.6)
13vPnC+TIV/placebo	577 (9.3)
Placebo+TIV/13vPnC	575 (9.3)
Preimmunized Subjects	1985 (32.0)
3000 (≥68 y)	1049 (16.9)
13vPnC	1049 (16.9)
3005 (≥70 y)	936 (15.1)
13vPnC/13vPnC	463 (7.5)
23vPS/13vPnC	473 (7.6)

Abbreviation: y = years.
a. Age cohort (study 004); or age at enrollment, per protocol.
b. The numbers in this row are used as the denominators for percentages.

Overall, 49.4% of vaccinated subjects were between 50 and 64 years of age at enrolment (per protocol), and 50.6% were ≥65 years of age.

In the 6 studies, 13vPnC was administered to a total of 5667 subjects, of which 3751 (66.2%) were naive to 23vPS at the time of study entry and 1916 (33.8%) had previously received 23vPS (were pre-immunized) at the time of study entry; 23vPS was administered to a total of 1391 subjects, of which 918 (66.0%) were naive to 23vPS at the time of study entry and 473 (34.0%) had previously received 23vPS (were pre-immunized) at the time of study entry (Table 35).

Table 35. Number (%) of Subjects Vaccinated With 13vPnC or 23vPS at Any Time During the Study, by Vaccination Status

	Vaccine Group (As Administered)	
Study (Age per Protocol)[a]	13vPnC Number (%) of Subjects	23vPS Number (%) of Subjects
TOTAL[b]	5667 (100.0)	1391 (100.0)
Naive Subjects	3751 (66.2)	918 (66.0)
3001 (50-59 y)	1094 (19.3)[c]	N/A
004 (50-59 y)	404 (7.1)	N/A
004 (60-64 y)	417 (7.4)	414 (29.8)
3010 (60-64 y)	701 (12.4)[d]	504 (36.2)[d]
3008 (≥65 y)	1135 (20.0)[c]	N/A
Preimmunized Subjects	1916 (33.8)	473 (34.0)
3000 (≥68 y)	1049 (18.5)	N/A
3005 (≥70 y)	867 (15.3)[d]	473 (34.0)[d]

Abbreviations: N/A = not applicable; y = years.

a. Age cohort (study 004); or age at enrollment, per protocol.
b. The numbers in this row are used as the denominators for percentages.
c. For studies 3001 and 3008, includes subjects who received dose 1 of 13vPnC+TIV/Placebo, and subjects who received dose 2 of Placebo+TIV/13vPnC.
d. For studies 3005 and 3010, subjects who received both 13vPnC and 23vPS (administered 1 year apart) are counted once in each column, while subjects who received 2 doses of 13vPnC are counted only once for 13vPnC.

A total of 1127 subjects naive to 23vPS received 13vPnC concomitantly with TIV (trivalent influenza vaccine). When summarised by age at the time of enrolment 2616 subjects (46.2%) vaccinated with 13vPnC were between 50 and 64 years of age and 3051 (53.8%) were ≥65 years of age; 1785 (31.5%) were 65 to 74 years of age and 1266 (22.3%) were 75 years of age and over. Among the 1391 subjects vaccinated with 23vPS, 918 subjects (66.0%) were between 60 and 64 years of age and 473 (34.0%) were ≥65 years of age.

Initial and subsequent study doses of pneumococcal vaccine administered 1 year apart were evaluated in 2 studies (studies 3010 and 3005**).** In these studies, a total of 1445 subjects received vaccination 2 in a sequence of 2 pneumococcal vaccines; at study entry, 650 of these subjects were naive to 23vPS, and 795 were pre-immunized (Table 36).

Table 36. Number (%) of Subjects Who Received Vaccination 2 of a 2-Vaccination Sequence (Study 3005 and Study 3010)

	Vaccine Sequence (as Administered)		
Study (Age per Protocol)[a]	13vPnC/13vPnC	13vPnC/23vPS	23vPS/13vPnC
TOTAL[b]	551 (100.0)	267 (100.0)	627 (100.0)
Naive to 23vPS			
3010 (60-64 y)	160 (29.0)	267 (100.0)	223 (35.6)
Preimmunized with 23vPS			
3005 (≥70 y)	391 (71.0)	N/A	404 (64.4)

Abbreviations: N/A = not applicable; y = years.

a. Age at enrollment, per protocol.
b. The numbers in this row are used as the denominators for percentages.

A total of 16 subjects were withdrawn from the studies because of adverse events (AEs). Among the subjects withdrawn because of AEs, 6 had received 13vPnC, 9 had received 23vPS, and 1 had received TIV+placebo.

Sixteen (16) subjects died during the 6 primary studies, 12 (0.21%) of the 5667 subjects who had received 13vPnC, and 4 (0.29%) of the 1391 subjects who had received 23vPS. None of the deaths were considered related to study vaccine.

Patient exposure

Population

Each of the 6 primary studies enrolled adults who were within a protocol-specified age range at study entry: 50 to 59 years (study 6115A1-3001 and study 6115A1-004-cohort 2); 60 to 64 years (study 6115A1-004-cohort 1, and study 6115A1-3010); ≥65 years (study 6115A1-3008); ≥68 years (study 6115A1-3000); or ≥70 years (study 6115A1-3005). The oldest subject vaccinated was 95 years of age. In the 4 studies in 23vPS-naive subjects, previous vaccination with a registered or an investigational pneumococcal vaccine was an exclusion criterion. In the 2 studies in 23vPS-preimmunized subjects, previous doses of 23vPS received at least 3 years (study 6115A1-3000) or at least 5 years (study 6115A1-3005) prior to study entry had to be documented by the subjects.

Limitations of the Safety Database

The study population encompassing all 6 primary trials included adults ≥50 years of age. Subjects with underlying chronic medical conditions not compromising the immune system were enrolled, provided that the disease was stable, i.e. not requiring significant change in therapy or hospitalization for worsening disease for 12 weeks before receipt of study vaccine. The safety of 13vPnC has not been evaluated in immunocompromised high-risk subjects. The safety and immunogenicity of 13vPnC will be assessed in post approval studies conducted in children and adults with human immunodeficiency virus (HIV) infection, children and adults after hematopoietic stem cell transplant, and children and adults with sickle cell disease.

The size of the safety database was small to detect rare AEs occurring at a frequency lower than 0.1%. Therefore, safety data from the 84,500 subjects in the ongoing efficacy study **(**CAPITA, 6115A1-3006) will be submitted as a postmarketing commitment.

Safety Results

Analysis of Adverse Reactions

The safety of 13vPnC was evaluated on the basis of solicited AEs, including local reactions and systemic events, as well as unsolicited AEs. Data for solicited AEs were recorded daily by the study subjects for 14 days after each dose. Because of the diversity of study designs and the different ages of the populations evaluated, no integration or meta-analyses of safety data were performed. Therefore, the overview of safety is based on individual study data and, when appropriate, comparison of data across studies.

Adverse events

Solicited Adverse Events

Local Reactions

Local reactions at the injection site that occurred within 14 days after vaccination were to be recorded by subjects daily in electronic diaries (e-diaries). Information was solicited for 4 types of local reactions: *redness, swelling, pain*, and *limitation of arm movement.*

Local Reactions After an Initial Study Vaccination of 13vPnC

The percentage of subjects reporting local reactions at the injection site within 14 days after an initial study vaccination of 13vPnC is summarised in Table 37 for each of the 6 primary studies.

The 13vPnC reactogenicity is compared 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 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 13vPnC injection site after administration of 13vPnC+TIV was similar to the percentage of subjects reporting the reaction after administration of 13vPnC alone. Table 37 includes pooled data for local reactions reported after dose 1 for subjects in the 13vPnC+TIV/placebo group and after dose 2 for subjects in the placebo+TIV/13vPnC group. (For studies 3005 and 3010, the table includes data for vaccination 1 only).

Table 37. 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.

The incidence of *redness* reported after an initial study vaccination of 13vPnC 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 13vPnC.

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 possible effects of vaccination status on reactogenicity are best 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). *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%); however, this difference was not considered clinically significant.

13vPnC in 23vPS-Naive and 23vPS-Preimmunized Subjects Across Studies

Pain at the injection site was more frequent in younger than in older subjects, ranging from 69.2% to 88.8% among subjects <65 years old and from 41.7% to 51.7% among subjects ≥65 years of age. 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% in study 6115A1-004-cohort 2, 4.5% in study 6115A1-3001 - Table 37). Similarly, the incidence of limitation of arm movement was higher in younger subjects: 39.1% to 40.7% in subjects 50 to 59 years of age, 23.5% to 28.5% in 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.

Comparison of Reactions After 13vPnC in 23vPS-Naive and 23vPS-Preimmunized Subjects

The incidence of most local reactions after vaccination with 13vPnC was similar between 23vPS-naive and 23vPS-preimmunized subjects of similar age (pre-immunized adults ≥68 years of age in studies 6115A1-3000 and 6115A1-3005, and naive adults ≥65 years of age in study 6115A1-3008). The exception was *pain*, which was reported somewhat more often in pre-immunized subjects (51.0% to 51.7%) than in 23vPS-naive subjects (41.7%).

In study 6115A1-3000 all subjects enrolled had only a single prior dose of 23vPS. The incidences of local reactions in study 6115A1-3000 were similar to those in study 6115A1-3005, for which a single prior dose of 23vPS was a requirement. Overall, these results suggest that vaccination with 23vPS 3 to more than 5 years before vaccination with 13vPnC did not affect local reactogenicity observed after vaccination with 13vPnC, other than some increase in *pain* for 23vPnC-preimmunized subjects.

Comparison of Reactions After 13vPnC in 23vPS-Naive and 23vPS-Preimmunized Subjects

The incidence of most local reactions after vaccination with 13vPnC was similar between 23vPS-naive and 23vPS-pre-immunized subjects of similar age (pre-immunized adults ≥68 years of age in studies 6115A1-3000 and 6115A1-3005, and naive adults ≥65 years of age in study 6115A1-3008). The exception was *pain*, which was reported somewhat more often in pre-immunized subjects (51.0% to 51.7%) than in 23vPS-naive subjects (41.7%).

In study 6115A1-3000 all subjects enrolled had only a single prior dose of 23vPS. The incidences of local reactions in study 6115A1-3000 were similar to those in study 6115A1-3005, for which a single

prior dose of 23vPS was a requirement. Overall, these results suggest that vaccination with 23vPS 3 to more than 5 years before vaccination with 13vPnC did not affect local reactogenicity observed after vaccination with 13vPnC, other than some increase in pain for 23vPnC-preimmunized subjects.

13vPnC Compared With 23vPS in 23vPS-Naive Subjects

In subjects 60 to 64 years of age and naive to 23vPS (studies 004 and 3010), *redness, swelling*, and *limitation of arm movement* were reported at similar incidences after vaccination with 13vPnC or 23vPS. *Pain* was reported in both studies more frequently after vaccination with 13vPnC (80.1% and 69.2%) than after vaccination with 23vPS (73.4% and 58.3%).

Table 38. 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

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.

