Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pneumococcal Polysaccharide Conjugate Vaccine 13 valent

Proprietary Product Name: Prevenar 13

Sponsor: Pfizer Australia Pty Ltd

December 2011

TGA Health Safety Regulation

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- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications, Changes to the Product Information
Decision:	Approved
Date of Decision:	28 October 2011
Active ingredient(s):	Pneumococcal polysaccharide conjugate vaccine 13 valent
Product Name(s):	Prevenar 13
Sponsor's Name and Address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form(s):	Suspension for Injection
Strength(s):	Potency is expressed in terms of the amounts of each polysaccharide in the 0.5mL dose. The vaccine contains 2.2 µg /dose of each of the serotypes, except for serotype 6B which is present at 4.4 µg/dose.
Container(s):	1mL glass syringe with latex-free rubber tip cap, sealed with a latex-free rubber stopper. The syringe presentation includes the following non-product contact components: plunger rod, backstop, and plastic rigid tip cap (PRTC) overseal.
Pack size(s):	Packs of 1 and 10
Approved Therapeutic use:	Active immunisation for the prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age. Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older. The use of Prevenar 13 should be guided by official recommendations.
Route(s) of administration:	Intramuscular injection
Dosage:	0.5 mL
ARTG Number:	158450

Product Background

Prevenar (pneumococcal polysaccharide conjugate vaccine 7-valent [7vPCV]) was initially registered in Australia in early 2001 for the active immunisation of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by Streptococcus pneumoniae. It was added to the National Immunisation

Program (NIP) for high risk children in 2001 and for all children up to 2 years of age from January 2005.

Prevenar 13 was registered in Australia for this indication in early 2010.[1] In 2011 it was announced that it will be added to the NIP and available as a three dose course for children aged 2, 4 and 6 months of age. This was rolled out in all Australian states and territories except the Northern Territory on 1 July 2011.

Clinically, the major syndromes of invasive pneumococcal disease (IPD) include pneumonia, meningitis and bacteraemia without a focus. Information from the Australian National Notifiable Diseases Surveillance System shows that the highest rates of IPD are reported in children <2 years and adults >85 years of age. Risk factors for IPD include chronic disease and their risk factors, immune deficiency (physical or functional cause), and being an Indigenous Australian.[2]

There are approximately 90 capsular antigenic types of the bacteria *Streptococcus pneumoniae* recognised to date.[2] Prevenar (7vPnC) is active against Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. Prevenar 13 (13vPnC) is active against an additional 6 serotypes, namely 1, 3, 5, 6A, 7F, and 19A.

The use of Prevenar has been associated with decreased disease caused by the pneumococcal serotypes included in the 7vPnC vaccine. However, concerns have been raised about serotype replacement and a potential for an increase in infections caused by serotypes not covered in the vaccine.

With respect to immunisation against pneumococcal disease in adults, a 23-valent pneumococcal polysaccharide vaccine (23vPPV, 23vPS) has been available since 1983. This has been available under the NIP for Indigenous Australians aged 50 years and over since 1999 and non-Indigenous Australians aged 65 years and over from January 2005.

This AusPAR describes the evaluation of an application by Pfizer Australia Pty Ltd (the sponsor) which sought to extend the indications for Prevenar 13 to include:

Active immunisation for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults aged 50 years and older.

One single 0.5 mL dose is recommended for adults aged 50 years and older.

Prevenar 13 is currently indicated for active immunisation for prevention of disease caused by *S. pneumonia* serotypes 1,3,4,5,6A, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age. This application also proposed a dosage amendment to include a recommendation for a "catch up" dose in infants who have completed their primary vaccination schedule with Prevenar (7 valent), to provide protection against the additional 6 serotypes included in Prevenar 13. Other product information changes were also proposed.

Regulatory Status

The product received initial ARTG Registration in 2010.

[1] TGA, AusPAR for Pneumococcal polysaccharide conjugate vaccine, May 2010. Available from http://www.tga.gov.au/pdf/auspar/auspar-prevenar13.pdf.

[2] Australian Technical Advisory Group on Immunisation. The Australian Immunisation Handbook, 9th Edition. Australian Government 2008. Available at http: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home

A similar application has been submitted in the European Union (EU), the USA, Switzerland and Canada. Prevenar 13 received a positive opinion in the EU on 22 September 2011 and the European Commission authorisation was granted on 24 October 2011.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Product

Included with this submission was a study on the effect of aluminium phosphate and polysorbate 80 on stability of the drug product in syringes. The clinical trial batches for the Phase I, II and early Phase III trials did not include polysorbate 80. Polysorbate 80 was included in later clinical trials as well as all commercial batches at 0.02% (w/w).

Aluminium phosphate and polysorbate 80 provided additive effects to protect against loss of antigenicity with agitation. The vaccine formulation evaluated in the initial submission for Prevenar 13 included polysorbate 80 and was evaluated at the time of the original submission.

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

Prevenar 13 is currently indicated for active immunisation for prevention of disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age. The sponsor applied to extend the indication to adults (50+ years old).

A female rabbit fertility and embryofetal development study (Good Laboratory Practice [GLP] compliant) was submitted to support use of the vaccine in human adults, in accordance with WHO and TGA-adopted EU guidelines.[3,4] Rabbits are a suitable test species as they show serotype specific immunoglobulin G (IgG) responses to vaccination with Prevenar 13.

Toxicology

Reproductive toxicity

In the rabbit fertility and embryofetal development study, vaccination 17 and 3 days prior to mating and on gestation Days 10 and 24 was shown to expose the does to antibodies throughout gestation, with antibody transfer to fetuses and pups. There were no treatment related effects on fertility, embryofetal or postnatal development. Injection site reactions were observed, as expected for an aluminium (Al) adjuvanted vaccine and were

[3] WHO Technical Report Series no. 927, 2005: Annex 1 WHO guidelines on nonclinical evaluation of vaccines.

[4] EMEA, Committee for Proprietary Medicinal Products (CPMP), 17 December 1997. Note for guidance on preclinical and pharmacological testing of vaccines (CPMP/SWP/465/95).

of a relatively low grade. Although male fertility was not investigated, the previous toxicity studies have not indicated any vaccine related effects on the male reproductive organs. The general toxicity of the vaccine has been adequately assessed in previous studies in juvenile and adult rats, and adult rabbits and monkeys.

Nonclinical Summary and Conclusions

A combined fertility and embryofetal development study (GLP compliant) was conducted in which female rabbits were administered the human intramuscular (IM) dose of the vaccine, or vehicle (adjuvant), 17 and 3 days prior to mating and on gestation Days 10 and 24. There were no treatment related effects of the vaccine or vehicle on mating, fertility, pregnancy, parturition, fetal gross external, soft tissue and skeletal alterations, and pup survival and growth. Serotype specific IgG against each of the 13 vaccine serotypes were detected in the serum of F0 does at Gestation Day (GD) 29, F1 fetuses at GD 29, and F1 pups at Post Natal Day (PND) 21 in the vaccine group.

There were no nonclinical objections to the proposed extension of indication (50+ years).

IV. Clinical Findings

Introduction

The submission included immunogenicity and safety data obtained from more than 3750 pneumococcal vaccine naïve adults ≥50 years of age and 1900 pre-immunised adults ≥ 68 years of age who received at least one dose of 13vPnC in 9 clinical trials. This application adds to the data available for the safety, immunogenicity and efficacy of 7vPnC (Prevenar) and 13vPnC (Prevenar 13) in infants and children for prevention of disease caused by serotypes of *S pneumoniae* included in the vaccine. The clinical development program was designed to support indications for 13vPnC immunisation of 23vPS naïve and 23vPS pre-immunised older adults. The context in which 13vPnC was developed includes the fact that:

- 23vPS is already licensed for prevention of pneumococcal disease in the populations studied
- 23vPS provides limited protection against IPD in older adults as demonstrated in controlled clinical trials and observational studies
- Opsonophagocytic antibody response as measured by opsonophagocytic activity (OPA) assay is the basis of this protection. The importance of OPA for protection against pneumococcal disease is well established.

The unmet medical need for an alternative pneumococcal vaccine is primarily in adults over the age of 65 years many of whom have already received 23vPS, which is thought to have limited efficacy. In the USA, the FDA agreed that the Accelerated Approval regulation (21 CFR 601.41) could be used as the mechanism for licensure of 13vPnC if it could be demonstrated to have a clear benefit in maintaining a potentially effective functional antibody response in comparison to continued use of 23vPS. The initial basis of licensure uses a surrogate for efficacy, the induction of antibacterial functional opsonophagocytic antibody (OPA). Following initial approval based on the surrogate data, further study of 13vPnC is required to confirm its effectiveness and validate the initial use of the surrogate marker. There is currently a placebo controlled effectiveness study being conducted in the Netherlands looking at its impact on projected pneumococcal disease. This trial is fully recruited and ongoing but it is not anticipated that the endpoint will be achieved until late 2012. The results from this trial will be submitted as a follow on supplement/variation when the study is complete.

Pharmacokinetics

The formulation of 13vPnC for adults is identical to the formulation of the vaccine for infants and children with which there is already extensive clinical experience. 13vPnC is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to the nontoxic variant of diphtheria toxin, CRM197 protein, as in Prevenar.

The 1x (0.5 mL) dose was chosen for trials in the adult 13vPnC program for the following reasons shown by the data in the adult study 6097A1-508:

- Absence of statistical differences in OPA response between the 1x, 2x, and 4x doses in pneumococcal vaccine naïve subjects
- Higher OPA responses after 1x conjugate vaccine compared to 23vPS for most all serotypes in common in vaccine naïve and experienced subjects,
- Statistically higher rate of reactions noted after the 4x dose.

The supportive study 6115A1-500 included a non-inferiority (NI) comparison of 13vPnC with and without aluminium phosphate (AlPO4) as a co-primary objective. The results of the study demonstrated that the presence of AlPO4 had no effect on the immunogenicity of the polysaccharide conjugates in adults. Hence, the 13vPnC formulation with AlPO4 was chosen for the adult Phase III program so that it was identical vaccine in composition to that used in the pediatric population.

No human pharmacokinetic studies were included in the submission as these are not generally required for vaccines except when new delivery systems, novel adjuvants or excipients are used. No new delivery systems or novel adjuvants are used for 13vPnC.

Efficacy

Introduction

The 13vPnC adult clinical development program was designed to address the following key hypotheses and satisfy licensing criteria for indications in pneumococcal vaccine naïve and 23vPS pre-immunised adults ≥50 years of age:

- 13vPnC is likely to provide improved immune response compared to 23vPS when administered to pneumococcal vaccine naïve adults ≥50 years of age.
- 13vPnC is the preferred choice for reimmunisation to enhance protection for adults ≥50 years of age who have been previously immunised with 23vPS.
- When possible, 13vPnC should be administered first to pneumococcal vaccine naïve adults ≥50 years of age to maximise immunologic benefit from this conjugate vaccine.
- 13vPnC can be coadministered with trivalent influenza vaccine in adults ≥50 years of age.
- The safety profile of 13vPnC is acceptable in pneumococcal vaccine naïve and pneumococcal vaccine experienced adults ≥50 years of age.

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

1. Individuals naïve to polysaccharide vaccine (23vPS) aged:

- ≥65 years
- 60-64 years
- 50-59 years

2. Individuals pre-immunised with polysaccharide vaccine (23vPS) aged:

- ≥68 years

Two pivotal non-inferiority (NI) trials were conducted in which 13vPnC response was compared to 23vPS immune response, one in naïve subjects 50-64 years of age (6115A1-004), and one in 23vPS pre-immunised subjects ≥70 years of age (6115A1-3005). The primary goal of these studies was to support 13vPnC licensure in both pneumococcal vaccine naïve and 23vPS pre-immunised populations.

A third Phase II NI trial comparing 13vPnC and 23vPS in naïve subjects ≥65 years of age was to provide supportive data (6115A1-500). The 500 study used a formulation that contained the same concentrations of conjugated serotypes but did not include 0.02% polysorbate 80 contained in the final 13vPnC formulation. This supportive study also included a comparison of 13vPnC with and without AlPO4 as a co-primary objective. The Phase II study 6115A1-500 and its 6115A1-3009 follow on study were to provide supportive data.

Study 6115A1-3010 was designed to evaluate sequential administration of 13vPnC and 23vPS in 23vPS naïve subjects 60 to 64 years of age. The primary goal of this study was to support the hypothesis that, whenever possible, 13vPnC should be given as the first pneumococcal vaccine.

Studies 6115A1-3001 (adults 50-59 years of age) and 6115A1-3008 (adults ≥65 years of age) were conducted in the USA and Europe, respectively, to demonstrate the compatibility of 13vPnC given concomitantly with influenza vaccine.

Main Clinical Studies

Treatments

13-valent Pneumococcal Conjugate Vaccine

The 13-valent pneumococcal conjugate vaccine (13vPnC) is composed of saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F individually conjugated to a nontoxic mutant form of diphtheria toxin cross reactive material 197 (CRM197). Each 0.5 mL dose contains 2.2 µg of each serotype, except for 6B, which is included at 4.4 µg. Each dose is formulated in 5.0 mM succinate and 0.85% sodium chloride (NaCl) at pH 5.8 with 0.125 mg AlPO4 and 0.02% polysorbate 80 (P80). The vaccine is prefilled into single dose syringes without preservatives.

23-valent Pneumococcal Polysaccharide Vaccine

The 23-valent pneumococcal polysaccharide vaccine (23vPS) is a licensed product (Merck and Company, Inc) that consists of a mixture of purified capsular polysaccharides from 23 types of *S pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The vaccine is formulated to contain 25 µg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine. Phenol is added as a preservative. The vaccine is a clear, colorless liquid.

Selection of Study Population

Each trial included healthy adults and immunocompetent subjects with stable underlying conditions such as cardiovascular disease, chronic pulmonary disease, renal disease and diabetes. Subjects with pre-existing stable disease were eligible.

Excluded subjects consisted of immunocompromised persons who had known or suspected immunodeficiency or who received treatment with immunosuppressive therapy. Also excluded were subjects with serious chronic disorder. Inclusion criteria were unremarkable and exclusion criteria included:

- Previous vaccination with any licensed or experimental pneumococcal vaccine.
- History of severe adverse reaction associated with a vaccine.
- Receipt of any vaccine within 30 days before study vaccination (except influenza vaccine).
- Vaccination with diphtheria containing vaccines within 6 months before study vaccine administration or anticipated receipt before study completion.
- Documented *S pneumoniae* infection within the past 5 years.