In study 004, the percentage of subjects reporting local reactions within 14 days after an initial study vaccination was slightly higher in the 13vPnC 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 38). The percentage of subjects reporting *limitation of arm movement* was similar in the 13vPnC 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 13vPnC group (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 13vPnC 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 13vPnC and 23vPS groups, respectively, for redness (12.2%, 11.2%), swelling (10.0%, 10.4%), and limitation of arm movement (23.5%, 28.2%). Pain was reported more frequently by subjects receiving 13vPnC 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.

13vPnC Compared With 23vPS in 23vPS-Preimmunized Subjects

In subjects ≥70 years of age who had previously received 1 dose of 23vPS at least 5 years before study entry (study 6115A1-3005), the incidences of redness, swelling, and limitation of arm movement were statistically significantly lower after an initial study vaccination of 13vPnC than after 23vPS. The differences between the vaccine groups were also statistically significant at each severity level (mild, moderate, severe), except for mild redness. The incidence of pain was lower after 13vPnC than after 23vPS, although the difference between the groups did not reach statistical significance (p=0.062).

The incidences reported for redness, swelling, and limitation of arm movement after 13vPnC ranged from 10.4% to 10.8%, and after 23vPS from 22.2% to 27.6%. Pain was the most frequently reported local reaction after 13vPnC (51.7%) and after 23vPS (58.5%) and was mostly mild (50.1% and 54.1%, respectively). Moderate and severe pain were reported more frequently after 23vPS (23.6% and 2.3%) than after 13vPnC (7.5% and 1.3%). 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.

13vPnC and 23vPS Administered in 2-Vaccine Sequences in 23vPS-Naïve Subjects

The reactogenicity of subsequent study vaccinations of 13vPnC or 23vPS was evaluated in naïve subjects 60 to 64 years of age (study 3010) and in pre-immunized subjects≥70 years of age (study 3005). Study 3010 evaluated the reactogenicity of a subsequent study vaccination of 13vPnC or 23vPSadministered 1 year after an initial study vaccination of 13vPnC or 23vPS in naive subjects. Subjects 60 to 64 years of age were randomized to receive vaccine sequences as follows:13vPnC/ 13vPnC, 13vPnC/23vPS, or 23vPS/13vPnC.

Comparisons Between Initial and Subsequent Vaccinations of 13vPnC or 23vPS

The incidence and severity of local reactions reported after a subsequent study vaccination (vaccination 2) were evaluated by comparing them with those reported after an initial study vaccination (vaccination 1). Comparisons were made between:

Vaccination 1		Vaccination 2	
13vPnC	and	13vPnC/13vPnC	(intragroup comparison)
13vPnC	and	23vPS/13vPnC	(intergroup comparison)
23vPS	and	13vPnC/23vPS	(intergroup comparison)

To compare the reactogenicity of an initial study vaccination of 13vPnC with the reactogenicity of a subsequent (second) vaccination of 13vPnC, data for subjects who received 2 vaccinations of 13vPnC 1 year apart (13vPnC/13vPnC) were evaluated using intragroup analysis methods.

Results of these analyses show that, among subjects who received both vaccinations, local reactions were reported at similar frequency after the initial vaccination and after the subsequent vaccination, respectively, for *redness* (14.8%, 11.5%), *swelling* (10.0%, 11.7%), *pain*(76.9%, 75.9%), and *limitation of arm movement* (26.2%, 24.6%). Most of the reactions were rated as mild, and for each type of reaction, the incidence of severe reports after each vaccination was ≤3.5%.

In study 6115A1-3010, subjects 60 to 64 years of age naive to 23vPS received an initial dose of either 13vPnC or 23vPS. Subjects who received 13vPnC were vaccinated 1 year later with either 13vPnC or 23vPS (vaccine sequences designated as 13vPnC/13vPnC or 13vPnC/23vPS, respectively); and subjects who received 23vPS were vaccinated 1 year later with 13vPnC (23vPS/13vPnC).

For each of the 4 types of local reactions, the incidence of reports after the second vaccination of 13vPnC was similar to the incidence observed after the initial vaccination of 13vPnC. *Pain* and *limitation of arm movement* were the 2 reaction types most frequently observed. After 13vPnC and 13vPnC/13vPnC, respectively, *pain* was reported by 76.9% and 75.9% of subjects, and *limitation of arm movement* was reported by 26.2% and 24.6% of subjects. *Redness* and *swelling* ranged between 10.0% and 14.8%. For each type of reaction, the incidence of severe reports after each vaccination was ≤3.5%.

The frequencies of local reactions after 23vPS/13vPnC were similar to the frequencies after 13vPnC, except for redness, which was reported for 12.2% of subjects after 13vPnC compared to 4.3% after 23vPS/13vPnC. Pain and limitation of arm movement were the 2 reaction types observed most frequently. After 13vPnC and 23vPS/13vPnC, respectively, pain was reported by 69.2% and 69.8% of subjects, and limitation of arm movement was reported by 23.5% and 18.5% of subjects. The incidence of redness and swelling ranged between 4.3% and 12.2%. For each reaction type, the incidence of severe reports after each vaccination was ≤2.3%

All 4 reaction types were reported at statistically significantly higher incidence after 13vPnC/23vPS than after 23vPS alone. Pain and limitation of arm movement were the 2 reaction types reported most frequently. After 23vPS and after 13vPnC/23vPS, respectively, pain was reported by 58.3% compared to 85.7% of subjects, and limitation of arm movement was reported by 28.2% compared to 53.4% of subjects. Likewise, redness was reported by 11.2% compared to 27.8% of subjects, and swelling was reported by 10.4% compared to 25.8% of subjects, respectively. The highest incidence of severe reports was observed for severe pain after 13vPnC/23vPS (12.9%).

After each of the 3 vaccine sequences (13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC), pain at the injection site was reported most frequently, followed by limitation of arm movement, while redness and swelling were reported at lowest incidence. For each type of local reaction, the incidence of reports was highest for the sequence 13vPnC/23vPS, followed by 13vPnC/13vPnC, and lowest for 23vPS/13vPnC. The incidence of pain, the most frequently reported local reaction, was lowest after 23vPS/13vPnC (69.8%), and highest after 13vPnC/23vPS (85.7%). Limitation of arm movement was reported at lowest incidence after 23vPS/13vPnC (18.5%) and at highest incidence after 13vPnC/23vP (53.4%). Redness and swelling were reported at lowest incidence after 23vPS/13vPnC (4.3% and 5.0%, respectively) and at highest incidence after 13vPnC/23vPS (27.8% and 25.8%, respectively). Severe reactions were most frequently reported after 13vPnC/23vPS, with 12.9% for pain and 8.1% for limitation of arm movement.

13vPnC and 23vPS Administered in 2-Vaccine Sequences in 23vPS-Preimmunized Subjects

In study 6115A1-3005, subjects ≥70 years of age pre-immunized with 1 dose of 23vPS 5 years or more prior to study entry received an initial study vaccination of either 13vPnC or 23vPS. One year later, all subjects received 1 dose of 13vPnC.

For each of the 4 types of local reactions, the incidence of reports after the second vaccination of 13vPnC (13vPnC/13vPnC) was similar to the incidence after the initial vaccination of 13vPnC. Pain was the most frequently reported local reaction after the initial dose of 13vPnC (55.0%) and after 13vPnC/13vPnC (57.4%). The incidence of redness, swelling, and limitation of arm movement ranged between 9.2% and 13.3%. For each type of local reaction, the incidence of severe reports after each vaccination was ≤1.7%.

All local reaction types were reported at similar frequency after the initial dose of 13vPnC and after 23vPS/13vPnC, except for limitation of arm movement, which was statistically significantly higher after 23vPS/13vPnC (19.9%) than after the initial vaccination of 13vPnC (10.5%). Pain was the most frequently reported local reaction, with an incidence of 51.7% after the initial vaccination of 13vPnC

and 56.6% after 23vPS/13vPnC. The incidence of redness and swelling ranged from 10.1% to 14.1%. For each type of local reaction, the incidence of severe reports after each vaccination was ≤1.7%.

For each of the 4 types of local reactions, the incidence of reports after 13vPnC/13vPnC was similar to the incidence after 23vPS/13vPnC. Pain was the most frequently reported local reaction, with 58.2% after 13vPnC/13vPnC and 56.6% after 23vPS/13vPnC. Redness, swelling, and limitation of arm movement ranged between 10.1% and 19.9%. For each type of local reaction, the incidence of severe reports after each vaccination was ≤1.8%.

13vPnC With Concomitant Administration of Trivalent Influenza Vaccine(TIV)

In subjects 50 to 59 years of age naive to 23vPS (study 6115A1-3001), for each type of local reaction, the incidence of reports after concomitant administration of 13vPnC+TIV was similar to the incidence after 13vPnC administered alone. The 2 types of local reaction reported most frequently after 13vPnC+TIV and after 13vPnC alone were pain (86.8% and 84.5%, respectively) and limitation of arm movement (35.6% and 42.5%, respectively). The incidence of redness and swelling ranged between 12.1% and 18.4%. For each type of local reaction, the incidence of severe reports after each vaccination was ≤4.8%.

In subjects ≥65 years of age naive to 23vPS (study 6115A1-3008), the incidence of each type of local reaction was similar after administration of 13vPnC+TIV and after 13vPnC administered alone. The local reaction reported most frequently after 13vPnC+TIV and after 13vPnC alone was pain (40.0% and 43.4%, respectively). The incidence of redness, swelling, and limitation of arm movement ranged between 10.2% and 16.6% after each vaccination. For each type of local reaction, the incidence of severe reports after each vaccination was ≤2.6%.

Generally, incidences for redness and swelling were similar among subjects 50 to 59 years of age (study 6115A1-3001) and among subjects ≥65 years of age (study 6115A1-3008). However, pain and limitation of arm movement were reported more frequently in the younger age group compared to the older age group. After 13vPnC+TIV and after 13vPnC alone, respectively, the incidence of pain was 86.8% and 84.5% among subjects 50 to 59 years of age, and was 40.0% and 43.4% among subjects ≥65 years of age, while limitation of arm movement was reported for 35.6% and 42.5% of subjects in the younger age group, and for 13.9% and 14.8% of subjects in the older age group. The incidence of severe pain was ≤4.8% among subjects 50 to 59 years of age and ≤2.6% among subjects ≥65 years of age. The incidence of severe limitation of arm movement was ≤3.4% in the subjects 50 to 59 years of age and ≤1.9% among subjects ≥65 years of age.

Conclusions: Local Reactions

The described local safety data can be summarised as follows:

After an Initial Vaccination of 13vPnC:

- *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% to40.7% among subjects 50 to 59 years of age; 23.5% to 28.5% among subjects 60 to6 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 13vPnC 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 13vPnC (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 13vPnC (p<0.001), while the incidence of pain was slightly higher in the 23vPS group (58.5%) than in the 13vPnCgroup (51.7%) (p=0.062).*

After a Subsequent Study Vaccination of 13vPnC 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 13vPnC 1 year apart (13vPnC/13vPnC),and in subjects who received 23vPS followed by 13vPnC 1 year later (23vPS/13vPnC), the incidence and severity of local reactions reported after the subsequent vaccination of 13vPnC were no greater than those reported after an initial study vaccination of 13vPnC; and*
- *In subjects who received 13vPnC followed by 23vPS 1 year later (13vPnC/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.*

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 13vPnC/23vPS than among those receiving 13vPnC/13vPnC or 23vPS/13vPnC; and*
- *The incidence of reports after vaccination 2 was higher in the 13vPnC/13vPnC group than in the 23vPS/13vPnC group, although the differences between the groups were significant only for redness and for swelling.*

In subjects ≥70 years of age who had received 1 dose of 23vPS at least 5 years before enrolment:

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

- *In subjects who received 2 vaccinations of 13vPnC 1 year apart (13vPnC/13vPnC) the incidence and severity of all 4 types of local reactions reported after the subsequent vaccination of 13vPnC were similar to those reported after the initial study vaccination of 13vPnC; and*
- *In subjects who received 23vPS followed by 13vPnC 1 year later (23vPS/13vPnC), the incidence and severity of redness, swelling, and pain reported after the subsequent vaccination of 13vPnC were similar to those reported after an initial study vaccination of 13vPnC, while the incidence of limitation of arm movement was statistically significantly higher after vaccination 2 of 23vPS/13vPnC (19.9%) than after the initial dose of 13vPnC (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/13vPnC group and the 13vPnC/13vPnC group.*

Concomitant Administration of 13vPnC 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 13vPnC+TIV were were similar to those after 13vPnC alone.*

Systemic Events

All reports of *fever >40°C (>104°F)* in all studies were confirmed to be e-diary data entry errors, except for 1 confirmed temperature of 104.4°F reported by 1 subject in study 6115A1-3005 after 13vPnC/13vPnC (vaccination 2). These erroneous reports are flagged as data entry errors in the SCS summary tables, but are not subtracted from the overall number of reports of "any fever". Therefore the overall incidences of *fever s*hown in the tables are somewhat higher than the actual values. To achieve a more realistic estimate for the incidence of *fever* in each study, post hoc analyses were conducted in which the erroneous values were excluded.

13vPnC in 23vPS-Naive and 23vPS-Preimmunized Subjects Across Studies

The incidence of systemic events reported within 14 days after an initial study vaccination of 13vPnC was assessed in 6 studies. The incidence of *fever* (ie, temperature ≥38°C) was similar across the studies, ranging from 1.0% (study 6115A1-3005) to 7.7% (study 6115A1-004-cohort 1, subjects 60 to 64 years of age) However, study 6115A1-004 had a large number of e-diary data entry errors. Results of the post-hoc analyses (excluding erroneous values) showed that, after in initial vaccination of 13vPnC, the incidence of *fever* ranged from 1.0% (in study 6115A1-3005) to 4.2% (study 6115A1-3010), with no apparent difference among the various age groups. All other types of systemic events were consistently reported at lower incidences in subjects ≥65 years of age than in younger subjects. Among all age groups, the systemic events reported most frequently were *fatigue, headache,* and *new generalized muscle pain.* (Table 39)

Table 39. Subjects Reporting Systemic Events 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 (%)
Systemic Event							
Any (≥38°C)	2.5	1.5	7.7	4.6	4.2	2.0	1.0
Mild (≥38°C but <38.5°C)	1.2	1.5	3.9	3.8	3.1	0.8	1.0
Moderate (≥38.5°C but <39°C)	0.8	0.0	0.6	0.8	1.0	0.0	0.0
Severe (≥39°C but ≤40°C)	0.4	0.0	0.0	0.4	0.0	0.3	0.0
Potentially life threatening (>40°C)[c]	0.0	0.0	4.4[c]	0.4[c]	0.7[c]	0.9[c]	0.0
Fatigue	51.8	63.3	63.2	50.5	28.5	34.4	34.0
Headache	50.9	65.9	54.0	49.7	24.7	26.1	23.7
Chills	24.6	19.6	23.5	19.9	9.1	7.5	7.9
Rash	9.5	14.2	16.5	8.6	6.8	8.4	7.3
Vomiting	6.1	6.9	3.9	3.1	1.7	0.9	1.7
Diarrhea	N/A	N/A	N/A	N/A	N/A	14.5	N/A
Decreased appetite	25.8	25.3	21.3	14.7	11.3	11.2	10.4
New muscle pain	59.1	61.8	56.2	46.9	23.4	25.3	36.8
Aggravated muscle pain	36.7	39.9	32.6	22.0	15.0	12.3	20.6
New joint pain	27.4	31.5	24.4	15.5	11.5	12.8	12.6
Aggravated joint pain	23.8	25.6	24.9	14.0	8.6	9.7	11.6
Use of medication to treat pain	32.8	N/A	N/A	31.3	9.9	17.0	22.0
Use of medication to treat fever	18.8	N/A	N/A	8.6	5.4	6.4	3.0

Abbreviation: N/A = not applicable; y=years.

a. For studies 3001 and 3008, data are shown for dose 2 of the Placebo+TIV/13vPnC sequence group, only.
b. For studies 3005 and 3010, data are shown for vaccination 1 (year 0) only.
c. All reports of fever >40°C after vaccination 1 were confirmed to be the result of e-diary data entry errors.

The incidence of most systemic events was similar between naive and pre-immunized subjects of similar age (naive subjects ≥65 years in study 6115A1-3008; pre-immunized subjects ≥68 years in study 6115A1-3000 and ≥70 years in study 6115A1-3005). One exception was *new muscle pain,* which was reported more frequently among pre-immunized subjects in study 6115A1-3005 (36.8%) than among naive subjects in study 6115A1-3008 (23.4%). However, the incidence in pre-immunized subjects in study 6115A1-3000 (25.3%) was similar to that in naive subjects.

13vPnC Compared With 23vPS in 23vPS-Naive Subjects

In subjects 60 to 64 years of age and naive to 23vPS, all types of systemic events, including *fever,* were reported at similar incidences after vaccination with 13vPnC or 23vPS, except *decreased*

appetite, aggravated generalized muscle pain, and *new generalized joint pain,* which were reported more frequently after 23vPS in study 6115A1-3010 (Table 40).

Table 40. 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-Value[b]
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, expressed 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.

13vPnC Compared With 23vPS in 23vPS-Preimmunized Subjects

In subjects ≥70 years of age who had previously received 1 dose of 23vPS at least 5 years before study entry, the incidence of most systemic events was similar after an initial study vaccination of 13vPnC or 23vPS, except for *fatigue, rash, new generalized muscle pain*, and *aggravated generalized muscle pain,* which were reported at statistically higher incidence after 23vPS compared with 13vPnC (table 2-14). After removing e-diary data entry errors from the analysis the incidence of fever >38°C was similar after 13vPnC (1.0%) and after 23vPS (2.3%).

13vPnC and 23vPS Administered as a 2-Vaccine Sequence in 23vPS-Naïve Subjects

Systemic events were assessed in adults 60 to 64 years of age naive to 23vPS. Subjects received an initial dose of either 13vPnC or 23vPS. 13vPnC recipients were vaccinated 1 year later with either 13vPnC or 23vPS. 23vPS recipients were vaccinated 1 year later with 13vPnC.

Comparing systemic events reported after the initial study dose of 13vPnC with those reported after the second study vaccination of 13vPnC 1 year later (13vPnC/13vPnC), all types of systemic events were reported at similar frequencies, including *fever,* which was reported in 9.1% after 13vPnC alone and 3.6% after 13vPnC/13vPnC. All occurrences of fever were either mild or moderate. The most frequently reported types of systemic events after 13vPnC and 13vPnC/13vPnC were *fatigue, headache,* and *new generalized muscle pain.*

Comparing systemic events after 13vPnC and after 23vPS/13vPnC, all types of systemic events were reported at similar frequencies, including fever, in 4.6% of subjects after 13vPnC alone and 0.9% of subjects after 23vPS/13vPnC. All occurrences of fever were either mild or moderate, except 1 case of severe fever (≥39°C but ≤40°C) after 13vPnC alone. *Medication to treat fever* was used more frequently after 23vPS/13vPnC vaccination 2 than after 13vPnC vaccination 1 (19.4% and 8.6%). The most frequently reported types of systemic events after 13vPnC and 23vPS/13vPnC were *fatigue, headache*, and *new generalized muscle pain.*

Comparing systemic events after 23vPS with those reported after 13vPnC/23vPS, most types of systemic events were reported at similar frequencies after the initial dose and after the second dose,

except for *rash,* which was reported more frequently after 13vPnC/23vPS (24.0%) than after 23vPS (13.4%) (p=0.025). *Fever* was reported in 1.6% of subjects after 23vPS alone and in 3.1% after 13vPnC/23vPS. All occurrences of fever were either mild or moderate, except 1 severe fever (≥39°C but ≤40°C) after 23vPS alone. The most frequently reported types of systemic events after 23vPS and 13vPnC/23vPS were *fatigue, headache*, and *new generalized muscle pain*.

Comparisons Between Subsequent Vaccinations of 13vPnC or 23vPS

Table 2-18 summarizes the results of analyses comparing the incidence of systemic events after subsequent vaccinations of 13vPnC or 23vPS (ie, after vaccination 2 of the 13vPnC/13vPnC, 13vPnC/23vPS, and 23vPS/13vPnC regimens). After excluding erroneous values from the analysis, *fever* was reported at similar incidence after 13vPnC/13vPnC (1.3%), 13vPnC/23vPS (3.1%), and 23vPS/13vPnC (0.9%) (p=0.514). For most types of systemic events, the incidence was highest after 13vPnC/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 frequent after 13vPnC/23vPS (p<0.001). *Fever, vomiting, decreased appetite*, and *aggravated generalized joint pain* were reported at similar incidence among the 3 groups. Pairwise comparisons showed no statistically significant differences between the 13vPnC/13vPnC and 23vPS/13vPnC groups in the incidence of any systemic events.

Comparing systemic events after the 3 vaccine sequences (13vPnC/13vPnC, 13vPnC/23vPS, 23vPS/13vPnC), the incidences for all types of systemic events were similar except for *rash,* which was highest after 13vPnC/23vPS (24%), followed by 13vPnC/13vPnC (10.5%) and 23vPS/13vPnC (8.3%); *new generalized muscle pain,* which was highest after 13vPnC/23vPS (61.2%), followed by 13vPnC/13vPnC (50%) and 23vPS/13vPnC (45%); and *aggravated generalized muscle pain*, which was highest after 13vPnC/23vPS (41.5%), followed by 23vPS/13vPnC (28.7%) and 13vPnC/13vPnC (26.6%). *Fever* was similar after all 3 sequences, with 2.5% after 13vPnC/13vPnC, 3.1% after 13vPnC/23vPS, and 0.9% after 23vPS/13vPnC. All occurrences of *fever* were either mild or moderate

13vPnC and 23vPS Administered as a 2-Vaccine Sequence in 23vPS-Preimmunized Subjects

In study 6115A1-3005, systemic events were assessed in adults ≥70 years of age pre-immunized with 23vPS at least 5 years previously. Subjects received an initial dose of either 13vPnC or 23vPS, and all subjects were vaccinated 1 year later with 13vPnC (vaccine sequences of 13vPnC/13vPnC or 23vPS/13vPnC). Comparing systemic events after the initial dose of 13vPnC and the subsequent dose of 13vPnC (13vPnC/13vPnC), all types of systemic events were reported at similar frequencies, except for *chills,* which was reported more often after 13vPnC (9.3%) than after 13vPnC/13vPnC (4.4%) (95% CI on the difference: -9.6, -0.2). *Fever* was reported by 1.7% of subjects after 13vPnC alone and by 2.2% after 13vPnC/13vPnC. After 13vPnC, all occurrences of fever were mild, while after 13vPnC/13vPnC, 1 subject reported severe fever (≥39°C but ≤40°C) and 1 subject had a confirmed report of a temperature of 40°C on day 2 after vaccination. The most frequently reported types of systemic events after both13vPnC and 13vPnC/13vPnC were *new generalized muscle pain* and *fatigue.*

Comparing systemic events after 13vPnC and after 23vPS/13vPnC, all types of systemic events were reported at similar frequencies, including *fever,* which was reported in 1% of subjects after 13vPnC alone and in 2.2% after 23vPS/13vPnC. In both groups, most cases of fever were mild. After 13vPnC/13vPnC, 1 case of severe fever was reported. Medication to treat fever was reported more frequently after 23vPS/13vPnC (7.4%) than after 13vPnC (3%). The most frequently reported types of systemic events after 13vPnC and 23vPS/13vPnC were *new generalized muscle pain* and *fatigue*.