Immunogenicity measurements

For Cohort 1 and Cohort 2, blood samples for immunogenicity assessments were obtained before study vaccine administration at Visit 1 (Day 1), approximately one month after study vaccine administration and approximately one year after study vaccine administration. Blood samples were also collected for Cohort 3. Functional antibody titres for the 13 pneumococcal serotypes contained in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) were determined for all subjects for blood samples collected at baseline and one month post-vaccination using OPA assays. In addition, OPA titres were determined for blood samples collected at one year post-vaccination for randomly selected subsets of 100 subjects in Cohort 1 (100 in each vaccine group), Cohort 2 and Cohort 3 (100 in each of the 3 age subgroups). An OPA titre was defined as the interpolated reciprocal serum dilution that resulted in complement mediated killing of 50% of the bacteria in each OPA assay. The lowest titre that can be determined in OPA assays is a titre of 1:8 (limit of detection, LOD) and is the same for each serotype specific OPA assay. Serum of serotype specific polysaccharide IgG binding antibodies were determined concentrations for each of the 13 pneumococcal serotypes contained in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) using a standardized enzyme linked immunosorbent assay (ELISA). Serotype specific polysaccharide IgG concentrations were determined for all 3 blood samples (baseline, one month post-vaccination, and one year post-vaccination) for the same subsets of 100 subjects selected for the one year post-vaccination OPA analyses. 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 one month after vaccination and approximately 12 months after vaccination.

Statistical considerations

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 may have been created for the evaluation of Vaccination 1 or Vaccination 2.

Immunogenicity data were based on results of assays performed using blood samples obtained at protocol specified time points. Studies 004, 500, 3005 and 3010 had non-inferiority (NI) objectives and were powered to assess NI of immune response to

pneumococcal serotypes. In addition, studies 3001 and 3008 were also powered to assess NI of immune response to the pneumococcal serotypes and to the influenza strains in trivalent inactivated influenza vaccine (TIV), when 13vPnC was given with the concomitant influenza vaccine.

In each study, except for studies 3001 and 3008 and the formulation analysis of study 500, the primary immunogenicity endpoint for pneumococcal response was the serotype specific OPA titres measured one month after each vaccination. The immunologic comparisons for pneumococcal response varied according to the individual study. In the NI 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 titres elicited by one 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 fourfold increase (that is, seroconverters) in haemagglutination inhibition assay (HAI) titres elicited by the 3 strains in TIV (A/H1N1, A/H3N2, and B). The comparisons of interest in these two 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.

Endpoints

Analysis of immunogenicity by OPA

The primary endpoints for the 12 serotypes common to 13vPnC and 23vPS in Phase III studies were serotype specific OPA responses. Non-inferiority (NI) comparisons between experimental groups of serotype specific OPA geometric mean titres (GMTs) measured one month after vaccination were performed to meet key objectives for the 004, 3005 and 3010 trials.

NI for selected predefined comparisons was declared if the lower bound of the 2-sided 95% confidence interval (CI) for the ratio of the GMTs (geometric mean ratio [GMR]) was greater than 0.5 (twofold criterion). Statistically significantly greater responses were declared if the lower bound of the 2-sided 95% CI for the GMR was greater than 1.

In studies where subjects received two successive doses of 13vPnC, geometric mean fold rises (GMFRs) were calculated based on GMTs obtained one month after each dose. For predefined NI comparisons in this circumstance, NI was declared if the lower bound of the 2-sided 95% CI for the GMFR was >0.5 (twofold criterion). Results were also provided for these comparisons for circumstances in which the GMFR was statistically lower (upper bound of the 2-sided 95% CI was <1) or statistically higher (lower bound of the 2-sided 95% CI was >1).

For each of the 12 serotypes in common and 6A, key prespecified analyses for some studies compared the proportion of subjects achieving an OPA titre ≥ LLOQ measured one month after vaccination across experimental groups. NI for a given serotype was demonstrated if the lower bound of the 2-sided 95% CI for the difference in proportions was greater than -0.10. Statistically greater responses were declared if the lower bound of the 2-sided 95% CI for the differences in proportions was greater than 0; statistically lower responses were declared if the upper bound of the 2-sided 95% CI for the differences in proportions was less than 0.

For serotype 6A in studies 004 and 3005, the primary endpoint was the proportion of subjects exhibiting a fourfold rise in anti-6A OPA titre. For serotype 6A in studies 004 and

3005, the primary analysis compared the proportion of subjects achieving a fourfold rise in OPA titre (from before vaccination to one month after vaccination) in the 13vPnC group with the proportion in the 23vPS group. Superiority of the response for 13vPnC was declared if the lower bound of the 2-sided, 95% CI for the difference in proportions (13vPnC – 23vPS) was greater than zero.

For serotype 6A in study 6115A1-004 (secondary objective) and study 6115A1-3005 (exploratory objective), objectives were designed to demonstrate that the lower bound of the 95% CI of the proportion of subjects administered 13vPnC and achieving an anti-6A OPA titre of at least the LLOQ was 85% or higher. For serotype 6A in studies 004 and 3005, secondary analyses compared the anti-6A OPA GMT measured one month after vaccination in the 13vPnC group with the GMT in the 23vPS group. Superiority of the response to serotype 6A after 13vPnC was declared if the lower bound of the 2-sided 95% CI for the GMR (GMT 13vPnC/GMT 23vPS) was greater than 2 (twofold criterion).

In some studies (004, 3001, 500) as a supportive analysis, GMTs were also evaluated using an analysis of covariance (ANCOVA). The dependent variable was the log transformed post-vaccination OPA value. The model included current smoking status as a covariate. In addition, descriptive statistics were applied as indicated by individual objectives.

Additional immunogenicity analyses

Anti-polysaccharide IgG concentration comparisons

Serum IgG GMCs were analysed using procedures similar to those used for the evaluation of OPA GMTs.

Persistence of antibody response

OPA and IgG responses at the one year time point were assessed using descriptive statistics and graphical displays.

Reverse cumulative distribution curves

Reverse cumulative distribution curves (RCDCs) were generated for post-vaccination OPA titres and IgG concentrations.

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 fourfold increase in the HAI titre, that is, the definition of seroconversion, for each influenza strain (A/H1N1, A/H3N2, and B) one month after vaccination with TIV. The same statistical methods as used in pneumococcal NI analyses.

Geometric means

Within each vaccine group and for each antigen separately, the geometric means of the TIV antibody titres measured one 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 NI of TIV + 13vPnC relative to TIV + placebo based on GMTs.

Immunogenicity analysis methods for evaluation of concomitant administration of 13vPnC and trivalent inactivated influenza vaccine

For the 3 virus subtypes contained in trivalent inactivated influenza vaccine (TIV), the proportion of subjects achieving a fourfold increase in haemagglutination inhibition assay (HAI) titres from before vaccination to one month after vaccination was computed by

vaccine group. NI for a given virus subtype was demonstrated if the lower limit of the 2-sided 95% CI, computed, for the difference in proportions (13vPnC+TIV – TIV alone) was >-0.10. Additional *post hoc* analyses of response were performed based on guidelines for seasonal TIV from the FDA and EMA.[5,6]

Pivotal studies

The pivotal studies are 6115A1-004 and 6115A1-005.

6115A1-004: Non-inferiority trial in pneumococcal vaccine-naïve adults ≥50 years of age

Specific objectives and methods

Study 004 was a Phase III, randomized, modified double blind, active controlled, multicentre trial conducted in the United States in subjects naïve to 23vPS. It was initially planned to compare the immunogenicity, tolerability and safety of 13vPnC and 23vPS in adults 60 to 64 years of age, using a randomized, modified double blind design. Subsequently, the protocol was amended to add a cohort of subjects 50 to 59 years of age (Cohort 2) and a cohort of subjects 18 to 49 years of age (Cohort 3). Both of these groups received open label 13vPnC. This submission includes data from Cohort 1 and Cohort 2 (Figure 1). Eligible subjects in Cohort 1 were prospectively randomly assigned in a 1:1 ratio to receive 13vPnC or comparator (23vPS). Subjects in Cohort 2 and Cohort 3 were assigned an enrolment number (equivalent to a randomization number) and received 13vPnC. In study 004, for Cohort 3, enrolment was to be evenly distributed within the following 3 age ranges: 18 to 29, 30 to 39 and 40 to 49 years of age.

Figure 1: Study 6115A1-004 Design

Age	Cohort	N	Year 0	Year 1
60-64y naive	1.1	370	13vPnC	Bleed
	1.2	370	23vPS	Bleed
50-59y naive	2	370	13vPnC	Bleed
18-49y naive	3	900	13vPnC	Bleed

Objectives

The primary objectives of this study were:

- to demonstrate that immune response to 13vPnC was non-inferior (NI) to that of 23vPS for the 12 serotypes common to both vaccines, as measured by serotype specific OPA titres and;
- to demonstrate that the proportion of subjects with a fourfold increase in anti-6A OPA titre was statistically significantly greater in the 13vPnC group than in the 23vPS group.

[5] US Food and Drug Administration. Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. Updated April 30, 2009. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm.

[6] EMEA, Committee for Proprietary Medicinal Products (CPMP), 12 March 1997. Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96); available at http://www.emea.europa.eu/pdfs/human/bwp/021496en.pdf.

Subjects (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.

Blinding

This study used a modified double blind design for Cohort 1. Cohort 2 and Cohort 3 were evaluated using an open label design. The term "modified double blind" means that the study staff dispensing and administering the vaccine were unblinded but all other study personnel were blinded, as well as the subject.

Selection of vaccination regimen

Each subject in Cohort 1 was to receive one dose of either 13vPnC or 23vPS and each subject in Cohort 2 and Cohort 3 was to receive one dose of 13vPnC.

Results

Cohort 1: adults 60 to 64 years of age

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. There was lower proportion of males to females, particularly in the 23vPS group (61.2% female, 38.8% male) when compared with the 13vPnC group (53.5% female, 46.5% male).

Results revealed 13vPnC to be as immunogenic as 23vPS for the 12 serotypes in common contained in 13vPnC as measured by serotype specific OPA titres one month after vaccination (first of two co-primary objectives). OPA response after 13vPnC was NI to the response after 23vPS for the 12 serotypes in common when administered to pneumococcal vaccine naïve adults 60 to 64 years of age. The serotype specific geometric mean ratios (GMRs) ranged from 0.9 for serotype 14 to 5.2 for serotype 23F and the lower bounds of the 2-sided 95% CI for the GMR exceeded 0.5 for all 12 serotypes in common. The proportion of subjects in the evaluable population with a fourfold increase in OPA titre for serotype 6A was significantly higher in the 13vPnC group (88.5%) than in the 23vPS group (49.3%). In the evaluable immunogenicity population, the lower limit of the 95% CI for GMR (13vPnC GMT/23vPS GMT) was 8.63. OPA GMTs were also evaluated in a supportive analysis using an ANCOVA model with smoking status included as a covariate. These results were consistent with the unadjusted analysis. The proportion of subjects achieving an anti-6A OPA titre ≥ LLOQ was 95.8% (93.3, 97.5). The proportion of subjects achieving an OPA titre ≥LLOQ to the 12 serotypes in common contained in 13vPnC in response to 13vPnC is NI to the proportion of subjects achieving an OPA titre ≥LLOQ in response to 23vPS measured one month after vaccination (secondary objective). The secondary NI objective was met for all of the 12 serotypes in common. The difference in proportions (13vPnC – 23vPS) of subjects achieving an OPA titre ≥ LLOQ one month after vaccination ranged from −0.9% for serotype 14 to 23.2% for serotype 23F and the lower limit of the 95% CI for the difference in proportions (13vPnC – 23vPS) was >-10% for all serotypes. Notably, for 7 of the 12 serotypes in common, the lower bounds of the 95% CIs exceeded 1.0 for the difference in the proportion of responders (13vPnC - 23vPS) achieving an OPA titre ≥ LLOQ meaning that 13vPnC was as immunogenic as 23vPS for the 12 serotypes in common contained in 13vPnC as measured by serotype specific IgG antibody concentrations obtained from serum collected one month after vaccination in a subset of 100 subjects (exploratory objective). The lower limit of the 95% CI for the GMR (13vPnC GMC/23vPS GMC) was >0.5 for all serotypes except serotype 14 (GMR 0.73, 95%

CI: 0.46, 1.16), indicating that this objective was satisfied for 11 of 12 serotypes and was just missed for serotype 14. GMRs ranged from 0.73 for serotype 14 to 2.05 for serotype 18C.

Persistence of antibody by IgG and OPA was assessed in a subset of subjects one year after vaccination (exploratory objective). OPA GMTs for all serotypes in both vaccine groups were generally lower at one year after vaccination than at one month after vaccination but were higher at one year after vaccination than at baseline, before vaccination. Serotype specific IgG responses revealed a similar pattern. For 8 serotypes in common (serotypes 1, 4, 6B, 7F, 9V, 18C, 19A, 23F) OPA titres one month after vaccination were statistically significantly greater after 13vPnC than after 23vPS and point estimates of titres remained higher in the 13vPnC group compared with the 23vPS group at one year (overlapping 95% CIs) for serotypes 1, 4, 6B, 7F, 18C and 23F; there were minimal differences in OPA titres for serotypes 9V and 19A. IgG responses revealed similar results.

Summary of immunogenicity results for Cohort 1

All primary and secondary objectives were achieved. OPA responses after 13vPnC were NI for all serotypes and statistically greater for 8 serotypes in common in comparison to responses after 23vPS. Immune responses to serotype 6A were statistically greater after 13vPnC than after 23vPS by all protocol defined measures. Antibody concentrations at one year after vaccination were generally maintained at higher levels after 13vPnC than after 23vPS.

Cohort 2: adults 50 to 59 years of age

The immune response to the 13 serotypes in 13vPnC in the 50 to 59 year old age group is NI to the immune response to 13vPnC in the 60 to 64 year old age group as measured by serotype specific OPA titres one month after vaccination for all serotypes (primary objective in 50 to 59 year old age group). The serotype specific GMRs ranged from 1.0 for serotype 3 to 1.7 for serotype 6A. The protocol did not pre-specify a superiority analysis but using the same criterion as in Cohort 1, the immune response one month after vaccination in Cohort 2 was statistically significantly higher than the response among subjects receiving 13vPnC in Cohort 1 for 9 serotypes: 1, 4, 5, 6A, 6B, 7F, 9V, 14 and 19A. For each of the 13 serotypes in 13vPnC, the proportion of subjects achieving a serotype specific OPA titre ≥LLOQ in the 50 to 59 year old age group (Cohort 2) is NI to the proportion of subjects achieving an OPA titre ≥LLOQ in the 60 to 64 year old age group (Cohort 1) measured one month after vaccination (secondary objective). The difference in proportions (Cohort 2 – Cohort 1) ranged from -0.9% for serotype 5 to 4.4% for serotype 7F and the lower limit of the 95% CI for the difference in proportions was >10% for each of the 13 serotypes. 13vPnC in the 50 to 59 year old age group is as immunogenic as 13vPnC in the 60 to 64 year old age group as measured by serotype specific IgG concentrations obtained one month after vaccination in a subset of 100 subjects (exploratory objective). Reverse cumulative distribution curves (RCDCs) for IgG responses one month after vaccination with 13vPnC in subjects 50 to 59 years of age were almost uniformly higher than those in the 60 to 64 year old age group, except for serotypes 3, 9V and 18C, for which the curves were similar. Persistence of antibody in the 50 to 59 year old age group by IgG and OPA was assessed in a subset of subjects one year after vaccination (exploratory objective). OPA GMTs for all serotypes were generally lower at one year after vaccination than at one month after vaccination but higher at one year after vaccination than at pre-vaccination. Point estimates for one year OPA values were higher for all serotypes in Cohort 2 compared to Cohort 1 (non-overlapping 95% CIs for serotypes 4, 6B, 9V, 14, 19A), except for serotype 3 for which curves showed little separation.