Comparing systemic events after 13vPnC/13vPnC and 23vPS/13vPnC, all types of systemic events were reported at similar frequencies, including *fever,* which was reported in 3.5% of subjects after

13vPnC/13vPnC and in 2.2% after 23vPS/13vPnC; most reports of fever were mild or moderate. The most frequently reported types of systemic events in both study groups were *new generalized muscle pain* and *fatigue.*

13vPnC With Concomitant Administration of Trivalent Influenza Vaccine (TIV)

After concomitant administration of 13vPnC+TIV in subjects 50 to 59 years of age (study 6115A1-3005) administered alone, except for a statistically higher frequency of *headache* after13vPnC+TIV (65.9%) than after 13vPnC alone (50.9%). The most frequently observed systemic reactions (after 13vPnC+TIV and after 13vPnC alone, respectively) were *headache* (65.9% and 50.9%), *new muscle pain* (65.5% and 59.1%), and *fatigue* (58.1% and 51.8%). *Fever* was reported in 3.4% of subjects after 13vPnC+TIV and in 2.5% of subjects after 13vPnC alone, most incidences being mild or moderate

In subjects ≥65 years of age (study 6115A1-3008), several types of systemic events were reported at significantly higher incidence after concomitant administration of 13vPnC+TIV than after 13vPnC alone; these were, respectively, *fatigue* (37.4% and 28.5%), *headache* (32.6% and 24.7%), *chills* (13.8% and 9.1%), *decreased appetite* (16.9% and 11.3%), *new joint pain* (16.2% and 11.5%), and *aggravated generalized joint pain* (15.7% and 8.6%). *Fatigue, headache*, and *new muscle pain* (26.9% and 23.4%) were the most frequently reported systemic events in each vaccine group. *Fever* was reported in 5.3% of subjects after 13vPnC+TIV and 4.2% of subjects after 13vPnC alone. All occurrences of fever were mild or moderate.

After either 13vPnC+TIV and after 13vPnC alone, incidences for all types of systemic events were higher in the younger (50 to 59 years) compared with the older age group (≥65 years), except for *fever*, which was similar in both age group.

The incidence of systemic events reported after 13vPnC+TIV was also compared with the incidence after TIV + placebo (referred to hereafter as "TIV alone"). In subjects 50 to 59 years of age, most systemic events were reported at statistically significantly higher incidence after 13vPnC+TIV than after TIV alone, except for *fatigue, vomiting,* and *aggravated generalized joint pain,* which were similar in both groups. The incidence of systemic events after 13vPnC+TIV ranged from 5.3% (*vomiting)* to 65.9% (*headache*), and after TIV alone from 3.4% (*vomiting)* to 56.5% (*headache*). The most frequently reported systemic events after administration of 13vPnC+TIV and after TIV alone were, respectively, *headache* (65.9% and 56.5%), *new muscle pain* (65.5% and 37.7%), and *fatigue.*

In subjects ≥65 years of age, similar frequencies for all systemic reactions were observed after concomitant administration of 13vPnC+TIV, compared with TIV administered alone, except for *chills* (13.8% and 9.1%), *rash* (6.9% and 3.4%) and *new muscle pain* (26.9% and 16.7%), which were reported at statistically significantly higher incidence after 13vPnC+TIV than after TIV alone. The most frequently reported types of systemic events after 13vPnC+TIV and after TIV alone were, respectively, *fatigue* (37.4% and 31.9%), *headache* (32.6% and 29.7%), and *new muscle pain* (26.9% and 16.7%). *Fever* was reported at similar incidence in both groups, with 5.3% after 13vPnC+TIV and 5.0% after TIV alone. Most occurrences of fever were mild to moderate.

Conclusions: Systemic Events

The described systemic safety data can be summarised as follows:

After an Initial Study Vaccination of 13vPnC:

- *Fever* was reported at similar incidence and severity across studies, regardless of subject age.
- *With the exception of fever, all types of systemic events were, in general, reported more frequently among subjects 50 to 64 years of age than among subjects ≥65 years of age.*

- *Among subjects ≥65 years of age, the incidence of fever and other types of systemic events was, in general, similar between naive subjects and pre-immunized subjects.*

After an Initial Study Vaccination of 13vPnC or 23vPS:

In subjects 60 to 64 years of age and naive to 23vPS:

- Most types of systemic events were reported at similar incidence after administration of 13vPnC or 23vPS. In one study, the incidences of *new generalized joint pain, aggravated generalized muscle pain, decreased appetite*, and use of medication to treat *fever* were statistically significantly higher in the 23vPS group than in the 13vPnC group.
- After administration of either 13vPnC or 23vPS, the most frequently reported types of systemic events (>45% of subjects) were fatigue, headache, and new generalized muscle pain.

In pre-immunized subjects ≥70 years of age:

- Most types of systemic events were reported at similar incidence after administration of 13vPnC or 23vPS, although *fatigue, rash, new generalized muscle pain,* and *aggravated generalized muscle pain* were reported at statistically higher incidence after administration of 23vPS than after 13vPnC.
- After administration of either 13vPnC or 23vPS, the most frequently reported types of systemic events (>20% of subjects) were fatigue, headache, new generalized muscle pain, aggravated generalized muscle pain, and use of medication to treat pain.

After a Subsequent Study Vaccination of 13vPnC or 23vPS:

In naive subjects 60 to 64 years of age:

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

- When 13vPnC was administered as a subsequent study vaccination one year after an initial study vaccination of either 13vPnC (13vPnC/13vPnC) or 23vPS (23vPS/13vPnC), the incidence of each type of systemic event after vaccination 2 was similar to or lower than that observed after the initial study vaccination of 13vPnC.
- However, the use of medication to treat fever was reported at statistically significantly higher incidence after 13vPnC/13vPnC and after 23vPS/13vPnC than after the initial vaccination of 13vPnC.
- When 23vPS was administered as a subsequent study vaccination one year after an initial study vaccination of 13vPnC (13vPnC/23vPS), the incidence of each type of systemic event after vaccination 2 was similar to that observed after an initial study vaccination of 23vPS, except for rash, which was reported at statistically significantly higher incidence after 13vPnC/23vPS than after an initial vaccination of 23vPS. The incidence of the use of medication to treat pain was also statistically significantly higher after 13vPnC/23vPS than after 23vPS.

Comparison of results between subsequent study vaccinations shows that:

- After administration of vaccination 2 of 13vPnC/23vPS, 13vPnC/13vPnC, or 23vPS/13vPnC, most types of systemic events were reported at highest incidence after 13vPnC/23vPS, although differences among the groups were statistically significant only for *rash, new generalized muscle pain*, and *aggravated muscle pain,* as well as for the *use of medication to treat pain*. *Fever, vomiting, decreased appetite,* and *aggravated generalized joint pain* were reported at similar incidence among the 3 groups, as was the *use of medication to treat fever.*
- After vaccination with 13vPnC/13vPnC and 23vPS/13vPnC, pairwise comparison showed no statistically significant differences between the groups in the incidence of any systemic event.

In pre-immunized subjects ≥70 years of age:

Comparison of results between initial and subsequent study vaccinations of 13vPnC shows that:

- When 13vPnC was administered as a subsequent study vaccination one year after an initial study vaccination of either 13vPnC (13vPnC/13vPnC) or 23vPS (23vPS/13vPnC), the incidence of each type of systemic event after vaccination 2 was similar to or lower than that observed after the initial study vaccination of 13vPnC. However, the *use of medication to treat fever* was significantly higher after 23vPS/13vPnC compared to 13vPnC.

Comparison of results between subsequent study vaccinations shows that:

- After vaccination 2 of 13vPnC/13vPnC and 23vPS/13vPnC, all types of systemic events were reported at similar incidence in the 2 groups. Although the incidence of *vomiting* was statistically significantly higher after 23vPS/13vPnC than after 13vPnC/13vPnC, the actual difference in the percentage of subjects reporting the event was small (3.1% versus 0.4%) and was not considered clinically meaningful.
- After vaccination 2 of 13vPnC/13vPnC and 23vPS/13vPnC, the most frequently reported types of systemic events were fatigue, headache, new generalized muscle pain, and aggravated generalized muscle pain; and the use of medication to treat pain was also reported frequently.

After Concomitant Administration of 13vPnC and 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 administration of 13vPnC+TIV compared with 13vPnC alone or TIV alone (≤5.3% after any vaccination).
- Both in younger subjects (50 to 59 years of age) and in older subjects (≥65 years the systemic events reported most frequently after administration of 13vPnC+TIV, 13vPnC alone, or TIV alone were fatigue, headache, and new generalized muscle pain.
- Among younger subjects (50 to 59 years of age), the incidence of systemic events reported after concomitant administration of 13vPnC+TIV was similar to the incidence after 13vPnC+TIV than after TIV alone.

Unsolicited Adverse Events

AEs occurring within 1 month after vaccination (ie, from vaccination to the postvaccination visit) were summarized separately for each vaccine (ie, separately for dose 1 and dose 2 in studies **3001** and **3008,** and separately for vaccination 1 and vaccination 2 in studies **3005** and **3010**). AEs occurring from the postvaccination visit to the 6-month follow-up contact were also summarized separately for each vaccine. Statistical analyses compared the incidence of AEs between vaccine groups.

Adverse Events After 13vPnC Across Studies

The incidence of AEs reported within 1 month after an initial study vaccination with 13vPnC was similar across all 6 studies, ranging from 11.4% to 19.2%, and did not appear to be affected by subject age or 23vPS immunization status (ie, naive or prei-mmunized subjects). The overall incidence of AEs occurring after administration of 13vPnC in subjects 50 to 64 years of age (studies 004, 3001, 3010) was similar to the incidence in subjects ≥65 years of age (studies 3000, 3005, 3008). Likewise, the incidence of AEs in subjects naive to 23vPS (studies 004, 3001, 3008, 3010) was similar to the incidence in subjects who had received 23vPS at least 3 years prior to study entry (Table 41).

Across the studies, the types of AEs reported most frequently were *infections and infestations* (3.3% to 8.6% of subjects), *musculoskeletal and connective tissue disorders* (1.6% to 4.1%), *general disorders*

and *administration site conditions* (0.6% to 3.1%), *gastrointestinal disorders* (0.5% to 2.6%), and *respiratory, thoracic, and mediastinal disorders* (0.4% to 2.3%). There were no apparent differences in the incidence or types of AEs reported among the various age groups. In all studies, the AEs reported were generally the types of diseases and conditions often observed in adults in these age groups.

AEs occurring after administration of 13vPnC and considered at least possibly related to study vaccine were also reported at similar frequencies across the 6 primary studies (1.1% to 3.1% of subjects) regardless of subject age or 23vPS vaccination status. The types of AEs most often reported as related to study vaccine were *administration site conditions*.

Only serious AEs (SAEs) and newly diagnosed chronic medical conditions were to be reported at the 6-month follow-up telephone contact. In studies that enrolled subjects <65 years of age, the percentage of subjects reporting AEs at the 6-month follow-up ranged from 1.5% to 10.7%. Among older subjects, the incidence was 10.2% in study 6115A1-3000 (subjects ≥68 years) and was 17.3% in study 6115A1-3005 (subjects ≥70 years). The somewhat higher incidence of AEs observed among older subjects (especially in study 6115A1-3005) was associated with a greater variety in the types of AEs reported. Differences in AE reporting between younger subjects (50 to 64 years of age) and older subjects (≥68 years of age) were discernable within certain SOCs (eg, *cardiac disorders,* and *musculoskeletal and connective tissue disorders*, and others). These trends are consistent with the increase in the incidence of serious medical disorders and conditions associated with increasing age in the general population .

Two (2) AEs reported at the 6-month follow-up contact were considered related to study vaccine:

One case with *arthralgia, bursitis, and tendonitis*, and one case of *Guillain-Barré syndrome*.

Adverse Events Considered Related to Study Vaccine

AEs occurring after administration of an initial study vaccination of 13vPnC and considered by the investigator at least possibly related to study vaccine were reported at similar frequencies across the 6 studies (1.1% to 3.1% of subjects) regardless of subject age or 23vPS vaccination status. The types of AEs most often reported as related to study vaccine were *administration site conditions*

The incidence of AEs was similar across all 6 primary studies, ranging from 11.4% to 19.2%, and did not appear to be affected by subject age or 23vPS immunization status (ie, naive or pre-immunized subjects). The overall incidence of AEs occurring after administration of 13vPnC in studies that enrolled subjects 50 to 64 years of age (studies 004, 3001, 3010) was similar to the incidence in

studies that enrolled subjects ≥65 years of age (studies 3000, 3005, 3008). Likewise, the incidence of AEs in studies that enrolled subjects naive to 23vPS (studies 004, 3001, 3008, 3010) was similar to the incidence in studies that enrolled subjects who had received 23vPS at least 3 years prior to study entry (studies 3000 and 3005 - Table 41)

In naive subjects 60 to 64 years old and in 23vPS-preimmunized subjects ≥70 years old, the incidence of related AEs after an initial study vaccination of 13vPnC was similar to the incidence after 23vPS.

Table 41. Overview of Adverse Events Reported After an Initial or Subsequent Study Vaccination of 13vPnC (Subjects preimmunised with 23vPS study 3005)

Age group	**50 -64 years**				**≥ 65 years**		
Study Number	**3001[a]**	**004**	**004**	**3010[b]**	**3008[a]**	**3000**	**3005[b]**
Age per protocol	**50-59 y**	**50-59 y**	**60-64 y**	**60-64 y**	**≥ 65 y**	**≥ 68 y**	**≥ 70 y**
Number of subjects	**543**	**403**	**417**	**478**	**558**	**1049**	**463**
Incidence of AEs occurring within 1 Month after vaccination							
Any AEs	11.8%	11.4%	17%	19.2%	15.8%	12.1%	14.9%
Related AEs	1.8%	2.2%	1.2%	3.1%	1.1%	1.5%	1.7%
Incidence of AEs reported at the 6-month follow-up contact							
Any AEs	7.2%	1.5%	2.9%	10.7%	Not applicable	10.2%	17.3%
Related AEs	0.0%	0.0%	0.0%		Not applicable	0.2%	0.0%

a. For studies 3001 and 3008, data are shown for dose 2 of the Placebo +TIV/13vPnC sequence group only
b. For studies 3005 and 3010, data are shown for vaccination 1(year 0) only.

In both 23vPS-naive and 23vPS-preimmunized subjects, related AEs were reported at similar incidence after vaccination 2 of either 13vPnC/13vPnC or 23vPS/13vPnC (0.6% to 2.6% of subjects) When 13vPnC was administered concomitantly with TIV, related AEs were somewhat more frequent in the younger age group (50 to 59 years of age; 3.1%) than in the older age group (≥65 years of age; 1.7%). Overall, incidences of related AEs after 13vPnC+TIV were low and represented events that are commonly associated with vaccination.

The incidence of AEs and related AEs reported within 1 month after the subsequent vaccination

(vaccination 2) was similar in the 13vPnC/13vPnC and 23vPS/13vPnC groups (Table 42)

Table 42. Overview of Adverse Events Reported After Subsequent Study Vaccination of 13vPnC (Subjects preimmunised with 23vPS, > 70 years study 3005)

	13vPnC/13vPnC N= 391	23vPS/13vPnC N= 404
Incidence of AEs occurring within 1 Month after vaccination 2		
Any AEs	17.9%	16.1%
Related AEs	2.6%	1.5%
Incidence of AEs reported at the 6-month follow-up contact after vaccination 2		
Any AEs	11.0%	12.1%
Related AEs	0.0%	0.5%

There were no statistically significant differences between the regimens in the incidence of any specific type of AE (SOCs or preferred terms) The incidence of AEs reported at the 6-month follow-up contact after vaccination 2 was also similar in the 2 vaccine groups . After 13vPnC/13vPnC, the most frequently reported types of AEs at the 6-month follow-up were *neoplasms* (1.8%) and *nervous system disorders* (1.8%), and after 23vPS/13vPnC, the most frequent were *neoplasms* (1.7%) and

infections and infestations (1.7%) The incidence of AEs classified as *respiratory, thoracic, and mediastinal disorders* was significantly higher among subjects who had received 23vPS/13vPnC

(1.5%) than among subjects who had received 13vPnC/13vPnC (0.0%) (p=0.016). The respiratory AEs reported in the 23vPS/13vPnC group included *sleep apnea.*

AEs reported at the 6-month follow-up contact after vaccination were seldom considered related to study vaccine. One (1) case of *Guillain Barré syndrome* developed on day 123 after 13vPnC, and was ongoing at the 6-month follow-up contact. The other cases reported were 1 case of *cutaneous lupus erythematosus* after vaccination with 23vPS, 1 case of *injection site nodule* after 13vPnC+TIV, 1 case of erythema after 23vPS/13vPnC, and 1 case of *idiopathic thrombocytopenic purpura (ITP)* after 23vPS/13vPnC ongoing at the 6-month follow-up contact.

Serious adverse events and deaths

Deaths

During the study period, death occurred in 16 subjects in the 6 studies. Nine (9) of the 16 cases occurred in study 6115A1-3005, a study that enrolled subjects ≥70 years of age. None of the deaths was considered vaccine-related. Overall, the observed number of 16 deaths out of over 6000 subjects vaccinated is low.

Serious Adverse Events

Overall, the incidence of serious adverse events (SAEs) reported within 1 month after an initial study vaccination of 13vPnC was low, ranging between 0.2% and 1.1%, with no apparent differences among age groups or between 23vPS-naive and 23vPS-preimmunized subjects.

In both naïve and in pre-immunised subjects the incidence and type of SAEs reported within a month of vaccination with 13vPnC were similar to those reported after 23vPS.

There were no clinically important differences between the incidence and types of SAEs reported within 1 month after vaccination 2 of the vaccine sequences 13vPnC/13vPnC, 13vPnC/ 23vPS, or 23vPS/13vPnC, compared with those after initial doses of 13vPnC or 23vPS SAEs reported within 1 month after 13vPnC+TIV were similar to those reported after 13vPnC alone and after TIV alone.

After an initial vaccination of 13vPnC, 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%). Most notably, *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. There were no clinically meaningful differences between vaccine groups in the incidence or types of SAEs reported at the 6-month follow-up contacts after either initial or subsequent study vaccinations

Two (2) of the SAEs were considered by the investigator to be at least possibly related to the study vaccine. In the first case*, a 78-year-old female subject developed Guillain-Barré-syndrome on day 123 after vaccination with 13vPnC*. Other possible risk factors included vaccination with influenza vaccine on day 29 after vaccination with 13vPnC, and an infectious origin (*varicella zoster* was suspected but not confirmed) (study 3000). In the second case, *an 81-year-old male subject was diagnosed with idiopathic thrombocyto- penic purpura (ITP) 133 days after receiving vaccination 2 in the vaccination sequence 23vPS/13vPnC* (study 3005)

Withdrawals and Vaccination Discontinuations

A total of 16 subjects were withdrawn from the studies because of AEs. Among the subjects withdrawn because of AEs, 6 had received 13vPnC, 9 had received 23vPS, and 1 had received TIV+placebo. The type of AE most frequently resulting in withdrawal was cancer.

All AEs reported during the 6 adult studies were reviewed to identify any additional ADRs. Criteria included the frequency of occurrence, the finding of a statistically significant difference in incidence between the 13vPnC and 23vPS groups, and the theoretical existence of a biologic mechanism by which the AE could be causally related to 13vPnC.

ADRs Determined for 13vPnC Adult

A trend towards fewer AEs was seen in subjects who were older (≥65 years old); however, the CIOMS category for each of the events was the same as that for younger subjects. No differences in frequencies of AEs were noted whether13vPnC was given as a first or as a second dose.

In studies 004 and 3010, a direct comparison was made with 23vPS, and no major differences were seen between the 2 vaccines.

Adverse drug reactions are listed in Table 5-1 in CIOMS frequency categories:

Very common: ≥10%

Common: ≥1% and <10%

Uncommon: ≥0.1% and <1%

Rare: ≥0.01% and <0.1%

Very rare: <0.01%

Table 43. 13vPnC – Adverse Drug Reactions

Adverse Reactions		Highest Frequency Observed in 6 Primary Studies of 13vPnC in Adults 50 Years of Age and Older
Injection site erythema		Very Common (20.2%)
Injection site induration /swelling		Very Common (21.7%)
Injection site pain/tenderness		Very Common (88.8%)
Limitation of arm movement*		Very Common (40.7%)
Fever		Common (4.2%)
Decreased appetite		Very Common (25.8%)
Fatigue*		Very Common (63.3%)
Headache*		Very Common (65.9%)
Chills*		Very Common (24.6.%)
Diarrhea		Very Common (14.5%)
Vomiting		Common (6.9%)
Rash		Very Common (16.5%)
New muscle pain/aggravated muscle pain*		Very Common (61.8%)
New joint pain/aggravated joint pain*		Very Common (31.5%)
Nausea*		Uncommon (0.7%)
Lymphadenopathy localized to the region of the injection site		Uncommon (0.2%)
Hypersensitivity reaction including face edema, dyspnea, bronchospasm		Uncommon (0.2%)

*Adverse drug reactions (ADRs) that are new in the 13vPnC adult program when compared with ADRs in the 13vPnC infant program.