Summary of immunogenicity results for Cohort 2

Both the primary objective and secondary objective for Cohort 2 were achieved. 13vPnC responses in subjects 50 to 59 years of age were NI for all serotypes and statistically significantly greater for 9 serotypes in subjects 50 to 59 years of age (Cohort 2) than in subjects 60 to 64 years of age (Cohort 1, 13vPnC group). Antibody levels generally remained higher at one year after 13vPnC in subjects 50 to 59 years of age compared with those 60 to 64 years of age and in some instances the relative difference in point estimates increased, compared to one month differences.

Overall summary of immunogenicity results

All primary and secondary objectives were achieved for subjects in both cohorts in this study (Table 1).

Table 1: OPA GMTs in adults aged 60-64 years given Prevenar 13 or 23vPS and in adults aged 50-59 years given Prevenar 13[a,b,c]

	Prevenar 13 50-59 Years N=350-384	Prevenar 13 60-64 Years N=359-404	PPSV23 60-64 Years N=367-402	Prevenar 13, 50-59 Relative to 60-64 Years		Prevenar 13 Relative to PPSV23, 60-64 Years	
Serotype	GMT	GMT	GMT	GM Ratio	(95% CI)	GM Ratio	(95% CI)
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6A†	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)

a Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
b Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
c For serotype 6A †, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR being greater than 2.

In both cohorts, 13vPnC was at least as immunogenic as 23vPS for all 12 serotypes in common and was statistically significantly more immunogenic than 23vPS for the majority of serotypes. Antibody levels at one month and one year after vaccination were consistently higher after 13vPnC than antibody levels at the same time points after 23vPS.

Pivotal study 6115A1-3005: Non-inferiority trial in 23vPS pre-immunised adults ≥70 years of age

Study 3005 was a Phase III, randomized, modified double blind, active control, multicentre 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 enrollment. The primary objectives of the study were:

- to demonstrate that OPA response to 13vPnC is non-inferior (NI) to that of 23vPS when measured one month after the initial vaccination; and

- to demonstrate that the proportion of subjects achieving a fourfold rise in anti-6A OPA titre is statistically significantly greater in the 13vPnC group than in the 23vPS group, when measured one month after Vaccination 1.

Objectives and methods

The study was designed as a parallel group study in which 938 subjects were randomly assigned in a 1:1 ratio to one of two vaccine groups: 13vPnC (n= 464) or 23vPS (n=474). All subjects received a dose of 13vPnC one year after the initial dose. The 3005 study evaluated the safety, tolerability and immunogenicity data of 13vPnC administered as a two dose sequence over 12 months (13vPnC in Year 0 and 13vPnC in Year 1) compared to a two dose sequence of 23vPS in Year 0 followed by 13vPnC in Year 1 in healthy adults ≥70 years of age immunised with 23vPS at least 5 years earlier. Revaccination with 13vPnC at a one year interval was chosen to provide stringent conditions to detect the potential impact of either 13vPnC or 23vPS on subsequent immune response to 13vPnC administered one year later. The design of the 3005 study is shown in Figure 2.

Figure 2: Study 6115A1-3005 Design

Subjects	Group	N	Year 0	Year 1
Prior PS ≥ 5years	1	462	13vPnC	13vPnC
	2	462	23vPS	13vPnC

Results

The evaluable immunogenicity population for Vaccination 1 included 93.7% subjects and for Vaccination 2 included 79.4% subjects. The all available immunogenicity population for Vaccination 1 included 99.8% subjects and for Vaccination 2 included 85.0% subjects. The two vaccine groups were similar with respect to sex, race and age at vaccination for both Vaccination 1 and Vaccination 2. The same NI criterion for OPA GMTs was used as in 3004.

Study 6115A1-3005 met all primary and secondary objectives. 13vPnC is as immunogenic as 23vPS for the 12 serotypes in common contained in 13vPnC as measured by serotype specific OPA titres one month after initial study vaccination (Year 0) (first of two co-primary objectives). OPA response after 13vPnC was NI to the response after 23vPS for the 12 serotypes in common when administered to adults ≥70 years of age who had received 23vPS at least 5 years earlier. GMTs ranged from 55 for serotype 3 to 1261 for serotype 6B after 13vPnC and from 36 for serotype 5 to 481 for serotype 18C after 23vPS in the evaluable immunogenicity population. The serotype specific GMRs ranged from 1.0 for serotype 14 to 3.7 for serotype 23F and the lower bounds of the 2-sided 95% CIs exceeded 0.5 for all 12 serotypes in common (lowest value 0.73 for serotype 14). The proportion of subjects receiving 13vPnC and exhibiting a fourfold rise in the serotype 6A OPA titre is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same fourfold rise, measured one month after initial study vaccination (Year 0) (second of two co-primary objectives). The proportion of subjects with a fourfold increase in OPA to 6A was significantly higher in the 13vPnC group (71.1%) than in the 23vPS group (27.3%) and the lower limit of the 95% CI for the difference in proportions of subjects (13vPnC – 23vPS) of 37.4% was >0.

Year 0 secondary objectives and results

13vPnC is statistically significantly more immunogenic than 23vPS for some of the 12 serotypes in common contained in 13vPnC as measured by serotype specific OPA titres one month after initial study vaccination (secondary objectives) as shown in Table 2.

Table 2: OPA GMTs in pneumococcal polysaccharide (PPSV23) vaccinated adults aged ≥ 70 years given either Prevenar 13 or PPSV23[a,b,c]

	Prevenar 13 N=400-426	PPSV23 N=395-445	Prevenar OPA GMT Titers Relative to PPSV23	
Serotype	OPA GMT	OPA GMT	Ratio	(95% CI)
1	81	55	1.5	(1.17 , 1.88)
3	55	49	1.1	(0.91 , 1.35)
4	545	203	2.7	(1.93 , 3.74)
5	72	36	2.0	(1.55 , 2.63)
6A†	903	94	9.6	(7.00 , 13.26)
6B	1261	417	3.0	(2.21 , 4.13)
7F	245	160	1.5	(1.07 , 2.18)
9V	181	90	2.0	(1.36 , 2.97)
14	280	285	1.0	(0.73 , 1.33)
18C	907	481	1.9	(1.42 , 2.50)
19A	354	200	1.8	(1.43 , 2.20)
19F	333	214	1.6	(1.17 , 2.06)
23F	158	43	3.7	(2.69 , 5.09)

a Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
b Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
c For serotype 6A †, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GM ratio greater than 2.

For the evaluable population, the lower limit of the 2-sided 95% CI for the GMR (13vPnC GMT/23vPS GMT) was >1 for 10 of the 12 serotypes in common: 1, 4, 5, 6B, 7F, 9V, 18C, 19A, 19F and 23F. RCDCs revealed that OPA values after 13vPnC, to varying degrees, were higher than the responses to 23vPS across the full range of antibody titres for 11 of 13 serotypes with the exceptions of 3 and 14 for which curves overlapped. The anti-6A OPA titre in the 13vPnC recipients is statistically significantly greater than the anti 6A titre in 23vPS recipients measured one month after initial study vaccination (secondary objective). For serotype 6A, the GMR (13vPnC GMT/23vPS GMT) was 9.6 (95% CI: 7.00, 13.26) and satisfied the criterion that the lower limit of the 2-sided 95% CI for the GMR was >2.

Year 1 secondary objectives and results

The immune response to a second dose of 13vPnC administered one year after an initial study dose of 13vPnC is NI to the immune response to the initial study dose of 13vPnC as measured by serotype specific OPA titres obtained one month after vaccination (secondary objective). GMTs ranged from 55 for serotype 3 to 1358 for serotype 6B after the first dose and from 55 for serotype 3 to 1590 for serotype 6B after the second dose of 13vPnC. The serotype specific GMRs ranged from 0.8 for serotypes 4, 5 and 7F to 1.9 for serotype 23F, and the lower bound of the 2-sided 95% CI exceeded 0.5 for all 13 serotypes (lowest value 0.65 for 7F). Although not a pre-defined objective, OPA responses to a second dose of 13vPnC were statistically significantly greater than the immune responses to an initial 13vPnC dose for serotypes 6A, 6B and 23F; the lower limit of the 2-sided 95% CI for the GMR was >1 for each of these serotypes (1.03, 1.02 and 1.60, respectively. OPA responses to 13vPnC/13vPnC were marginally lower compared to those after 13vPnC for serotypes 4 and 5 (upper limit of 95% CI <1; 0.92 and 0.94, respectively). RCDCs reveal that for most serotypes, the 13vPnC/13vPnC curves were similar to the 13vPnC curves. The statistically greater immune response after 13vPnC compared to 23vPS observed after the first dose was maintained after a second dose of 13vPnC one year later.

The immune response to a second dose of 13vPnC administered one year after an initial study dose of 13vPnC is NI to the immune response to 23vPS (Year 0) for the 12 serotypes in common contained in the 13vPnC as measured by serotype specific OPA titres obtained one month after vaccination (secondary objective). Although not a pre-defined objective, OPA response to a second dose of 13vPnC was statistically significantly greater than the immune response to an initial study dose of 23vPS for 9 of 12 serotypes in common, excluding serotypes 3, 7F and 14. RCDCs reveal that the proportions of 13vPnC/13vPnC responders were higher than those for 23vPS up to an antibody titre of at least 500 for all serotypes except serotypes 3, 7F and 14 for which the curves converge beginning at low OPA titre.

The anti–serotype 6A titre in recipients of a second dose of 13vPnC administered one year after the initial study dose of 13vPnC is statistically significantly greater than the anti–serotype 6A titre in recipients of an initial study dose of 23vPS (Year 0), measured one month after vaccination (secondary objective). The second 13vPnC study dose was statistically significantly more immunogenic than the Year 0 23vPS dose for serotype 6A, as measured by the IgG.

Year 0 exploratory objectives and results

The proportion of subjects achieving an OPA titre of at least the serotype specific LLOQ to the 12 serotypes in common contained in 13vPnC in response to 13vPnC is NI to the proportion of subjects achieving an OPA titre of at least the serotype specific LLOQ in response to 23vPS measured one month after initial vaccination (exploratory objective). The difference in proportions (13vPnC – 23vPS) of subjects achieving an OPA titre ≥ LLOQ one month after vaccination ranged from 1.0% for serotype 14 to 21.3% for serotype 23F and the lower limit of the 95% CI for the difference in proportions (13vPnC – 23vPS) was >-10% for all 12 serotypes in common. For 9 of the 12 serotypes in common (exceptions 3, 14, 19F), the lower limit of the 95% CI exceeded 0 for the difference in the proportion of responders (13vPnC - 23vPS) achieving an OPA titre ≥ LLOQ. The lower bound of the 95% CI on the proportion of subjects administered 13vPnC and achieving an anti-serotype 6A OPA titre of at least the LLOQ one month after initial vaccination is 85% or higher (exploratory objective). The proportion of subjects with an anti-serotype 6A OPA titre ≥ LLOQ was 89.8% (95% CI: 86.5%, 92.5%). The proportion of subjects receiving 13vPnC and exhibiting an anti–serotype 6A OPA response of at least the LLOQ is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same response when measured one month after initial vaccination (exploratory objective). The difference in the proportion of subjects achieving an OPA titre ≥ LLOQ in the 13vPnC group compared to the 23vPS group was 24.7% (95% CI: 19.3, 30.1) (that is, the lower limit of the 95% CI for the difference in proportions (13vPnC - 23vPS) was >0.

Year 1 exploratory objectives and results

The immune response to a second dose of 13vPnC administered one year after the initial study dose of 13vPnC is statistically significantly greater than the immune response to a study dose of 13vPnC administered one year after the initial study dose of 23vPS for 11 of 12 serotypes, as measured by serotype specific OPA titres obtained one month after vaccination (exploratory objective). For the evaluable population, the lower limit of the 2-sided 95% CI for the GMR (13vPnC/13vPnC GMT versus 23vPS/13vPnC GMT) was >1 for 11 of the 12 serotypes in common (exception serotype 14; GMR 1.2, 95% CI: 0.89, 1.68). RCDCs reveal OPA responses that are greater for all serotypes after 13vPnC/13vPnC compared to 23vPS/13vPnC throughout most of the OPA range. OPA responses to a dose of 13vPnC after 23vPS were statistically significantly lower than the immune response to an initial 13vPnC dose for all 13 serotypes. RCDCs revealed that the curves for 13vPnC were higher than those for 23vPS/13vPnC across a wide range of antibody titres for 11 of

13 serotypes (all except serotypes 6A and 19A, which were convergent at low OPA titres). When second dose pre-immunisation OPA GMTs are plotted against second Dose 13vPnC post-immunisation OPA GMTs, responses in subjects who received an initial dose of 13vPnC trend higher than responses in those who received 23vPS for the same pre-vaccination antibody titre for 8/12 common serotypes (1,3, 6b, 7F, 9V, 18C, 19F, 23F) at the lower end of pre-immunisation OPA range. This result is most prominent in subjects within the first quartile of pre-immunisation titres at the time of the second dose, that is, those most likely to remain susceptible to pneumococcal infection one year after Dose 1; for 13 of 13 serotypes, point estimate OPA GMFRs to a second 13vPnC dose were higher in those who received 13vPnC as a first dose compared to those who received a first study dose of 23vPS, and the lower limits of the 95% CI for the GMR were >1 for 6 of 13.

Overall immunogenicity results

All primary and secondary objectives were achieved in study 6115A1-3005 for both the first and second years of the study. In adults ≥70 years of age immunised at least 5 years earlier with 23vPS, 13vPnC immune response is NI to 23vPS for the 12 serotypes in common as measured by GMR and 13vPnC is statistically significantly more immunogenic than 23vPS for most of the 12 serotypes in common when measured by GMRs or proportion of responders. For most comparisons in pre-immunised elderly after a single dose of 13vPnC or 23vPS, OPA titres are higher throughout the full range of OPA responses; OPA response to serotype 6A after 13vPnC was consistently greater than that after 23vPS and all serotype 6A study objectives were achieved. The immune response to a second dose of 13vPnC administered one year after an initial study dose of 13vPnC in comparison to the OPA response to the initial study dose of 13vPnC met the pre-specified NI criteria for all 13 serotypes. The immune response to a second dose of 13vPnC administered one year after an initial study dose of 13vPnC is NI to the immune response to 23vPS (Year 0) and statistically greater for 9 of 12 serotypes in common. In contrast, OPA responses to a dose of 13vPnC one year after 23vPS were statistically significantly lower than the immune response to an initial 13vPnC dose for all 13 serotypes. Antibody levels decreased over time for both vaccine groups after Vaccination 1 but remained higher for the 13vPnC/13vPnC group compared to the 23vPS group at all time points for most serotypes.

Supportive studies

Study 6115A1-3010: Evaluation of sequential 13vPnC and 23vPS immunisation in pneumococcal vaccine-naïve adults 60 to 64 years

Methods and objectives

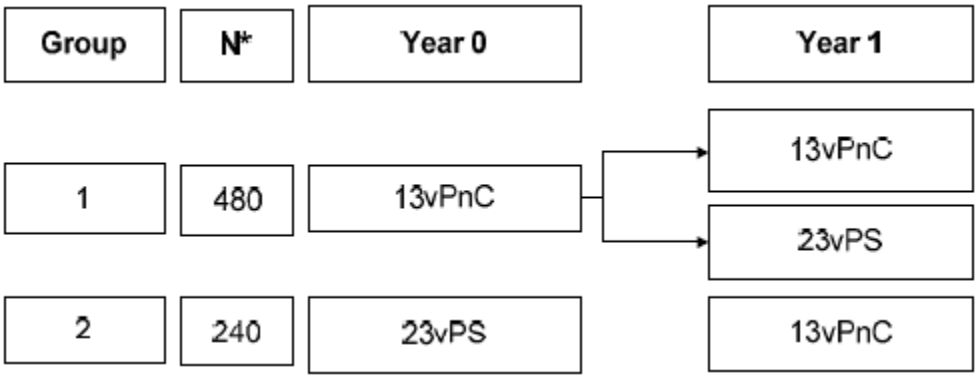
Study 3010 was a Phase III, parallel group, randomized, active controlled, modified double blind multicentre trial (Figure 3). The study was conducted to assess the immunogenicity, tolerability and safety of the sequential use of two doses of 13vPnC or 13vPnC followed, or preceded, by 23vPS when administered to adults aged 60 to 64 years who were naïve to 13vPnC. The primary objectives of the study were:

- to demonstrate non-inferiority (NI) of OPA response to 23vPS administered one year after an initial dose of 13vPnC (that is, 13vPnC/23vPS) relative to a dose of 23vPS alone; and
- to demonstrate NI of OPA response to 23vPS administered one year after an initial dose of 13vPnC (13vPnC/23vPS) relative to 13vPnC administered one 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. Group 1.1 (180 subjects) received 13vPnC at Year 0 and 13vPnC at Year 1 (that is, 13vPnC/13vPnC).

Group 1.2 (302 subjects) received 13vPnC at Year 0 and 23vPS at Year 1 (13vPnC/23vPS). Group 2 (238 subjects) received 23vPS at Year 0 and a subsequent dose of 13vPnC at Year 1 (23vPS/ 13vPnC).

Figure 3: Study 6115A1-3010



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 one month after each vaccination.

Results

The Vaccination 1 evaluable immunogenicity population included a total of 706 subjects (98.1%): 176 subjects (97.8%) in the 13vPnC/13vPnC group; 294 subjects (97.4%) in the 13vPnC/23vPS group; and 236 subjects (99.2%) in the 23vPS/13vPnC group. The Vaccination two evaluable immunogenicity populations included a total of 569 subjects (79.0%): 133 subjects (73.9%) in the 13vPnC/13vPnC group; 237 subjects (78.5%) in the 13vPnC/23vPS group; and 199 subjects (83.6%) in the 23vPS/13vPnC group. The demographic and baseline characteristics in the evaluable immunogenicity population at each vaccination were similar in subjects randomly assigned to each vaccine sequence with respect to sex, race, and age. Study 6115A1-3010 met both primary objectives.

13vPnC/23vPS relative to 23vPS

The immune response to 23vPS administered one year after an initial study dose of 13vPnC is as immunogenic as the immune response to an initial study dose of 23vPS for the 12 serotypes in common as measured by serotype specific OPA titres obtained one month after vaccination. OPA GMTs were compared after Vaccination 2 (Year 1) in subjects receiving 13vPnC/23vPS and after Vaccination 1 (Year 0) in those receiving 23vPS. Responses were statistically significantly greater (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, 19Fand 23F the 95% CI lower bound for the ratio was > 1.0.OPA GMTs in the 13vPnC/23vPS recipients ranged from 125 for serotype 3 to 1385 for serotype 4. In subjects receiving 23vPS at Vaccination 1, OPA GMTs ranged from 70 for serotype 23F to 1357 for serotype 4. GMRs ranged from 0.8 for serotype 14 to 2.8 for serotype 23F. Lower bounds of the 95% CIs were all greater than 0.5, thus meeting the twofold NI criterion for all 12 serotypes in common.

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

The immune response to 23vPS administered one year after an initial study dose of 13vPnC is NI to the immune response to 13vPnC administered one year after an initial study dose of 23vPS for the 12 serotypes in common in 13vPnC, as measured by serotype specific OPA titres one month after vaccination. The OPA GMTs for 13vPnC/23vPS recipients were NI to those for 23vPS/13vPnC recipients for all 12 serotypes in common.

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, that is, not > 1.00). OPA GMTs ranged from 125 for serotype 3 to 1385 for serotype 4 in the 13vPnC/23vPS group and from 50 for serotype 3 to 935 for serotype 4 in the 23vPS/13vPnC group.

13vPnC/13vPnC relative to 13vPnC

The immune response to a second dose of 13vPnC administered one year after an initial study dose of 13vPnC is NI to the immune response to the initial dose of 13vPnC for most but not all serotypes, as measured by serotype specific OPA titres one month after the Year 0 and Year 1 vaccinations. For responses after 13vPnC/13PnC compared to those after 13vPnC, for 9 of the 13 serotypes the lower limits of the 95% CIs for the GMFRs exceeded 0.5 (serotypes 1, 3, 6A, 6B, 14, 18C, 19A, 19F and 23F, but not 4, 5, 7F and 9V). A total of 7 of 13 serotypes were statistically significantly lower after the second dose (upper limit of 95% CI GMFR <1, serotypes 1, 4, 5, 7F, 9V, 18C and 19A) compared to the first dose of 13vPnC. For serotype 23F, the lower limit of the 95% CI for the ratio exceeded 1.0, indicating that the OPA response was statistically significantly greater after 13vPnC/13vPnC than after 13vPnC. For most serotypes (exceptions 7F and 9V), the RCDCs revealed 13vPnC/13vPnC OPA values similar or increased for that proportion of the population with lower OPA responses after the first dose, indicating an improvement in antibody response after 13vPnC/13vPnC in the segment of the population with the lowest response to a single dose of 13vPnC. Point estimates for proportions were similar or higher after 13vPnC/13vPnC than after 13vPnC alone for 11 of 13 serotypes (all except serotypes 7F and 9V). The proportions of responders were statistically significantly higher after 13vPnC/13vPnC for serotypes 3, 19F and 23F. Responses after a second dose of 13vPnC one year later were comparable or higher than after the first dose for the large majority of serotypes, particularly for the segment of the population with the lowest response to a single dose of 13vPnC.

13vPnC/23vPS relative to 13vPnC

The immune response to 23vPS administered one year after an initial study dose of 13vPnC is NI to the immune response to an initial study dose of 13vPnC for most but not all of the 12 serotypes in common as measured by serotype specific OPA titres one month after vaccination. The lower bound of the 95% CI of the GMFR (GMT13vPnC/23vPS/GMT13vPnC) was greater than 0.5 for serotypes 1, 3, 5, 6B, 14, 18C, 19A and 19F, but missed by a small margin for serotypes 4, 7F, 9V and 23F, for which the lower limits of the 95% CIs were 0.49, 0.35, 0.41 and 0.50, respectively. Responses were statistically significantly lower after the 23vPS dose in the series for 8 of 12 serotypes in common (upper limit of 95% CI GMFR <1, serotypes 1, 4, 6B, 7F, 9V, 18C, 19A, 23F). Responses were statistically significantly greater for 13vPnC/23vPS relative to 13vPnC for serotype 3, with a value at the lower limit of the 95% CI of 1.

13vPnC relative to 23vPS/13vPnC

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 titres ≥ LLOQ after 13vPnC met the NI criterion used in the pivotal NI study (that is, 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 pre-specified objective, an *ad hoc* analysis showed that OPA GMTs were statistically significantly higher (that is, 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 NI (that is, 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 titres ≥ LLOQ in the 13vPnC group met the NI criterion used in the pivotal NI study 004 (that is, 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 NI 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 (0.44) and serotype 14 (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 titres ≥ LLOQ after 13vPnC/13vPnC relative to 23vPS met the NI criterion used in the pivotal NI study (that is, 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

Comparison of OPA responses between the 13vPnC/13vPnC and the 23vPS/13vPnC groups revealed that the responses in the former group were statistically significantly greater for 10 of the 13 serotypes. In addition, the NI criterion used in the pivotal NI study was met for all serotypes after 13vPnC/13vPnC relative to 23vPS/13vPnC. OPA titres before the second immunisation were plotted with respect to those after the second immunisation. At the lower range of pre-vaccination 2 antibody titres, OPA GMTs after Vaccination 2 with 13vPnC/13vPnC were higher than those after 23vPS/13vPnC for a given level of pre-vaccination 2 antibody for most serotypes in common (serotypes 1, 3, 5, 6B, 9V, 14, 18C, 19F and 23F). This was most prominent in subjects within the first quartile of pre-immunisation titres at the time of the second dose, that is, those most likely to remain vulnerable to pneumococcal infection one year after Dose 1; for 12 of 13 serotypes point estimate OPA GMFRs to a second 13vPnC dose were higher in those who received 13vPnC as a first dose compared to those who received a first study dose of 23vPS, and the lower limits of the 95% CI for the ratios of the GMFRs were >1 for 5 of 13 serotypes.

23vPS/13vPnC relative to 23vPS

In an *ad hoc* analysis, OPA GMTs were statistically significantly lower (that is, 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 (that is, 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 two groups. For 8 of 12 common serotypes the ad hoc analysis showed that the proportion of responders at OPA titres ≥ LLOQ after 23vPS/13vPnC met the NI criterion applied in the pivotal NI study (that is, 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.

Reverse Cumulative Distribution Curves (RCDCs)

RCDCs in study 3010 showed the following:

1. After Vaccination 1, the RCDCs for 13vPnC were higher than those for 23vPS across the full range of antibody titres for most serotypes.
2. The RCDCs after Vaccination 2 with 13vPnC/23vPS were higher than those after 23vPS alone up to an OPA titre of at least 100, suggesting that initial vaccination with 13vPnC enhances the subsequent response to 23vPS in low titre responders. The RCDCs for 23vPS alone slightly exceeded those for 13vPnC/23vPS for some serotypes at high antibody titres of 1000 or greater but these differences may not result in clinical effect.
3. At antibody titres lower than 100, RCDCs for 13vPnC/23vPS were similar to, or higher than, curves for 13vPnC alone, for most common serotypes. At antibody titres of 1000 or greater, the curves were consistently higher for 13vPnC than for 13vPnC/23vPS, except for serotype 3.
4. For most serotypes, RCDCs for 23vPS/13vPnC were lower than those for 13vPnC alone, suggesting that 23vPS may have an inhibitory effect on a subsequent dose of 13vPnC.
5. For most serotypes the curves for 23vPS/13vPnC were lower throughout the range of antibody titres than the curves for 13vPnC/23vPS and 13vPnC/13vPnC.
6. The RCDCs for 13vPnC/13vPnC were similar to, or slightly higher than, the curves for 13vPnC alone up to an antibody titre of at least 100. For most serotypes, the curves for 13vPnC alone were slightly higher than those for 13vPnC/13vPnC at high antibody levels.

Overall immunogenicity results for study 6115A1-3010

In this study, immunogenicity was assessed in subjects who were randomly assigned to receive 1 of 3 vaccine sequences (13vPnC/13vPnC, 13vPnC/23vPS, 23vPS/13vPnC), in which the two pneumococcal vaccines were administered approximately one year apart. This study satisfied both primary objectives and their associated secondary objectives:

OPA responses to 13vPnC/23vPS were NI to OPA responses to 23vPS for all 12 serotypes in common (primary objective) and were statistically significantly greater for 6 of 12 serotypes (secondary objective) and OPA responses to 13vPnC/23vPS were NI to OPA responses after 23vPS/13vPnC (primary objective) and were statistically greater for 11 of the 12 serotypes in common (exception serotype 14). Additionally, OPA responses were statistically significantly greater after 13vPnC compared to 23vPS/13vPnC for all 12 serotypes in common (Table 3).

Parallel *post hoc* analyses of the proportion of subjects achieving an OPA titre ≥ LLOQ supported these results.