Conclusions: Adverse Events

The provided data can be concluded as follows:

In all studies, the AEs reported were generally the types of diseases and conditions often

observed in adults over 50 years of age.

After an Initial Study Vaccination of 13vPnC:

- The incidence of AEs occurring within approximately 1 month after vaccination was similar across all 6 primary studies, ranging from 11.4% to 19.2%, and did not appear to be affected by subject age or 23vPS immunization status (ie, in naive or pre-immunized subjects).
- The most frequently reported types of AEs were generally infections and infestations (3.3% to 8.6%) and musculoskeletal and connective tissue disorders (1.6% to 4.1%).
- Few AEs were considered related to study vaccine. Related AEs were reported for 1.1% to 3.1% of subjects, and most were administration site conditions.
- At the 6-month follow-up contact, where only serious AEs and newly diagnosed medical conditions were to be reported, the percentage of subjects reporting AEs was lower among subjects <65 years of age (1.5% to 10.7%) than among subjects ≥65 years of age (10.2% to 17.3%).

After an Initial Study Vaccination of 13vPnC or 23vPS:

In subjects 60 to 64 years of age naive to 23vPS, and in subjects ≥70 years of age who had received 23vPS at least 5 years before study entry:

- The incidence and types of AEs reported after administration of 13vPnC were, in general, similar to those observed after the administration of 23vPS, and few AEs were considered related to study vaccine.
- There were some statistically significant differences between the 13vPnC and 23vPS vaccine groups in the incidence of musculoskeletal and connective tissue disorders. However, the data were inconsistent between studies and do not suggest an increased incidence of these types of AEs after administration of 13vPnC relative to 23vPS. Further, there are no patterns suggestive of inflammatory arthritis.

After a Subsequent Study Vaccination of 13vPnC or 23vPS:

In naive subjects 60 to 64 years of age:

- The incidence and types of AEs reported after administration of 13vPnC were similar, in general, whether the vaccine was administered as an initial study vaccination or as a subsequent study vaccination 1 year after an initial study vaccination of either 13vPnC or23vPS. Similarly, the incidence and types of AEs reported after administration of 23vPS as a subsequent study vaccination 1 year after 13vPnC were generally similar to those observed after an initial study vaccination of 23vPS. There were no clinically important differences in the incidence and types of AEs between the groups compared.

In pre-immunized subjects ≥70 years of age:

- The incidence and types of AEs reported after administration of 13vPnC were similar, in general, whether the vaccine was administered as an initial vaccination or as a subsequent study vaccination 1 year after an initial study vaccination of either 13vPnC or 23vPS.

After Concomitant Administration of 13vPnC and TIV:

- 13vPnC+TIV versus 13vPnC alone: In subjects 50 to 59 years of age, the percentage of subjects reporting any adverse event within 1 month after vaccination was significantly higher after 13vPnC+TIV (16.7%) than after 13vPnC alone (11.8%) (p=0.020), while in subjects ≥65 years of age, the incidence of any AE was similar in the 2 groups. In both studies, there were no other medically important differences between the groups in the incidence and types of AEs reported after administration of 13vPnC+TIV as compared with 13vPnC alone.
- 13vPnC+TIV versus TIV alone: In both studies, the percentage of subjects reporting an adverse event within 1 month after vaccination was similar after 13vPnC+TIV and after TIV alone. In subjects ≥65 years of age, the percentage of subjects reporting any AE considered related to study vaccine was significantly higher after 13vPnC+TIV (1.7%) than after TIV alone (0.2%) (p=0.006), although the actual difference in incidence was small and not clinically significant.
- In subjects 50 to 59 years of age, the incidence of AEs classified as musculoskeletal and connective tissue disorders was significantly higher after 13vPnC+TIV (2.7%) than after TIV alone (0.9%) (p=0.022), while in subjects ≥65 years of age, the incidence of musculoskeletal AEs was similar between the groups (approximately 2% in each).
- There were no other medically important differences between the groups in the incidence and types of AEs reported after administration of 13vPnC+TIV as compared with TIV Alone

Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events

- A total of 16 subjects died during the 6 primary studies of 13vPnC: 12 (0.21%) of the5667 subjects who received 13vPnC; and 4 (0.29%) of the 1391 subjects who received23vPS. None of the deaths were considered related to study vaccine.
- The incidence of SAEs reported within approximately 1 month after vaccination with13vPnC was similar across studies, regardless of subject age, while the incidence of SAEs reported at the 6-month follow-up 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%). Most notably, cardiac/cerebrovascular events, neoplasms, respiratory disorders, and fractures occurred more frequently among subjects ≥65 years of age than among younger subjects.
- The incidence of serious AEs reported after 13vPnC was generally similar to the incidence after 23vPS.
- 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-Barre syndrome. Both of these resolved
- A total of 16 subjects were withdrawn from the studies because of adverse events: 6 had received 13vPnC, 9 had received 23vPS, and 1 had received only placebo+TIV. None of these adverse events were considered related to study vaccine.

Safety in Special Groups and Situations

Intrinsic Factors

The safety and tolerability of 13vPnC in older adults (≥65 years of age) were evaluated by examining data for 4 age subgroups (subjects 65 to 69 years of age, 70 to 74 years of age, 75 to 79 years of age,

and ≥80 years of age). In addition, the safety and tolerability of 13vPnC were evaluated separately for males and females, using data from the 2 pivotal trials (studies 004 and 3005). Finally, safety data from all studies were evaluated for subgroups of subjects who had chronic medical conditions that could potentially put them at increased risk of pneumococcal disease.

The conclusions made based upon comparison of data among studies enrolling subjects 50 to 59 years of age, 60 to 64 years of age,or ≥65 years of age are that, following vaccination with an initial study dose of 13vPnC:

- The incidence of some local reactions varied across age groups. While *redness* and *swelling* were reported at similar incidence in all 3 age groups, *pain* was reported more frequently among subjects <65 years of age than among subjects ≥65 years of age, and the incidence of *limitation of arm movement* decreased with increasing age.
- Fever was reported at similar incidence across age groups. All other types of systemic events, and the use of medications to treat pain and fever, were consistently reported at lowest incidence among subjects ≥65 years of age and at highest incidence among subjects 50 to 59 years of age.
- The incidences and types of AEs reported within approximately 1 month after study vaccination were similar across all 6 primary studies, and did not appear to be affected by subject age or 23vPS immunization status. In all studies, the AEs reported were generally consistent with the types of diseases and conditions often observed in adults in these age groups. Serious adverse events occurring within 6 months after study vaccination were reported somewhat more frequently among subjects ≥65 years of age than among younger subjects.

Local Reactions in Older Adults After Vaccination With 13vPnC

After an Initial Study Vaccination

It has already been shown that, after an initial study vaccination of 13vPnC, *redness* and *swelling* were reported at similar incidence across all studies, regardless of the protocol specified age, and generally within the range of 10% to 20%. In contrast, *pain* and *limitation of arm movement* were reported at lower frequency in studies enrolling subjects ≥65 years of age than in studies enrolling younger subjects. Among subjects ≥65 years of age, the incidence of *redness* and *swelling* was similar across the 4 age subgroups, ranging from 8.5% to 17.7% for *redness* and from 8.7% to 14.2% for *swelling*, and showing no apparent trends related to subject age.

In contrast, the percentages of subjects reporting *pain* and *limitation of arm movement* varied widely (ranging from 26.1% to 65.3% for *pain*, and from 6.2% to 18.5% for *limitation of arm movement*), although no trends associated with subject age were discernable.

After Vaccination 2 of a 2-Vaccination Sequence

Study 3005 was the only study in which subjects ≥65 years of age received 13vPnC administered as vaccination 2 in a 2-vaccination sequence. There were no subjects 65 to 69 years of age in the study.

Across the subgroups 70 to 74, 75 to 79, and ≥80 years of age, respectively, the incidence of *redness* increased with age both after 13vPnC/13vPnC (8.4%, 14.8%, and 18.8%) but was variable after 23vPS/13vPnC (12.0%, 5.5%, and 12.8%). In contrast, the incidence of *pain* decreased with increasing age after vaccination with 23vPS/13vPnC (64.7%, 52.0%, and 42.6%,respectively), and after vaccination with 13vPnC/13vPnC the incidence of *pain* was higher among subjects 70 to 74 years of age (64.0%) than among subjects 75 to 79 years of age (52.1%)or subjects ≥80 years of age (54.8%). In both vaccine groups, the percentages of subjects reporting *swelling* and *limitation of arm*

movement were variable across the 3 age subgroups, with no appreciable trends associated with subject age.

Systemic Events in Older Adults After Vaccination With 13vPnC

After an Initial Study Vaccination

After an initial study vaccination of 13vPnC, *fever* was reported at similar incidence across studies, regardless of subject age, while all other systemic events were reported at lower incidence among subjects ≥65 years of age than among younger subjects. Among subjects ≥65 years of age, the incidence of each type of systemic event, including *fever,* was generally similar across the 4 age subgroups examined, with no consistent trends toward increasing or decreasing incidence with increasing age.

After Vaccination 2 of a 2-Vaccination Sequence

In subjects ≥70 years of age (**study 3005**), after vaccination 2 of the regimens 13vPnC/13vPnC and 23vPS/13vPnC, all types of systemic events were, in general, reported at frequencies that varied across the 3 age subgroups with no apparent trends related to subject age.

Related AEs in Older Adults After Vaccination With 13vPnC

After an Initial Study Vaccination

Among subjects ≥65 years of age, in each study, related AEs occurring within 1 month after vaccination were reported for ≤ 2.6% of subjects in each of the 4 age subgroups examined. At the 6-month follow-up phone contact, related AEs were reported for only 2 subjects, who were both between 75 and 79 years of age.

After Vaccination 2 of a 2-Vaccination Sequence

In subjects ≥70 years of age (study **3005**), after vaccination 2 of the regimens 13vPnC/13vPnC and 23vPS/13vPnC, related AEs occurring within 1 month after vaccination were reported for

≤4.8% of subjects in each of the 3 age subgroups. At the 6-month follow-up phone contact, related AEs were reported for only 2 subjects.

High-Risk Populations

Adults with certain chronic medical conditions may be at increased risk of invasive pneumococcal disease (IPD), and preventive vaccination of such individuals against *S pneumoniae* is of particular importance. Each trial included immunocompetent subjects with stable underlying conditions such as *chronic cardiovascular disease*, *chronic pulmonary disease, chronic liver disease including alcoholic liver disease and alcoholism, renal disorders,* and *diabetes mellitus* that could potentially predispose them to IPD. Descriptive information regarding the safety and reactogenicity of 13vPnC among subjects in these high-risk populations is provided in this submission Safety and reactogenicity patterns were similar in these high-risk adults compared to the overall adult population.

Serious AEs in Older Adults After Vaccination With 13vPnC

After an Initial Study Vaccination

Among subjects ≥65 years of age, in each study, the incidence of serious AEs occurring within 1 month after vaccination was ≤2.0% in each of the 4 age subgroups which is similar to the incidence observed in younger subjects in **studies 004, 3001**, and **3010** (0.2% to 1.1%) At the 6-month follow-up phone contact, SAEs were reported at a slightly higher incidence among subjects ≥65 years of age

(3.9% to 5.8%) than among younger subjects (1.2% to 3.1%). In the 4 age subgroups examined, serious AEs were reported at the 6-month follow-up for between 3.4% and 6.1% of subjects in each age subgroup in each study with no trends toward increasing incidence with increasing age.