Table 3: Pneumococcal OPA GMTs and GMFRs for all vaccine groups/sequences in study 6115A1-3010 – evaluable immunogenicity population

			Sampling Time[a]								
			Prevaccination[b]			Postvaccination[b]			Fold Rise		
Serotype	Vax #	Vaccine Group/Sequence (as Randomized)	n[c]	GMT[d]	(95% CI[e])	n[c]	GMT[d]	(95% CI[e])	n[c]	GMFR[f]	(95% CI[e])
1	1	13vPnC	449	6	(5.8, 7.0)	449	206	(176.8, 239.6)	449	32.4	(27.59, 37.95)
		23vPS	226	7	(5.9, 7.8)	226	149	(118.3, 186.9)	226	21.9	(17.40, 27.65)
	2	13vPnC/13vPnC	128	54	(40.2, 73.0)	128	140	(110.4, 177.3)	128	2.6	(2.06, 3.24)
		13vPnC/23vPS	225	57	(45.4, 70.4)	225	148	(123.6, 177.5)	225	2.6	(2.23, 3.08)
		23vPS/13vPnC	192	47	(36.7, 61.3)	192	76	(60.0, 97.0)	192	1.6	(1.39, 1.86)
3	1	13vPnC	444	6	(5.4, 6.4)	444	75	(65.4, 84.9)	444	12.7	(11.05, 14.61)
		23vPS	224	6	(5.5, 7.2)	224	79	(66.1, 94.1)	224	12.5	(10.44, 15.08)
	2	13vPnC/13vPnC	117	20	(15.4, 25.9)	117	91	(77.0, 107.4)	117	4.6	(3.61, 5.74)
		13vPnC/23vPS	214	24	(19.4, 28.7)	214	122	(105.8, 141.7)	214	5.2	(4.35, 6.19)
		23vPS/13vPnC	182	26	(20.5, 31.8)	182	51	(41.3, 63.1)	182	2.0	(1.71, 2.33)
4	1	13vPnC	396	39	(29.2, 50.7)	396	2418	(2059.3, 2839.6)	396	62.8	(47.72, 82.65)
		23vPS	198	32	(22.2, 47.6)	198	1327	(978.3, 1799.1)	198	40.8	(27.70, 60.18)
	2	13vPnC/13vPnC	119	646	(445.3, 937.5)	119	1262	(956.5, 1665.6)	119	2.0	(1.54, 2.49)
		13vPnC/23vPS	224	597	(454.4, 783.8)	224	1426	(1208.8, 1681.9)	224	2.4	(1.95, 2.93)
		23vPS/13vPnC	177	394	(284.5, 545.1)	177	942	(737.0, 1203.1)	177	2.4	(1.87, 3.05)
5	1	13vPnC	428	6	(5.1, 6.0)	428	213	(174.7, 260.8)	428	38.7	(31.62, 47.24)
		23vPS	217	5	(4.8, 6.3)	217	134	(101.9, 176.8)	217	24.5	(18.51, 32.41)
	2	13vPnC/13vPnC	115	39	(26.0, 57.1)	115	96	(67.7, 135.5)	115	2.5	(1.94, 3.19)
		13vPnC/23vPS	206	61	(46.1, 80.6)	206	202	(162.0, 250.8)	206	3.3	(2.70, 4.05)
		23vPS/13vPnC	175	49	(36.3, 65.4)	175	85	(63.8, 112.3)	175	1.7	(1.46, 2.07)
6B	1	13vPnC	394	33	(25.0, 42.8)	394	1903	(1550.7, 2336.4)	394	58.2	(43.98, 76.98)
		23vPS	199	26	(18.2, 38.0)	199	632	(455.9, 876.9)	199	24.0	(16.58, 34.80)
	2	13vPnC/13vPnC	117	486	(314.1, 753.0)	117	1894	(1436.4, 2497.7)	117	3.9	(2.73, 5.55)
		13vPnC/23vPS	224	466	(341.4, 634.8)	224	1210	(955.4, 1532.3)	224	2.6	(2.08, 3.25)
		23vPS/13vPnC	180	182	(124.7, 264.8)	180	709	(522.3, 962.9)	180	3.9	(2.94, 5.18)
7F	1	13vPnC	429	7	(6.2, 8.6)	429	1009	(817.7, 1244.9)	429	137.9	(107.04, 177.55)
		23vPS	207	7	(5.6, 8.6)	207	305	(212.9, 437.3)	207	43.9	(29.75, 64.89)
	2	13vPnC/13vPnC	124	149	(92.6, 240.5)	124	323	(212.8, 490.1)	124	2.2	(1.56, 3.00)
		13vPnC/23vPS	217	111	(78.1, 158.0)	217	523	(409.8, 666.7)	217	4.7	(3.48, 6.35)
		23vPS/13vPnC	179	65	(43.2, 96.3)	179	120	(80.8, 178.6)	179	1.9	(1.39, 2.49)
9V	1	13vPnC	399	14	(11.2, 17.6)	399	747	(596.6, 936.6)	399	53.4	(40.35, 70.71)
		23vPS	194	16	(11.5, 22.9)	194	285	(191.4, 424.0)	194	17.6	(11.49, 26.85)
	2	13vPnC/13vPnC	120	106	(63.9, 175.0)	120	340	(218.7, 527.7)	120	3.2	(2.15, 4.80)
		13vPnC/23vPS	223	73	(50.8, 105.8)	223	360	(257.4, 503.7)	223	4.9	(3.60, 6.71)
		23vPS/13vPnC	174	53	(34.6, 80.8)	174	116	(76.5, 175.6)	174	2.2	(1.63, 2.94)
14	1	13vPnC	410	31	(24.2, 39.6)	410	623	(497.6, 780.1)	410	20.1	(15.29, 26.42)
		23vPS	202	46	(32.3, 65.8)	202	716	(522.5, 981.6)	202	15.5	(10.92, 22.10)
	2	13vPnC/13vPnC	123	206	(133.8, 316.4)	123	391	(269.3, 567.3)	123	1.9	(1.42, 2.54)
		13vPnC/23vPS	225	257	(188.4, 351.2)	225	614	(477.0, 790.7)	225	2.4	(1.91, 2.99)
		23vPS/13vPnC	187	298	(213.7, 416.1)	187	418	(308.3, 567.6)	187	1.4	(1.20, 1.64)
18C	1	13vPnC	414	25	(19.8, 30.4)	414	1604	(1338.4, 1923.2)	414	65.4	(51.23, 83.45)
		23vPS	215	32	(23.3, 45.1)	215	755	(555.5, 1026.5)	215	23.3	(16.75, 32.38)
	2	13vPnC/13vPnC	122	416	(281.6, 615.3)	122	996	(738.0, 1344.1)	122	2.4	(1.77, 3.24)
		13vPnC/23vPS	221	442	(336.5, 581.9)	221	1052	(851.0, 1300.8)	221	2.4	(1.92, 2.94)
		23vPS/13vPnC	182	325	(229.7, 458.6)	182	541	(397.8, 736.2)	182	1.7	(1.41, 1.97)

			Sampling Time[a]								
			Prevaccination[b]			Postvaccination[b]			Fold Rise		
Serotype	Vax #	Vaccine Group/Sequence (as Randomized)	n[c]	GMT[d]	(95% CI[e])	n[c]	GMT[d]	(95% CI[e])	n[c]	GMFR[f]	(95% CI[e])
19A	1	13vPnC	381	24	(19.8, 28.7)	381	699	(605.7, 806.0)	381	29.3	(24.03, 35.75)
		23vPS	200	25	(18.9, 32.0)	200	366	(291.2, 461.1)	200	14.9	(11.46, 19.40)
	2	13vPnC/13vPnC	115	194	(143.0, 262.7)	115	413	(336.7, 507.4)	115	2.1	(1.73, 2.63)
		13vPnC/23vPS	203	198	(161.9, 241.5)	203	461	(396.9, 536.4)	203	2.3	(2.02, 2.69)
		23vPS/13vPnC	179	142	(108.6, 186.8)	179	291	(236.3, 358.4)	179	2.0	(1.68, 2.48)
19F	1	13vPnC	404	20	(15.9, 24.3)	404	726	(607.1, 869.2)	404	37.0	(29.41, 46.49)
		23vPS	205	16	(12.3, 22.0)	205	491	(367.5, 656.8)	205	29.9	(21.30, 41.92)
	2	13vPnC/13vPnC	115	135	(88.1, 206.4)	115	478	(362.9, 629.2)	115	3.5	(2.55, 4.92)
		13vPnC/23vPS	209	161	(119.7, 215.8)	209	778	(640.9, 945.4)	209	4.8	(3.77, 6.22)
		23vPS/13vPnC	171	134	(96.2, 186.9)	171	277	(208.1, 369.7)	171	2.1	(1.62, 2.64)
23F	1	13vPnC	427	9	(7.8, 10.8)	427	332	(265.0, 416.6)	427	36.1	(28.68, 45.50)
		23vPS	200	8	(6.4, 9.9)	200	64	(44.9, 89.8)	200	8.0	(5.84, 10.95)
	2	13vPnC/13vPnC	120	76	(49.1, 117.5)	120	434	(302.2, 622.6)	120	5.7	(4.04, 8.06)
		13vPnC/23vPS	227	86	(63.6, 117.2)	227	202	(154.1, 265.5)	227	2.3	(1.91, 2.87)
		23vPS/13vPnC	183	31	(21.9, 42.9)	183	122	(86.5, 173.3)	183	4.0	(3.07, 5.18)
6A	1	13vPnC	423	19	(15.5, 24.4)	423	2734	(2284.8, 3272.7)	423	140.8	(110.05, 180.05)
		23vPS	208	14	(10.3, 19.0)	208	250	(172.1, 361.8)	208	17.9	(12.34, 25.93)
	2	13vPnC/13vPnC	125	493	(318.0, 765.0)	125	2410	(1839.0, 3158.3)	125	4.9	(3.32, 7.20)
		13vPnC/23vPS	217	692	(523.1, 915.2)	217	1348	(1078.8, 1684.9)	217	1.9	(1.64, 2.32)
		23vPS/13vPnC	175	92	(62.0, 135.9)	175	1145	(874.0, 1500.5)	175	12.5	(8.52, 18.28)

a. Statistical analysis plan–specified timing for blood sample collection.
b. For Vaccination 1, pre-vaccination is the blood draw before Vaccination 1 and post-vaccination is the blood draw one month after Vaccination 1. For Vaccination 2, pre-vaccination is the blood draw before Vaccination 2 and post-vaccination is the blood draw one month after Vaccination 2.
c. n = Number of subjects with a determinate OPA antibody titre to the given serotype at both blood draws.
d. Geometric mean titres (GMTs) were calculated using all subjects with available data for both the specified blood draws.
e. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titres, or mean fold rises.
f. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both the pre-vaccination and post-vaccination blood draws.
Abbreviation: Vax = vaccination.

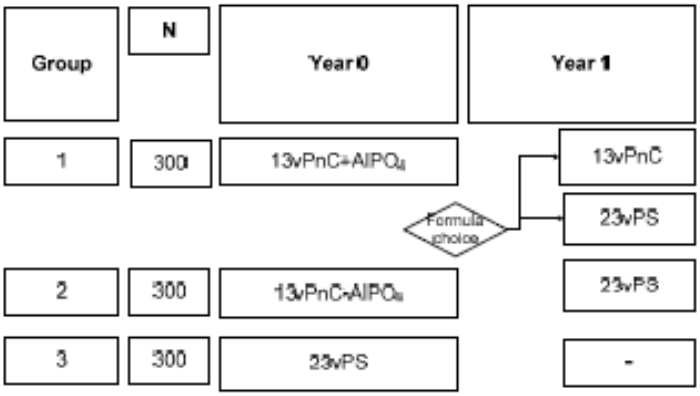
Study 6115A1-500: Phase II evaluation of formulation and sequential 13vPnC and 23vPS immunisation in pneumococcal vaccine-naïve adults ≥65 years of age

Objectives and Design

Study 500 was a randomized, open label, active control, Phase II multicentre trial to evaluate the safety, tolerability and immunogenicity of two different 13vPnC formulations, that is, 13vPnC given with aluminum phosphate (13vPnC + AlP04) versus 13vPnC given without aluminum phosphate (13vPnC - AlP04). Study 500 was conducted at multiple sites in South Africa in subjects aged 65 years and older who were naïve to previous immunisation 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 4). This Phase II study was the first study to evaluate antibody responses to 13vPnC in adults and was intended to provide preliminary data that would address questions and inform the design of the Phase III clinical program in adults. Data obtained after the first dose allowed for selection of the final 13vPnC formulation to be used in the adult 13vPnC Phase III trials. Subjects in the group receiving the selected 13vPnC formulation were to receive either a subsequent dose of 23vPS or a second dose of the selected 13vPnC formulation 12 months after initial vaccination. Subjects in the 13vPnC group that were not selected were to receive a subsequent dose of 23vPS, 12 months after initial vaccination. Subjects who received 23vPS for the first dose did not receive a second dose.

The formulation of Prevnar/Prevenar (7vPnC) and Prevnar 13/Prevenar 13 contains AlPO4 as an excipient, which may enhance immune response. Prevnar 13/Prevenar 13 is licensed for infants and children in the US, Europe and many other countries. To determine whether AlPO4 should be included in the final adult 13vPnC formulation, study 500 evaluated the non-inferiority (NI) of IgG response induced by 13vPnC with AlPO4 (13vPnC+AlPO4) relative to 13vPnC without AlPO4 (13vPnC-AlPO4), that is, the first co-primary objective. Another co-primary objective was to demonstrate NI of the selected 13vPnC formulation relative to 23vPS, based on functional antibody (OPA) responses to the 12 serotypes common to both 13vPnC and 23vPS. The study was also designed to assess the immune responses elicited by subsequent doses of 13vPnC or 23vPS given one year after an initial dose of 13vPnC.

Figure 4: Study Schema - 6115A1-500



The formulation decision was made based on an interim analysis of data obtained after the first vaccination. The evaluable immunogenicity population for the formulation decision analysis (Vaccination 1 only) included a total of 893 (97.6%) subjects; 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. For the final analysis at Vaccination 1, a total of 889 (97.2%) subjects were included in the evaluable immunogenicity population at Vaccination 1; 299 (96.8%) in the 13vPnC + ALPO4 group, 295 (96.7%) in the 13vPnC - ALPO4 group and 295 (98.0%) in the 23vPS group.

At Vaccination 2, the final analysis included a total of 804 (92.10%) subjects: 131 (96.32%) in the 13vPnC + ALPO4 /13vPnC + ALPO4 group, 126 (96.18%) in the 13vPnC + ALPO4/23vPS group, 268 (87.87%) in the 13vPnC - ALPO4/23vPS group and 279 (92.69%) in the 23vPS/None group. Blood samples were taken on the day of each vaccination (before vaccine administration) and one month after each vaccination for measurement of capsular binding antibodies by IgG ELISA and of functional antibody response by the OPA assay.

Results

Formulation Analysis

The 3 vaccine groups were similar with respect to sex, ethnic origin and age at vaccination. 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 ≥ fourfold rise in pneumococcal IgG antibody concentration. The NI of IgG response after 13vPnC-AlPO4 relative to 13vPnC+AlPO4 was assessed using the twofold criterion and 95% CIs; NI was declared if the lower limit of the 95% CI for the ratio (13vPnC-AlPO4 to 13vPnC+AlPO4) was > 0.5. The NI 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 NI to values in the 13vPnC+AlPO4 group for all 13 serotypes. IgG GMCs were similar when adjusted for age, sex, current smoking status and pre-vaccination 1 value. The NI criterion was met for all serotypes. The GMFRs for each serotype from before to after Vaccination 1 were comparable in the two groups of the formulation analysis.

Proportion of subjects achieving prespecified IgG antibody levels

The NI criterion for proportion of subjects achieving a ≥fourfold rise (that is, responders) in serotype specific IgG was met for 9 of 13 serotypes.

IgG RCDCs

The distribution of IgG responses before and after vaccination in the two formulation groups was generally similar to those for the 13vPnC+AlPO4 group for most serotypes. The post-vaccination curve for 13vPnC-AlPO4 was higher than the 13vPnC+AlPO4 curve over a wide range of responses for serotypes 7F and 14 only.

Final analysis

Based on results from the formulation decision analysis (and logistics), 13vPnC+AlPO4 was the selected 13vPnC formulation and was used in the final analysis. The primary endpoint for the final analysis was the serotype specific OPA antibody titres. The proportion of subjects achieving serotype specific OPA titres ≥ LLOQ and the IgG concentrations were secondary endpoints.

The primary objective of the final analysis was to assess the NI of OPA GMTs after 13vPnC+AlPO4 relative to those after 23vPS. The same twofold NI criterion, as used in the formulation analysis was used for the final comparison. Differences between vaccine groups in the proportion of subjects achieving prespecified OPA titres (secondary objective) were also assessed.

The demographic characteristics for the 804 subjects in the Vaccination 2 evaluable immunogenicity population were similar with respect to sex, ethnic origin and age at vaccination.

OPA GMTs (Vaccination 1)

Comparisons of OPA GMTs after 13vPnC+AlPO4 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 NI 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+AlPO4 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 pre-vaccination 1 value.

Proportion of subjects achieving prespecified OPA antibody levels (Vaccination 1):

Results showed that the proportion of responders at an antibody titre ≥LLOQ in the 13vPnC+AlPO4 group was NI (that is, criterion of >-10% at the lower limit of the 95% CI for the difference [13vPnC+AlPO4 – 23vPS]) to that of the 23vPS group for all 12 common serotypes; responses were statistically significantly higher in the 13vPnC +AlPO4 group for 6 of 12 common serotypes. Results showed that the proportion of responders with OPA antibody titre ≥1:8 after Vaccination 1 in the 13vPnC+AlPO4 group was NI to that of the 23vPS group for all serotypes.

Vaccination 1 and Vaccination 2

13vPnC+AlPO4/13vPnC+AlPO4 relative to 13vPnC+AlPO4: OPA GMTs were similar or lower after 13vPnC+AlPO4/13vPnC+AlPO4 than after 13vPnC+AlPO4 alone for all serotypes except 23F. GMFRs (Vaccination 2/Vaccination 1) ranged from 0.4 (serotype 5) to 1.4 (serotype 23F) and the lower limits of the 95% CIs for the GMFRs ranged from 0.35 (serotype 5, 9V) to 1.02 (serotype 23F). OPA GMTs were statistically significantly lower after 13vPnC+AlPO4/13vPnC+AlPO4 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+AlPO4/13vPnC+AlPO4 than after 13vPnC+AlPO4 alone. For the proportion of responders at ≥ LLOQ, only descriptive analyses were performed. Point estimates for the proportions of responders were higher after 13vPnC+AlPO4/13vPnC+AlPO4 than after 13vPnC+AlPO4 for 11 of 13 serotypes (all except serotypes 9V and 14 with slightly lower responses after Dose 2). The proportions of responders to 13vPnC+AlPO4/13vPnC+AlPO4 ranged from 84.7% (serotype 9V) to 99.2% (serotype 19A), and to 13vPnC +AlPO4 alone ranged from 86.5% (serotype 23F) 98.3% (serotype 4). 13vPnC+AlPO4/23vPS relative to 23vPS: OPA GMTs were statistically significantly higher (that is, lower limit of the 95% CI for the GMR was >1.0) after 13vPnC+AlPO4/23vPS for 7 of 12 common serotypes (1, 3, 5, 6B, 9V, 19F, 23F) and were similar in the two groups for the other common serotypes. The GMRs (Vaccination 2 to Vaccination 1) ranged from 0.81 (serotype 14) to 2.88 (serotype 6A), and the lower limits of the 95% CIs for the GMRs ranged from 0.54 (serotype 14) to 1.78 (serotype 6A). Point estimates for the proportions of subjects achieving an OPA titre ≥ LLOQ after 13vPnC+AlPO4/23vPS were higher than after 23vPS alone for all serotypes. After 13vPnC+AlPO4/23vPS, the proportions of responders ranged from 79.7% (serotype 9V) to 98.3% (serotype 4) and after a single dose of 23vPS values ranged from 72.8% (serotype 9V) to 97.1% (serotype 19A).

IgG response

Vaccination 1

IgG GMCs

To address a secondary endpoint, IgG GMCs after Vaccination 1 with 13vPnC+AlPO4 were compared with values observed after 23vPS, by determination of the ratio (13vPnC+AlPO4 to 23vPS) of GMCs in the two vaccines. Results showed that IgG responses to all serotypes in the 13vPnC group met the NI criterion of a lower limit of the 95% CI for the ratio (13vPnC to 23vPS) of >0.5. In addition, responses were statistically significantly higher (that is, a lower limit of the 95% CI for the ratio of >1.0) for 10 of 12 common serotypes (all except 7F and 14).

Proportion of subjects achieving prespecified IgG antibody levels:

A descriptive analysis only was performed for the proportion of responders after Vaccination 1. In the 13vPnC+AlPO4 group, the point estimates for proportion of subjects achieving a fourfold rise in IgG concentration after Vaccination 1 ranged from 47.8%

(serotype 3) to 81.6% (serotypes 4 and 18C) for the 12 common serotypes. The proportion of responders in the 23vPS group ranged from 33.6% (serotype 3) to 78.3% (serotype 4). Point estimates for proportions were higher in the 13vPnC+AlPO4 group for 10 of 12 common serotypes (except for serotypes 7F and 14) and for 7 of these 10 serotypes, the 95% CIs for the proportions in the two groups did not overlap.

Vaccination 2 and Vaccination 1

13vPnC+AlPO4/23vPS relative to 23vPS

IgG GMCs were statistically significantly higher for 7 of 12 common serotypes (serotypes 1, 3, 6B, 9V, 19A, 19F and 23F) and were similar for the remaining common serotypes. Point estimates for proportion of subjects achieving a fourfold rise in IgG concentrations were lower after 13vPnC+AlPO4/23vPS than after a single dose of 23vPS for all common serotypes. Proportions ranged from 4.8% (serotype 6B) to 26.2% (serotype 3) after 13vPnC+AlPO4/23vPS and from 33.6% (serotype 3) to 78.3% (serotype 4) after 23vPS.

13vPnC+AlPO4/13vPnC+AlPO4 relative to 13vPnC+AlPO4

IgG GMCs were similar or lower after two doses of 13vPnC+AlPO4 than after a single dose. For 8 of 13 serotypes IgG GMCs were statistically significantly lower (that is, upper limit of the 95% CI for the GMFR of < 1.0) after 13vPnC+AlPO4/13vPnC+AlPO4 than after 13vPnC+AlPO4 alone (all except 6A, 6B, 14, 19F and 23F). However, for serotypes 6A, 19F and 23F the lower limit of the 95% CI for the GMFR was >1.0, indicating statistically significantly higher responses after 13vPnC+AlPO4/13vPnC+AlPO4 than after 13vPnC+AlPO4. The GMFRs (Vaccination 2/Vaccination 1) ranged from 0.48 (serotype 5) to 1.29 (serotype 19F) and the lower limits of the 95% CIs for the GMFRs ranged from 0.40 (serotype 5) to 1.05 (serotype 19F). Point estimates for proportion of subjects achieving a fourfold rise in IgG concentrations were lower after 13vPnC+AlPO4/ 13vPnC+AlPO4 than after a single dose of 13vPnC+AlPO4 for all common serotypes. Proportions ranged from 3.8% (serotype 18C) to 29.0% (serotype 23F) after 13vPnC+AlPO4/ 13vPnC+AlPO4 and from 47.8% (serotype 3) to 81.6% (serotypes 4, 18C) after 13vPnC+AlPO4.

Antibody response curves

OPA GMTs and IgG GMCs rose from baseline to one month after Vaccination 1. At one year after Vaccination 1 (before Vaccination 2) OPA and IgG antibody levels remained higher than pre-vaccination 1 levels for all serotypes in each group. After Vaccination 2 all OPA and IgG antibody levels were higher than pre-vaccination 2 levels and exceeded values after Vaccination 1 for a few serotypes.

Reverse Cumulative Distribution Curves

OPA RCDCs

After Vaccination 1 in study 500 the OPA curve for the 23vPS group was consistently lower than that of the 13vPnC group across a wide range of antibody responses for all common serotypes, except for serotypes 7F and 14. After Vaccination 2, differences between OPA curves were small. For several common serotypes (serotypes 1, 3, 4, 5, 6B, 9V) the curves for 23vPS at Vaccination 1 were lower than the curves for 13vPnC+AlPO4, 13vPnC+AlPO4/13vPnC+AlPO4 and 13vPnC+AlPO4/23vPS, particularly up to OPA titres of at least 1000. The curves for 13vPnC+AlPO4 were somewhat higher than curves for the other groups or sequences at antibody titres of 100 or higher for the majority of serotypes.

IgG RCDCs

After Vaccination 1 the IgG curves for the 23vPS group were lower than those of 13vPnC+AlPO4, 13vPnC+AlPO4/13vPnC+AlPO4 and 13vPnC+AlPO4/23vPS across a wide range of antibody responses for serotypes 1, 4, 6B, 9V, 18C, 19A, 19F and 23F. The curves

for 13vPnC+AlPO4 relative to the other groups were higher across a wide range of responses for serotypes 5 and 18 C. Compared with all groups, the curves were highest in the 13vPnC+AlPO4/13vPnC+AlPO4 group for serotypes 4, 6A, 6B, 19A, 19F and 23F at IgG concentrations of approximately 10.0 µg/mL or less.

Immunogenicity Summary

Overall, the results of the formulation analysis indicate that the immunogenicity of 13vPnC in adults older than 65 years, as measured by IgG GMCs, did not differ whether 13vPnC was formulated with or without AlPO4. Results of the final analysis showed that the selected 13vPnC+AlPO4 formulation was as immunogenic as 23vPS, as determined by measurements of serotype specific OPA antibody titres and IgG concentrations. 13vPnC+AlPO4 given before 23vPS enhanced the immune response to 23vPS for most serotypes

Study 3009

Objectives and Design

Study 3009 was an open label, single arm, multicentre 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 +AlPO4 (selected formulation) at Vaccination 1 and 23vPS a year later at Vaccination 2 (13vPnC +AlPO4/23vPS) in study 500. One hundred and five (105) subjects were given a single dose of 13vPnC in study 3009 (Figure 5). The primary objective of the study was to compare serotype specific OPA responses to 13vPnC given in study 3009 (that is, Vaccination 3 of the sequence 13vPnC/23vPS/13vPnC) with OPA responses elicited by 13vPnC given as the first dose in study 500 (that is, 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 one year after the second vaccination in study 500. The immunogenicity analyses were based on results of OPA assays and IgG ELISAs performed on blood samples obtained on the day of vaccination (before vaccine administration) and approximately one month after vaccination. The primary endpoint for the immunogenicity analyses was the serotype specific OPA GMTs. Another immunogenicity endpoint was the serotype specific IgG GMCs.

Figure 5: Study 6115A1-3009 Design

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

Results

The evaluable immunogenicity population included 98 subjects (93.3%).

OPA GMTs

Vaccination 3 versus Vaccination 1

To address the primary objective, serotype specific OPA GMTs measured approximately one month after Vaccination 3 were compared to GMTs one month after Vaccination 1 of vaccine sequence 13vPnC/23vPS/13vPnC (that is, 13vPnC/23vPS/13vPnC relative to 13vPnC). 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 (that is, 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. These results reflect the notable decrease in immune response after the vaccine sequence 13vPnC/23vPS/13vPnC relative to a single dose of 13vPnC.

Vaccination 3 versus Vaccination 2

A secondary objective was to compare the OPA GMTs after Vaccination 3 relative to those after Vaccination 2 of the vaccine sequence 13vPnC/23vPS/13vPnC in the evaluable immunogenicity population. Point estimates for OPA GMTs were lower after Vaccination 3 relative to Vaccination 2 for 10 of 13 serotypes. For 8 of these serotypes (serotypes 1, 3, 5, 9V, 7F, 14, 19A, 19F), the responses were statistically significantly lower. OPA GMTs were statistically significantly higher after Vaccination 3 than after Vaccination 2 for serotypes 6A, 6B and 23F for serotype 6A, and for 9 of 13 serotypes (serotypes 3, 4, 5, 6A, 6B, 14, 18C, 19A, 23F) the lower limits of the 95% CIs for the GMFRs were >0.5 (non-inferior).

For most serotypes, a decrease in immune response was observed after the vaccine sequence 13vPnC/23vPS/13vPnC relative to 13vPnC/23vPS, although this decrease was not as pronounced as the difference between 13vPnC/23vPS/13vPnC and 13vPnC. Findings are consistent with the reduced OPA response seen in study 6115A1-3010, when 13vPnC was administered after 23vPS in vaccine naïve subjects and compared to 23vPS alone. 13vPnC administered before 23vPS does not ameliorate this effect.

Before and after Vaccination 3

OPA GMTs were statistically significantly higher after Vaccination 3 than before Vaccination 3 for 12 of 13 serotypes. The lower limit of GMFRs 95% CI were >1.0 for all serotypes except serotype 14 (0.97) and ranged from 0.97 (serotype 14) to 3.14 (serotype 6A). Hence, subjects were able to respond to 13vPnC given as a third dose but generally not to the level seen after the first or second dose in the series 13vPnC/23vPS/13vPnC for most serotypes

Vaccination 3 versus Vaccination 1

IgG GMCs were statistically significantly lower (that is, upper limit of the 95% CI for the GMFR of <1.0) after Vaccination 3 than after Vaccination 1 (secondary objective) in the sequence 13vPnC/23vPS/13vPnC for all serotypes except for serotype 6A (95% CI upper limit of 1.10. The IgG results, like those of the OPA analysis, showed a decrease in immune response after the vaccine sequence 13vPnC/23vPS/13vPnC relative to a single 13vPnC dose.

Vaccination 3 versus Vaccination 2

IgG GMCs were statistically significantly lower (that is, upper limit of the 95% CI for the GMFR of <1.0) after Vaccination 3 than after Vaccination 2 for 10 of 13 serotypes (all

except serotypes 6A [not included in 23vPS], 6B and 23 F. GMFRs (Vaccination 3 relative to Vaccination 2) were <1 for all serotypes except 6A, 6B and 23F and ranged from 0.54 for serotype 19F to 1.49 for serotype 6A. However, after Vaccination 3, the lower limits of the 95% CIs for the GMFRs were >0.5 for all serotypes except serotypes 3 (0.48) and 19F (0.47). Although IgG responses were not consistent with OPA responses for all serotypes, the IgG analysis, like the OPA, demonstrated decreased immune response after the vaccine sequence 13vPnC/23vPS/13vPnC relative to 13vPnC/23vPS.

Before and after Vaccination 3

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 one month after Vaccination 1. For all serotypes, OPA GMTs and IgG GMCs decreased over the year, from one 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 one 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 post-vaccination responses to be either similar or somewhat less after each subsequent vaccination in the vaccine sequence 13vPnC/23vPS/13vPnC, with pre-vaccination levels of all subsequent vaccines still well above the baseline values.