After Vaccination 2 of a 2-Vaccination Sequence

In subjects ≥70 years of age (**study 3005),** after vaccination 2 of the regimens 13vPnC/13vPnC and 23vPS/13vPnC, serious AEs occurring within 1 month after vaccination were reported for ≤2.4% of subjects in each of the 3 age subgroups represented in the study. At the 6-month follow-up, serious AEs were reported for ≤5.3% of subjects in each of the 3 age subgroups, except after administration of 23vPS/13vPnC in subjects ≥80 years of age, where the incidence of serious AEs was 9.6%.

Local Reactions

After administration of 13vPnC, the incidence of all types of local reactions tended to be higher among female subjects than among male subjects, both after an initial study vaccination of 13vPnC in naive or pre-immunized subjects and after a 2-vaccination sequence (13vPnC/13vPnC or 23vPS/13vPnC) in pre-immunized subjects.

Differences between males and females in the incidence of injection site reactions have been reported previously for a number of vaccines, including pneumococcal polysaccharide vaccine.

After an Initial Study Vaccination

After an initial study vaccination of 13vPnC in study 004, all 4 types of local reactions (*redness*, *swelling, pain,* and *limitation of arm movement)* were reported at substantially higher incidence in females than in males. Similar results were seen in study 3005 for redness, swelling, and limitation of arm movement, although the differences between the sexes were not as pronounced as in study 004. *Pain* was reported at similar rates in males and females in study 3005. Of interest, differences in reactogenicity between males and females were also observed after vaccination with 23vPS in study 3005, with all 4 types of local reactions reported at higher incidence in females than in males. In contrast, after vaccination with 23vPS in study 004, all 4 types of local reactions were reported at similar incidence in males and females

After Vaccination 2 of a 2-Vaccination Sequence

In study 3005, the incidences of all 4 types of local reactions were substantially higher in females than in males after administration of vaccination 2 in both the 13vPnC/13vPnC and 23vPS/13vPnC sequence groups .

Systemic Events

After an initial vaccination of 13vPnC in naive subjects 60 to 64 years of age (study 6115A1-004), most types of systemic events were reported more frequently among female subjects than among male subjects, except for *fever*, which was reported at similar incidence in both sexes. In contrast, after administration of 13vPnC in pre-immunized subjects ≥70 years of age (study 6115A1-3005), most types of systemic reactions were reported at similar incidence in male and female subjects.

In pre-immunized subjects, after the vaccination sequence 13vPnC/13vPnC, most systemic events were reported at similar incidence in male and female subjects. However, after 23vPS/13vPnC, *fatigue*, *headache*, *rash*, and *muscle pain* were reported at higher incidence in female subjects than in male subjects .

Adverse Events

In both naive and in pre-immunized subjects, the incidence of all AEs and related AEs reported within 1 month after an initial vaccination of 13vPnC was similar between male and female subjects In pre-immunized subjects, the incidence of all AEs and related AEs reported within 1 month after the second vaccination in a 2-vaccine sequence was similar between male and female subjects; however, at the 6-month follow-up contact, AEs were reported slightly more frequently among male subjects than among females subjects, respectively, both after 13vPnC/13vPnC (12.6% and 9.2%) and after 23vPS/13vPnC (17.3% and 6.9%). This difference was due to somewhat higher incidences of *cardiac disorders, gastrointestinal disorders*, and *musculoskeletal disorders* in male subjects.

Serious Adverse Events

In both naive and pre-immunized subjects, the incidence of SAEs reported within 1 month after an initial dose of 13vPnC was ≤1.2% in both male and female subjects, and the incidence of SAEs reported at the 6-month follow-up contact was also similar between males and females.

In pre-immunized subjects, the incidence of SAEs reported within 1 month after vaccination 2 of 13vPnC/13vPnC and 23vPS/13vPnC was similar in males and females. However, the incidence of SAEs reported at the 6-month follow-up contact was slightly more frequent in male than in females, respectively, both after 13vPnC/13vPnC (5.8%, 2.7%) and after 23vPS/13vPnC (7.4%, 3.0%), due to a higher incidence of *cardiac disorders, infections and infestations*, and *neoplasms* in male subjects.

3.3.8. Safety Conclusions

Based on the results of the 6 clinical studies, the reactogenicity profile of 13vPnC has been shown to be acceptable and comparable to 23vPS in 23vPS-naive subjects. In subjects pre-immunized with 23vPS, greater reactogenicity was observed after vaccination with 23vPS than after 13vPnC.

Overall, safety and reactogenicity data indicate that subjects naive to 23vPS can be safely vaccinated with 13vPnC. Even a second dose of 13vPnC given at a stringent 1-year interval does not increase reactogenicity (13vPnC/13vPnC). In contrast, administration of a study dose of 23vPS to adults ≥70 years of age previously immunized at least 5 years earlier with 23vPS, or administration of 13vPnC followed by 23vPS 1 year later (13vPnC/23vPS) in younger adults showed higher local reactogenicity, and an increase for some systemic events.

The common feature for each of these immunization regimens is receipt of 23vPS with its high pneumococcal polysaccharide load (25 µg for each polysaccharide) in a setting of pre-existing antibody from prior vaccination. This high polysaccharide load in the setting of prior antibody is likely to be responsible for the increased reactions seen. Higher pre-existing antibody titers have been associated with increased reactions after 23vPS whether present at the time of initial vaccination or at revaccination.

Subjects vaccinated with 23vPS followed 1 year later by 13vPnC (23vPS/13vPnC) showed an acceptable safety profile, indicating subjects vaccinated with 23vPA could be safely vaccinated with 13vPnC, even at a stringent 1-year interval, if needed. When subjects had an interval of 5 or more years between the 23vPS dose and a 13vPnC dose, the safety profile was similar or even improved compared to the 1-year interval. Overall, subjects pre-immunized with 23vPS had significantly fewer local and systemic events when vaccinated with 13vPnC compared to revaccination with 23vPS. It was also shown that pre-immunized subjects vaccinated with 13vPnC can safely receive a second dose of 13vPnC. Those revaccinated with 23vPS may also safely receive a subsequent dose of 13vPnC if needed.

The safety and immunogenicity of 13vPnC will be assessed in post approval studies conducted in children and adults with human immunodeficiency virus (HIV) infection, children and adults after hematopoietic stem cell transplant, and children and adults with sickle cell disease.

Safety data from the 84,500 subjects in the ongoing efficacy study (CAPITA, 6115A1-3006) will be provided as a postmarketing commitment.

3.4. Pharmacovigilance

3.4.1. Risk Management Plan

The EU-RMP as proposed by the MAH is quite thorough in its discussion of safety concerns and is well planned in its plan to address the safety concerns in post authorisation safety studies. The EU-RMP is well written and its presentation is in accordance with Volume 9A.

The greatest concerns with regards to risk management perhaps lie in the potential changes in the epidemiology of non-vaccine serotypes of S. pneumoniae and other organisms which cause the targeted disease outcomes of pneumonia, otitis media and meningitis. The Applicant has appropriately recognized these risks, amongst others, and has provided a foundation for risk management.

From the extensive review of epidemiology provided in the RMP, it is evident that overall rates of IPD disease have decreased in children since the introduction of 7vPnC. Furthermore, there is also evidence of a decreased rate in adults in the US, likely secondary to the effects of herd immunity. A less marked effect in adults has been seen in Europe. However, review of the serotype distribution involved in IPD, both overall and in adults, shows a decrease in coverage of both 7vPnC and 13vPnC since introduction of 7vPnC, of up to 10-15%.

Also, there is evidence presented of a decrease in hospital admissions for all pneumonia, outpatient visits for otitis media, and incidence rates of pneumococcal meningitis in children. However, there is also evidence of increasing amounts of disease caused by non vaccine serotypes and other bacterial agents, such as M. Catarrhalis and H. Influenzae.

The MAH also presented data to show that increasing ages in adults are associated with increases in outpatient treatment, hospitalisation and mortality from community acquired pneumonia.

More specific comments follow:

1) Safety specification

Important identified risks: None

Important potential risks:

Unanticipated safety signals not seen in clinical trials of 13vPnC

Vaccine failure in subjects who are fully vaccinated according to local recommendations

Important missing information:

- Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC vaccine (infants / children)
- Effectiveness of 13vPnC (adults)
- Long term vaccine effectiveness
- Potential changes in the epidemiology of non vaccine S pneumonia serotypes that may occur (infants / children)
- Safety and immunogenicity in high risk paediatric populations:

i) HIV-infected subjects
ii) Premature infants born at < 37 weeks gestational age
iii) Immunocompromised subjects including those with bone marrow transplant and sickle cell disease

- Age group > 5 to < 50 years
- Impact of 13vPnC on nasopharyngeal carriage, including monitoring replacement with non-vaccine serotypes and non-pneumococcal bacteria in the nasopharyngeal flora of children
- Safety of more than 4 doses of CRM-based pneumococcal conjugate vaccine when 13vPnC is administered for protection against the 6 additional serotypes in subjects previously vaccinated with a primary series of 7vPnC (infants / children)
- Immunogenicity of 1 booster dose of 13vPnC against the 6 additional serotypes after a primary series of 7vPnC (infants / children)
- No evidence of an association between wheezing diagnoses and vaccination was noted in postmarketing trials with 7vPnC or in clinical trials with 13vPnC; however, wheezing diagnoses will be monitored post-authorisation (infants / children)
- Paediatric transition plan
- Effect of antipyretics on immune response to vaccination (infants / children)
- Safety of more than 1 dose of 13vPnC in adults administered < 1 year apart
- Vaccine exposure during pregnancy and lactation

Safety concerns specific to the adult population include vaccine effectiveness, safety and immunogenicity in high risk adults, safety of more than 1 dose of 13vPnC administered < 1 year apart, and vaccine exposure during pregnancy and lactation.

2) Pharmacovigilance plan

From review of pharmacovigilance plan it is evident that the Applicant is attempting to address each of the safety concerns using various clinical studies.

Regarding the most serious safety concern of changing epidemiology by both non vaccine serotypes and other bacterial organisms causing the same targeted clinical diseases, which is of concern with both paediatric and adult use, the MAH has made extensive collaborations with several national agencies to perform population based surveillance as described below.

Population-based surveillance in 5 European countries is planned to be used to address the safety concerns of post approval and long-term effectiveness (IPD, pneumonia and AOM-related outcomes) and the changing epidemiology of non-vaccine serotypes. At least one of these surveillance systems, ACTIV in France, is to be used for monitoring the concern of the impact of vaccine on nasopharyngeal carriage. A synopsis of these surveillance systems was provided, and the developing protocols are anticipated during the application process. The applicant should discuss how these surveillance systems will be used to specifically address the concerns of decreased immunogenicity of 13vPnS as compared to 7vPnC and the decreased functional immune response for 4 of the additional 6 serotypes (1, 3, 5 and 19A). The safety concern of the impact of 13vPnC on nasopharyngeal carriage will be investigated through both observational surveillance after vaccine introduction (as mentioned above) and in a clinical trial, comparing isolates obtained from children receiving 7vPnS with those obtained from children receiving 13vPnC, a study which is currently ongoing in Israel.

Additional parts of the pharmacovigilance plan to address concerns for adult use are a study in HIV infected adults and clinical extension studies which will investigate safety with more than 1 dose of 13vPnC.

3) Risk minimisation

The proposal of routine risk minimisation activities addressing the safety concerns is adequate.

There are no additional risk minimisation activities recommended for its use in the adult population.

3.5. Changes to the product information

The detailed changes can be found in the final approved highlighted SmPC, Annex II and PL attached to this report.

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH:

1) Changes in section 4.1 Indication were accepted with revisions;
2) Changes in section 4.2 Posology and method of administration were accepted with revisions;
3) 4.4 Special warnings and precautions for use: update was accepted;
4) 4.5 Interaction with other medicinal products and other forms of interactions: changes were accepted with revisions
5) 4.6 Fertility, Pregnancy and lactation: changes were accepted;
6) 4.8 Undesirable effects: changes were accepted;
7) 4.9 Overdose: changes were accepted;
8) 5.1 Pharmacodynamics properties: changes in this section were accepted;
9) 5.3 Preclinical safety data: changes were accepted

The changes of the product information were also reflected in the PL. The MAH took the opportunity to update the local representatives.

3.6. Overall conclusions and benefit-risk assessment

Benefits

Beneficial effects

The currently available 23vPS vaccine has shown efficacy against invasive pneumococcal disease in elderly. Therefore this vaccine serves as an acceptable control for this indication. The MAH has chosen to compare the immune responses to Prevenar 13 and 23vPS vaccine using OPA. OPA measures functional antibodies and is considered the best available option for serological comparisons between the two vaccines. In children and infants the OPA responses were shown to correlate to protection against IPD after vaccination with the 7-valent pneumococcal conjugate vaccine. Although the clinical picture differs somewhat between children and adults, it is very likely that protection is mediated through the same mechanism, i.e. opsonising antibodies. The ad hoc expert group also concluded that it is reasonable to accept OPA responses as a surrogate marker for vaccine efficacy in IPD.

It is acknowledged that no protective threshold for prevention of invasive disease has been defined in adults, but a non-inferiority comparison is considered valid.

The immune responses as measured with OPA to the 13vPnC vaccine have been shown to be non-inferior to the responses to the 23vPS vaccine for the 12 common serotypes, and for several of these serotypes the responses were also superior. The immune response to serotype 6A, which is unique to the 13vPnC vaccine, has been shown to be similar to the responses to the other 13vPnC vaccine serotypes. Consistent results were obtained in naïve subjects 60-64 years, and ≥65 years, as well as subjects ≥70 years of age who had received 23vPS vaccine more than 5 years previously. The immune

responses to the 23vPnC vaccine in subjects 50-59 years of age were shown to be non-inferior to those in older subjects.

Thus, the demonstrated non-inferiority of the OPA responses of the 13vPnC vaccine to the 23vPS indicates that the 13vPnC vaccine also has at least the same immediate protective efficacy against invasive disease caused by the common serotypes.

A conjugate vaccine is expected to have benefits over a polysaccharide vaccine, in terms of boostability, immunological memory and generally improved immune responses, due to the T-cell dependent characteristics of the immune response. The 13vPnC vaccine has demonstrated all these characteristics in children, and fundamental differences in adults are not expected. The recently submitted data from study 6115A1-004 indicate that the 13vPnC vaccine induces immunological memory in subjects 60-64 years of age as well, while the 23vPS vaccine clearly does not. The duration of the immunological memory has been demonstrated 3-4 years after primary vaccination.

A negative effect of the 23vPS vaccine on subsequent vaccination with 13vPnC or 23vPS vaccine one year later has consistently been shown (hyporesponsiveness). Hyporesponsiveness was not seen following the administration of 13vPnC vaccine.

The study population included healthy subjects, and immunocompetent subjects with stable underlying conditions.

The immune responses to trivalent influenza vaccine administered concomitantly with the 13vPnC vaccine were very similar to the responses to influenza vaccine given alone. Likewise, the responses to the pneumococcal antigens were non-inferior with the exception of serotype 19F in study 3008, which indicates that the two vaccines may be given concomitantly.

Uncertainty in the knowledge about the beneficial effects

The protective efficacy against non-invasive disease (e.g. community acquired pneumonia) has not been clearly demonstrated for the 23vPS vaccine. The efficacy has been limited and inconsistently shown in several published clinical studies. The ad hoc expert group concluded that it will not be justifiable to claim efficacy of 13vPCV against other (non-invasive) pneumococcal infections based only on comparison of serological responses. Therefore, it is currently unknown if Prevenar 13 protects against CAP. However, a Phase 4 Clinical Trial (CAPiTA) of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease is currently ongoing, and the results are expected in December 2013.

The duration of immunity is currently not known. Data on antibody persistence is currently limited to one year, and preliminary data on immunological memory are limited to 3-4 years.

Data in high-risk immunocompromised populations is currently lacking. The clinical studies in elderly included healthy subjects and subjects who were immunocompetent with stable underlying conditions.

The relative value of improved immune responses of the 13vPnC over the broader strain coverage of the 23vPS vaccine is a very important issue. The data described previously from the USA and England and Wales demonstrates that the coverage of the 13vPnC vaccine decreased from around 70% to 50% when pneumococcal vaccination with 7vPnC was introduced in the childhood vaccination program. This is likely to be attributed to herd protection, i.e. decreased circulation of the vaccine strains. This also affects the coverage of the 23vPS vaccine, as 12 of the serotypes are common to both vaccines.

Epidemiological surveillance to ensure early detection of serotype replacement is considered of outmost importance. The MAH has committed to report the results of ongoing surveillance. Serotype

replacement has been seen as a result of childhood vaccinations, and may occur regardless of adult vaccinations.

Risks

Unfavourable effects

There are no differences in the safety profile of 13vPnC in adults and older adults as compared to that observed in the young population. Furthermore, the safety profiles of 23vPS and 13vPnC are also similar and no new or significant safety issues have been identified when comparing the two vaccines in the present study populations.

The local reactions are generally slightly higher with 13vPnC as compared with 23vPS and more pronounced in the younger group i.e. 59-64 years. The incidence is higher in males. The gender difference is not so pronounced for systemic adverse events and not considered to be of clinical relevance.

Comparatively few serious adverse events were observed in the submitted studies. One case of GBS in the older populations was described as were one case of idiopathic thrombocytopenia, one case of lupus erythematosus and a few cases of arthralgia. This may indicate activation of autoimmune disease. Adverse reactions such as rash, injection site reactions, pain, pyrexia, myalgia, arthralgia, headache and fatigue are all listed in the summary of product characteristics. One case of sleep apnoea was described at the 6 month follow-up visit (Apnoea in very premature infants (≤ 28 weeks gestation) is listed for 13vPnC.)

Uncertainty in the knowledge about the unfavourable effects

Further close monitoring of all cases of autoimmune reactions must continue. The predisposition for activation of such reactions is pronounced in the referred study population including older age groups.

The size of the safety database may be too small to detect rare AEs occurring at a frequency lower than 0.1%. For this reason, the MAH should provide safety data from the ongoing study (CAPiTA, 6115A1-3006) as a post-marketing commitment.

Balance

Importance of favourable and unfavourable effects

Invasive pneumococcal disease is an important health problem in the elderly population. The annual incidence of IPD in subjects ≥65 years is reported to be from 24 to 85 cases/100 000 population (WHO position paper: 23 valent pneumococcal polysaccharide vaccine, WER 83: 373-384, 2008). The existing 23vPS vaccine is recommended in several EU countries with varying coverage. Several clinical observational studies have documented the efficacy of the 23vPS vaccine against IPD caused by vaccine serotypes. The protection wanes over 5-10 years, and revaccination is generally not recommended with shorter intervals than 5 years due to hyporesponsiveness following vaccination.

In Europe and the United States*, S. pneumoniae* is estimated to cause approximately 30–50% of community-acquired pneumonias (CAPs) requiring hospitalization in adults.

The non-inferiority to the 23vPS vaccine is considered relevant and acceptable surrogate for protection against IPD. However, the lack of proven efficacy against non-invasive pneumococcal disease by the 23vPS vaccine makes an extrapolation of efficacy of this indication to the 13vPnC vaccine inappropriate until further data is available.

The issue of strain coverage is considered very important, and needs close epidemiological surveillance in order to continuously assess the absolute benefit of vaccinating with the 13vPnC vaccine.

The safety issues do not involve any immediate unfavourable effects or exert any negative influence on the balance between favourable and unfavourable effects.

Benefit-risk balance

The expected benefit in terms of protection against invasive pneumococcal disease clearly outweighs the risk of adverse reactions in adults 50 years and older for Prevenar 13. The benefit is expected to be smaller in subjects 50-59 years as the risk of disease is greater from 60 years of age onwards, but the balance is still positive.

For non-invasive pneumococcal disease the benefit is not considered demonstrated currently, and therefore it is not possible to conclude a positive benefit-risk balance for this indication.

The benefit of giving Prevenar13 concomitantly with the seasonal trivalent influenza vaccine also outweighs the risk of increased reactogenicity.

3.7. Discussion on the benefit-risk assessment

A conjugate vaccine is expected to elicit an immune response with all the characteristics of a T-cell dependent response, e.g. IgG response, affinity maturation of antibodies with repeated exposure, induction of immunological memory, and long lasting immunity. The responses to free polysaccharide vaccines on the other hand are generally expected to be mainly IgM, in the absence of previous immune memory, of shorter duration and no immunological memory. Therefore, a conjugate vaccine has many advantages, especially in long-term protection. The immune responses to the primary vaccination were shown to be non-inferior or superior to most serotypes in the 13vPnC vaccine compared to the 23vPS vaccine, as expected. In recently submitted preliminary data there is a strong indication of immunological memory 3-4 years following a primary vaccination with 13vPnC. In the same study the 23vPS vaccine was clearly shown not to induce immunological memory.

The 23vPS vaccine was shown to induce hyporesponsiveness to subsequent vaccination, regardless of whether 23vPS or 13vPnC vaccine is used. The 13vPnC vaccine did not elicit immune responses to a subsequent dose that were superior to the responses to the first dose, which can be expected. The responses were very similar after the second and first dose when given one years apart. Considering that this vaccine has demonstrated all characteristics of a T-cell dependent antigen in children, it is unlikely that any other effect would be seen in adults. Final data from study 6115A1-004 are requested as well as longer term follow-up.

It is very likely that protection against non-invasive disease requires higher antibody levels than what is required for invasive disease, as the antibodies must transudate to the site of infection in order to protect. Therefore it is not considered possible to conclude on efficacy against non-invasive disease based on serological bridging to the 23vPS vaccine.

The benefit-risk balance of Prevenar 13 for prevention of invasive disease caused by *S. pneumoniae* is therefore considered positive. However, it is beyond the scope of the CHMP to conclude on the relative role of Prevenar13 versus the 23-valent vaccine. Whether one or the other vaccine, or both vaccines, should be used in national programmes is the decision of national authorities.

4. Conclusion

On 22 September 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.