Conclusions

The IgG GMCs and OPA GMTs for most serotypes were highest after Vaccination 1 and gradually decreased, or remained similar, after each subsequent vaccination in the vaccine sequence 13vPnC/23vPS/13vPnC. IgG and OPA responses after Vaccination 3 were statistically significantly lower than after Vaccination 1 of the vaccine sequence 13vPnC/23vPS/13vPnC for the majority of serotypes. OPA GMTs and IgG GMCs measured before Vaccination 2 and before Vaccination 3 remained higher than baseline (pre-vaccination 1) levels.

As shown in study 6115A1-500, a single dose of 13vPnC induced NI and, for the majority of serotypes (11 of 13 serotypes), statistically significantly higher OPA and IgG responses than a single dose of 23vPS. When 13vPnC was followed by 23vPS, antibody responses were similar or higher than responses observed after 23vPS alone, which indicates that 13vPnC given first enhances the immune response to at least a number of serotypes in 23vPS (study 6115A1-500). However, OPA and IgG responses to the sequence 13vPnC/23vPS remained at similar or, for the majority of serotypes, lower antibody levels than responses to a single dose of 13vPnC (study 6115A1-500). After the sequence 13vPnC/23vPS/13vPnC in this study, OPA antibody levels were even further diminished compared to a single dose of 13vPnC for all serotypes except 23F. These results indicate that 13vPnC administered one year before 23vPS does not prevent the apparent negative effect of 23vPS on immune responses following a subsequent dose of 13vPnC when given as Vaccination 3 in the vaccine sequence 13vPnC/23vPS/13vPnC. This negative immunologic effect of 23vPS given before 13vPnC has been noted in other studies. OPA responses to 13vPnC/23vPS/13vPnC were also lower than responses to 13vPnC/23vPS for the majority of serotypes.

Study 6115A1-3001 and 3008: Concomitant administration of 13vPnC and TIV in adults 50 to 59 years of age

Studies 3001 and 3008 were conducted at multiple sites in the United States and Europe in subjects naïve to 23vPS. The primary objectives of the studies were:

1) to demonstrate that immune responses induced by the licensed influenza vaccine TIV when given concomitantly with 13vPnC were non-inferior (NI) to immune responses elicited by TIV alone (that is, TIV given with placebo) as measured by the standard haemagglutination inhibition assay (HAI) for the A/H1, A/H3, and B vaccine strains); and

2) to demonstrate that the serotype specific IgG responses to 13vPnC when given concomitantly with TIV are NI to IgG responses elicited by 13vPnC alone when given one month after administration of TIV.

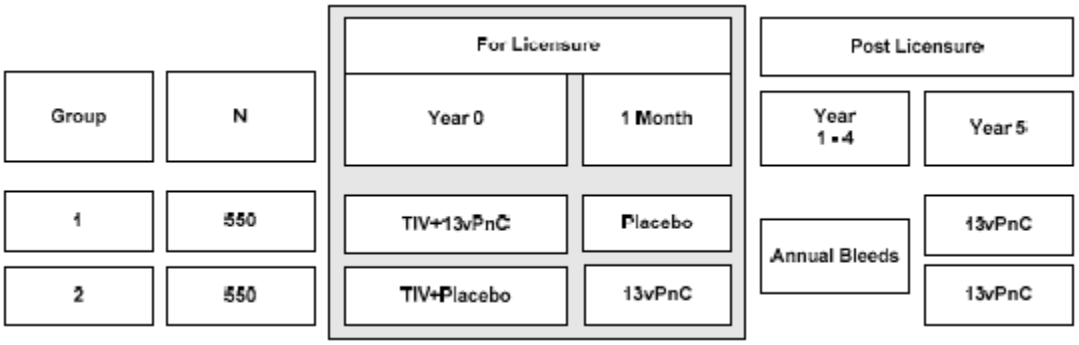
Over 1000 subjects were enrolled in each study and randomly assigned to two groups: one group received 13vPnC and TIV (Fluarix, GlaxoSmithKline Biologicals), followed by placebo (13vPnC+TIV/placebo); the other group received placebo and TIV followed by 13vPnC (placebo+TIV/13vPnC) one month later.

Study 3001

Design

Study 3001 was a Phase III, parallel group, randomized, double blind, multicentre trial to evaluate the immunogenicity, safety, and tolerability of 13vPnC when administered concomitantly with TIV (13vPnC+TIV) in healthy adults aged 50 to 59 years who were naïve to 23vPS (Figure 6).

Figure 6: Study Schema - 6115A1-3001



A total of 1116 subjects were randomly assigned in a 1:1 ratio to two treatment groups: Group 1 received 13vPnC with concomitant TIV followed one month later by placebo (13vPnC + TIV/placebo, n = 554); Group 2 received placebo with TIV followed one month later by 13vPnC (placebo + TIV/13vPnC, n = 562). This study will also allow assessment of the recall response to a second dose of 13vPnC given 5 years after the initial dose. This submission presents data from the initial part of the study only, referred to as Year 0. It includes the period from study start through the one month post-dose 2 blood draw and a 6 month follow up telephone contact. Follow up data from Years 1 through 5 will be presented in a subsequent report.

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 one month after the second vaccination. To assess immune response to TIV, the standard haemagglutination inhibition assays (HAIs) were used to measure antibody response to the A/H1N1, A/H3N2 and B vaccine strains. IgG ELISA was used to measure serotype specific response to 13vPnC.

Results

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 fourfold increase in the HAI titre (that is, proportion who seroconverted) elicited by each influenza strain included in the vaccine. The NI criterion for the proportion of subjects achieving a ≥ fourfold rise in HAI titre was met for all 3 strains of TIV after Dose 1. The proportions of seroconverters in the TIV + 13vPnC group and in the TIV+ placebo group, respectively, were: A/H1N1, 84.0% and 81.2%; A/H3/N2, 71.1% and 69.5%; and B, 60.6% and 60.3%. The differences between the two vaccine groups were 2.8%, 1.6% and 0.3% for the 3 strains, respectively, and the differences at the lower limits of the 95% CIs were -1.8%, -3.9% and -5.6%, respectively. The proportion of seroconverters for each TIV strain in both groups exceeded the US Food and Drug Administration (FDA) guidance value for seroconversions since the lower bound of the 95% CI for ≥ fourfold rise was ≥40%. Other endpoints for the assessment of response to TIV included the proportion of subjects achieving HAI titres ≥40 and the GMTs for the 3 influenza vaccine strains. The proportions of subjects receiving 13vPnC+TIV who achieved HAI titres ≥40 were 96.4%, 98.7% and 72.5% for A/H1N1, A/H3N2, and B, respectively in Group 1. The FDA guideline that the lower limit of the 2-sided 95% CI of subjects achieving an HAI antibody titre ≥40 be ≥70% was met by the A strains, but not the B strain; the lower limit of the 95% CI for the proportion was 68.4% for the B strain. Similar proportions were observed after administration of placebo+TIV, with values of 97.0%, 97.6% and 77.6% for A/H1N1, A/H3N2 and B, respectively in Group 2. In the placebo+TIV group, the FDA guideline that the lower bound of the 2-sided 95% CI for the proportion of subjects achieving HAI antibody titre ≥40 be ≥70% was met by all 3 strains; for the B strain this value was 73.8.

Response to 13vPnC

Pneumococcal responses were assessed approximately one month after vaccination in a subset of 605 subjects. The primary endpoint for the pneumococcal analysis was the GMCs for each serotype. NI of IgG response to 13vPnC + TIV relative to 13vPnC alone was assessed based on the GMR and the twofold NI criterion. The NI criterion was met for all serotypes. GMFRs from baseline (before Dose 1) to one month after each dose were also assessed for each serotype in the two groups. GMFRs from before to after Dose 1 with 13vPnC+TIV ranged from 2.60 (serotype 3) to 11.95 (serotype 18C). 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. 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.

Conclusions

13vPnC and U.S. licensed TIV are immunologically compatible when administered together. The proportions of responders who had a ≥ fourfold increase in HAI titre for TIV vaccine antigens were similar after 13vPnC+TIV and placebo+TIV (Dose 1, Groups 1 and 2, respectively). The predefined NI criterion (lower limit of the 95% CI for the difference in proportion of responders >-10%) was met for all 3 antigens in TIV. Comparison of

pneumococcal IgG GMCs measured one month after 13vPnC+TIV (Dose 1) relative to one month after 13vPnC alone (Dose 2) in Groups 1 and 2, respectively, showed that the NI criterion (that is, the lower limit of the 2-sided 95% CI for the GMR of >0.5) was met for all serotypes.

Study 3008

Design and objectives

Study 3008 was a Phase III, parallel group, randomized, double blind, multicentre 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 7). 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 non-inferior (NI) to immune responses elicited by TIV given with placebo (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 NI to IgG responses elicited by 13vPnC alone when given one month after administration of TIV.

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

Figure 7: Study Schema - 6115A1-3008

Group	N	Year 0	1 Month
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 one 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. IgG ELISA was used to measure serotype specific IgG response to 13vPnC.

Results

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 (responders) achieving at least a fourfold increase in HAI titre

elicited by each influenza strain in TIV (A/H1N1, A/H3N2 and B vaccine strains) approximately one month after vaccination. The NI criterion was achieved for each virus strain if the lower limit of the 95% CI for the difference (13vPnC + TIV – placebo + TIV) in proportions of responders was greater than -10%. The NI criterion for the proportion of subjects achieving a ≥ fourfold increase in HAI titre (proportion who seroconverted) was met for the A/H1N1 and B vaccine strains but was missed by a very small margin for A/H3N2 (missing the predefined NI criterion by 0.4%). Differences between the two 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 NI criterion of >-10%.

However, the EMA guidance value for proportion of seroconversions of greater than 30% 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%. Additional endpoints for the assessment of response to TIV were the GMTs and GMFRs for each TIV strain. GMTs elicited by 13vPnC+TIV and by placebo+TIV, respectively, were: A/H1/N1, 195.5 and 191.9; A/H3/N2, 327.4 and 413.2; and B, 90.4 and 88.5. The GMFRs for each strain in each vaccine group also surpassed the EMA guidance value for a geometric mean increase after vaccination of greater than 2.0. GMFRs from baseline (before Vaccination 1) to post-vaccination 1 with 13vPnC+TIV or placebo+TIV, respectively, were: A/H1N1, 9.0 and 8.5; A/H3N2, 5.2 and 6.3, and B, 4.1 and 3.9. An additional endpoint was the proportion of subjects achieving HAI titres ≥40 (responders). The proportion of responders was similar in the two vaccine groups and exceeded the EMA guidance value of 60% for each vaccine strain. Values after 13vPnC + TIV and placebo + TIV, respectively, were: A/H1N1, 94.0% and 94.1%; A/H3N2, 96.5% and 97.4%; and B, 81.9% and 81.3%.

Response to 13vPnC

Pneumococcal responses were assessed before Dose 1 and approximately one 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. NI of IgG response to 13vPnC + TIV relative to 13vPnC alone was assessed based on the GMR and the twofold NI criterion. All serotypes met the NI criterion, except for serotype 19F. IgG GMCs ranged from 1.08 µg/mL (serotype 3) to 11.93 µg/mL (serotype 19A) in subjects receiving Dose 1 with 13vPnC+TIV and from 1.15 µg/mL (serotype 3) to 17.10 µg/mL (serotype 19A) in those receiving 13vPnC alone at Dose 2. GMFRs from baseline (before Dose 1) to one 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.

Conclusions

In summary, 13vPnC does not interfere with immune response to TIV when both vaccines are administered concomitantly. The NI criterion was missed by a small margin for the A/H3N2 strain, all response criteria proposed in the EMA guidance for influenza vaccines were surpassed in the 13vPnC+TIV group for each influenza strain. IgG responses to 13vPnC when given with TIV were comparable to those elicited by 13vPnC alone, although there was a trend toward lower antibody levels after 13vPnC + TIV. All serotypes met the NI criterion, except for serotype 19F (with a lower bound of 0.49 thereby missing the NI criterion). Overall, these results show 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.

Clinical studies in special populations

Evaluation of 13vPnC in high risk populations

When results were adjusted for a history of smoking, the 004 and 3001 trials revealed comparable results to those in the unadjusted population. Each trial included immunocompetent subjects with stable underlying conditions such as chronic cardiovascular disease, chronic pulmonary disease, chronic liver disease, diabetes mellitus and renal disorders, because it is known that these are common conditions in adults at increased risk of serious pneumococcal CAP and IPD. Subjects with preexisting stable disease were eligible. When examining serial responses after one or two doses in both 23vPS naïve and pre-immunised subjects, patterns of response were comparable to the study group from which they were derived. Each high risk group demonstrated a rise in antibody titre compared to pre-immunisation titres after each of one or two doses were administered. In circumstances in which statistically higher responses were observed after 13vPnC by GMFRs or comparisons of GMTs, point estimates trended higher in these subgroups. These findings indicate that these high risk adults are likely to receive analogous benefits to those in healthier older adults.

Sex

Because distribution by sex in study 6115A1-004 was statistically significantly different in the two vaccine groups in Cohort 1 (p=0.0285), enrolling more female than male subjects, a *post hoc* analysis of serotype specific OPA titres and proportion of subjects achieving an OPA titre ≥LLOQ for each serotype one month after vaccination was performed for each sex. For study 6115A1-004, the analyses revealed no apparent impact on the overall study conclusion. An additional *post hoc* analysis of immune response by sex was performed in 6115A1-3005.

Age

In study 6115A1-3005, a descriptive analysis to assess potential age related decreases of OPA antibody responses was performed in 23vPS pre-immunised subjects 70 years of age and older. Subjects were split into age groups 70 to 74 years, 75 to 79 years and ≥ 80 years of age (Table 4). The two age groups, 70 to 74 years and 75 to 79 years, had similar antibody responses after 13vPnC and these responses were well above responses after 23vPS. Subjects ≥ 80 years of age showed some reduction of the antibody responses after 13vPnC but these still exceeded responses after 23vPS.

Table 4: OPA GMTs by age in subjects >70 years of age pre-immunised with 23vPS in study 6115A1-3005 – evaluable immunogenicity population

Age (Years)	Group (N)	Serotypes												
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
70-74	13vPnC (171 – 183)	81	55	658	68	1111	1309	316	234	311	961	407	364	192
	23vPS (173 – 197)	66	59	295	44	98	587	210	114	371	605	255	234	46
75-79	13vPnC (131 – 144)	101	67	603	92	930	1478	217	198	249	945	343	331	136
	23vPS (130 – 150)	52	44	149	36	113	397	164	103	339	534	176	201	45
≥80	13vPnC (93 – 101)	59	42	333	56	599	944	182	98	274	769	290	284	135
	23vPS (89 – 98)	41	41	156	24	65	226	89	46	134	254	147	197	35

Analysis performed across trials (pooled analyses and meta-analysis)

Interpretation of study findings, additional analyses and application to immunisation strategy

Three trials in the adult 13vPnC program provided an opportunity to evaluate responses to 13vPnC compared to responses elicited by 23vPS in pneumococcal vaccine naïve older adults. Comparisons of 13vPnC and 23vPS responses were also performed as an additional analysis in the 3010 trial (60-64 years of age) and to satisfy a primary objective in the supportive Phase II study 6115A1-500 trial (≥65 years of age). In the pivotal 004 trial, OPA responses after 13vPnC were NI to the responses after 23vPS for all 12 common serotypes; the 95% CI of the GMR (13vPnC/23vPS) was > 0.5 for each of the 12 serotype comparisons and satisfied the primary objective of the study. In addition, for 8 of 12 serotypes (1, 4, 6B, 7F, 9V, 18C, 19A and 23F) the GMR 13vPnC/23vPS was >1.0, thus satisfying the secondary objective that 13vPnC was statistically significantly more immunogenic than 23vPS for "at least some" serotypes. Findings were consistent in studies 3010 and 500 to those of the pivotal NI 004 trial, as shown in Table 5. The 95% CI of the GMR (13vPnC/23vPS) were >0.5 for all serotypes in all studies, except for serotype 7F (GMR 0.46) in the 500 supportive study. For all but 2 serotypes this GMR criterion was >1 in at least two studies, and for serotypes 1, 4,6B, 9V, 18C, 19A, 23F was >1 in all 3 studies. These consistent observations show that 13vPnC elicits a statistically higher OPA response after 13vPnC compared to 23vPS for most serotypes in common.

Table 5: OPA responses after 13vPnC compared to those after 23vPS – evaluable immunogenicity population

	95% Lower CI GMR (13vPnC/23vPS) by Serotype											
Study	1	3	4	5	6B	7F	9V	14	18C	19A	19F	23F
004 (Pivotal noninferiority, age 60-64 years)	>1	>0.5	>1	>0.5	>1	>1	>1	>0.5	>1	>1	>0.5	>1
3010 (Post-hoc analysis, age 60-64 years)	>1	>0.5	>1	>1	>1	>1	>1	>0.5	>1	>1	>1	>1
500 (Supportive, age ≥65 years)	>1	>1	>1	>1	>1	0.46	>1	>0.5	>1	>1	>1	>1

Note: A value at the lower limit of the 95% CI for the GMR of >1 indicates a statistically significantly higher OPA GMT in the 13vPnC group. A value at the lower limit of the 95% CI for the GMR of >0.5 indicates that the OPA GMT after 13vPnC satisfied the non-inferiority criterion specified in study 6115A1-004.

Study 6115A1-004 also fulfilled the secondary objective to demonstrate that the proportion of subjects achieving an OPA titre ≥LLOQ to the 12 common serotypes contained in 13vPnC in response to 13vPnC is NI to the proportion of subjects achieving an OPA GMTs for all serotypes in both vaccine groups decreased over one year but OPA values were higher at one year after vaccination than at pre-vaccination. Overall, the observations are consistent with either greater or comparable responses after 13vPnC for all serotypes.

Study 6115A1-004 included a co-primary objective in pneumococcal vaccine naïve adults 60 to 64 years of age to demonstrate that the proportion of subjects receiving 13vPnC and exhibiting a fourfold increase in the serotype 6A OPA titre was statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same fourfold increase. Secondary objectives included demonstration that anti-6A OPA titres were statistically significantly greater in 13vPnC recipients than 23vPS recipients and that the proportion of 13vPnC recipients achieving a 95% lower CI OPA ≥LLOQ was both ≥85% and NI to 23vPS response; an exploratory objective was to determine that the proportional difference for 6A response (13vPnC-23vPS) was statistically significantly greater. For the 12 common serotypes in 004, as an exploratory objective, the NI of 13vPnC anti-polysaccharide IgG serotype specific responses relative to 23vPS was assessed and this criterion was met for all serotypes in the 13vPnC+AlPO4 group compared to the 23vPS group. These findings suggest that 13vPnC is more likely to generate a greater amount of functional antibody than 23vPS for a given IgG response (but this is just an exploratory analysis).

Overall, these results confirm NI OPA responses for all 12 of the common serotypes in 004, statistically significantly greater OPA responses for most serotypes in all studies, and statistically significantly greater OPA responses for serotype 6A after 13vPnC compared to 23vPS, as measured by GMR or proportion of responders above the OPA LLOQ. There is also evidence that 13vPnC favors more robust functional antibody response per binding IgG antibody compared to 23vPS. Hence, 13vPnC is likely to provide comparable or better protection than23vPS against IPD and VT-CAP in older vaccine naïve adults, due to serotypes in common and serotype 6A.

Use of 13vPnC in adults 50 to 59 years of age

The 004 study was also designed to evaluate the potential value of 13vPnC in unimmunised adults 50 to 59 years of age. This was done by comparing responses in this age group (Cohort 2) to responses after 13vPnC in adults 60 to 64 years of age (Cohort 1) (to serve as a bridge to comparisons with 23vPS). The 004 study met the primary objective, demonstrating that OPA response to the 13 serotypes in 13vPnC in the 50 to 59

year-old age group (Cohort 2) is NI to the immune response to 13vPnC in the 60 to 64 year old age group (Cohort 1) as well as the secondary objective demonstrating that the proportion of subjects achieving an OPA titre ≥LLOQ in Cohort 2 was NI to the proportion achieving this titre in Cohort 1 for all serotypes. GMTs were statistically higher for 9 of 13 serotypes and the proportion of responders was statistically higher for 2 of 13 serotypes in the 50 to 59 year old age group. Similarly, If the anti-polysaccharide IgG response in Cohort 2 relative to Cohort 1 was demonstrated and for 7 serotypes, the responses elicited in the 50 to 59 year old group were significantly greater than those in the older age group. The RCDCs for both the OPA responses and the IgG responses generally paralleled the respective GMR results. 13vPnC responses in Cohort 2 were high and curves were more separated for those serotypes for which statistically significant differences were identified. These differences widened when evaluating responses at one year.

13vPnC is the preferred choice for reimmunisation to extend protection for adults who have been previously immunised with 23vPS

The observations from study 6115A1-3005 support the conclusion that in such subjects, reimmunisation with 13vPnC may enhance and maintain protection against pneumococcal disease more effectively than with 23vPS. In the 3005 study, conducted in individuals ≥70 years of age who had been immunised with 23vPS at least 5 years earlier, 13vPnC was found to be NI to 23vPS for all 12 common serotypes; most importantly, 13vPnC induced statistically significantly greater functional antibody responses compared with 23vPS for 10 of 12 serotypes. RCDC comparisons generally demonstrated higher responses after 13vPnC compared with 23vPS throughout the full range of observed values, consistent with the overall observations. Antibody response curves demonstrated that higher responses were maintained for most serotypes for at least one year.

13vPnC should be administered first to pneumococcal vaccine naïve adults when 23vPS is under consideration to extend coverage to additional serotypes

Study 6115A1-3010 examined the sequence of administration of 13vPnC and 23vPS. Sequences compared were 13vPnC/23vPS, 23vPS/13vPnC and 13vPnC/13vPnC with each vaccine spaced a year apart in adults 60-64 years of age at the time of the first vaccine dose. Studies 6115A1-500 and 6115A1-3009 provided supportive data with evaluations of 13vPnC/23vPS, 13vPnC/13vPnC, and 13vPnC/23vPS/13vPnC in adults ≥65 years of age. The response to administration of 13vPnC followed by either 23vPS or 13vPnC appears to be preferable to the response observed when 23vPS is given first followed by a dose of 13vPnC. As one of the two primary objectives demonstrated in 3010, the immune response to 23vPS administered one year after an initial study dose of 13vPnC was at least as great as the immune response to an initial study dose of 23vPS for the 12 common serotypes as measured by serotype specific OPA titres. This sequence was significantly more immunogenic than an initial study dose of 23vPS for 6 of 12 common serotypes, satisfying an exploratory objective. Findings for an exploratory objective in supportive study 6115A1-500 were very similar. As an analysis that was not prespecified in 6115A1-3010, the lower limit of the 95% CI for the difference in proportion of responders above the OPA LLOQ was greater than 0 for 9 of 12 serotypes in common when 13vPnC/23vPS was compared with a single dose of 23vPS. RCDC curves for the 13vPnC/23vPS group were consistent with this observation. Of interest, there may be immunologic cost if the 13vPnC/23vPS sequence of immunisation is reversed, as shown by the second of two co-primary objectives and a secondary objective for study 6115A1-3010. 13vPnC/23vPS OPA responses were statistically greater for all serotypes (except serotype 14) compared to responses following the 23vPS/13vPnC sequence. The second dose of 13vPnC is common to both regimens, suggesting that 23vPS has a significant negative effect in diminishing antibody response to subsequent challenge that does not exist for 13vPnC. Importantly,

when OPA titres prior to the second dose were plotted against responses after the second dose, 13vPnC/13vPnC recipients at the lower end of the OPA range trended to have higher responses for a given pre-immunisation titre than 23vPS/13vPnC recipients for most common serotypes. Therefore, pre-immunisation titres alone prior to the second dose could not explain the disparity between groups, indicating that establishment of a more effective immune memory response after prior 13vPnC compared to 23vPS may play a role. Therefore, these data all support the perspective that sequential immunisation with 13vPnC followed by 23vPS is preferred to administration of 23vPS followed by 13vPnC, if both vaccines are used.

Coadministration with trivalent influenza vaccine in adults ≥50 years of age

Study 6115A1-3001 in adults 50 to 59 years of age and study 6115A1-3008 in adults 65 years of age and older were performed to demonstrate that immune responses to concomitantly administered trivalent influenza vaccine (TIV) and 13vPnC were compatible and that the safety profile was acceptable, compared to administration of either vaccine alone. In study 6115A1-3001, NI of the immune response to TIV was met for all 3 strains. The proportions of subjects receiving 13vPnC+TIV in Group 1 (13vPnC+TIV/placebo) who achieved HAI titres ≥40 were 94.0%, 96.5%, and 81.9% for A/H1N1, A/H3N2 and B, respectively; these proportions exceeded the EMA guidance value of >60%. Similar proportions were observed after administration of placebo+TIV in Group 2. In study 6115A1-3001, comparison of pneumococcal IgG GMCs measured one month after 13vPnC+TIV (Dose 1) relative to one month after 13vPnC alone (Dose 2) in Groups 1 and 2, respectively, showed that the NI criterion was met for all serotypes. In study 6115A1-3008, comparison of pneumococcal IgG GMCs measured one month after 13vPnC+TIV (Dose 1) relative to one month after 13vPnC alone (Dose 2) in Group 1 (13vPnC+TIV/placebo) and in Group 2 (placebo+TIV/13vPnC), respectively, showed that NI was met for all serotypes except for 19F; the lower limit of the 95% CI for GMR for 19F was 0.49. The overall immunologic profile supports concomitant use of these TIV and 13vPnC in adults ≥50 years of age.

Evaluator's overall conclusions on clinical efficacy

The burden of invasive pneumococcal disease begins to increase in adults over 50 years of age and effective immunisation of these unimmunised older adults against pneumococcal disease is an important strategy. In the US, Australia and in much of Europe, 23vPS is currently licensed and recommended for immunisation of healthy adults ≥65 years of age, as well as younger adults with specified underlying high risk conditions. The studies submitted in this dossier support the following conclusions:

- Irrespective of age or pre-immunisation status with 23vPS, 13vPnC is the preferred vaccine to elicit or extend protective levels of anti-pneumococcal functional antibodies.
- 13vPnC is compatible with use of 23vPS but should be administered first as it can partially enhance the immune response to a subsequent dose of 23vPS.
- In contrast, 23vPS elicits a "negative" immunologic state that results in lower functional antibody responses following a subsequent administration of 13vPnC. Immunocompetent adults with underlying risk conditions that place them at increased risk of pneumococcal disease are also likely to benefit from this strategy.
- The compatible immunologic profile of TIV and 13vPnC supports concomitant use of the two vaccines.

Additional studies are underway and necessary to evaluate the interval for re-immunisation with 13vPnC to best maintain functional OPA.

Safety

Introduction

Safety and tolerability data were collected in all clinical trials. Over 6000 subjects were evaluated with respect to safety. A total of 1100 PS naïve subjects received 13vPnC concomitantly with influenza vaccine. In addition to the safety assessment performed in study 6115A1-3005, a large scale safety study, 6115A1-3000, was performed in 1053 subjects vaccinated with one dose of 13vPnC at least 3 years after one or more non-study doses of 23vPS. Table 6 summarises these studies.

The tolerability and safety information arising from the formulation study 6115A1-500 (and follow on study 6115A1-3009) and the precursor study, 6097A1-508 were considered as supportive data and not included in these analyses. The precursor 6097A1-508 trial was performed with 7vPnC to evaluate the potential of pneumococcal conjugate vaccine to add value to a comprehensive approach to prevention of pneumococcal disease. This 7vPnC study explored the relationship of immune response and safety profile to vaccine dosage. Based on results of the 6097A1-508 study, the standard 0.5 mL dose licensed for use in children was chosen for investigation in the adult 13vPnC program.

Table 6: Studies contributing data to the summary of clinical safety of 13vPnC in adults

Study/Country	Objective	Subject Age[a]	Design	Vaccines or Vaccine Sequence Administered	Number of Subjects Vaccinated (as Randomized)	Data Reported in Submission
Studies in Subjects Naive to 23vPS						
6115A1-004[b] United States 5.3.5.1 Adult, 004-cohorts 1&2	Pivotal noninferiority study	Cohort 1 = 60-64 y	Single dose with 6-mo FU	13vPnC 23vPS	417 414	Fully reported (Cohorts 1 and 2 only)
		Cohort 2 = 50-59 y		13vPnC	404	
6115A1-3010 United States 5.3.5.1 Adult, 3010	Subsequent vaccination	60-64 y	2 vaccinations, administered 1 year apart Initial dose (Vaccination 1, Year 0) with 6-mo FU; and Subsequent dose (Vaccination 2, Year 1) with 6-mo FU	**Year 0 / Year 1** 13vPnC / 13vPnC 13vPnC / 23vPS 23vPS / 13vPnC	 177 301 237	Fully reported
6115A1-3001[c] United States 5.3.5.1 Adult, 3001-year 0	Compatibility with TIV	50-59 y	2 doses, administered 1 month apart, with 6-mo FU	**Dose 1 / Dose 2** 13vPnC+TIV / Placebo Placebo+TIV / 13vPnC	 551 560	Fully reported (Year 0 only)
6115A1-3008 Belgium Germany Hungary Netherlands 5.3.5.1 Adult, 3008	Compatibility with TIV	≥65 y	2 doses, administered 1 month apart	**Dose 1 / Dose 2** 13vPnC+TIV / Placebo Placebo+TIV / 13vPnC	 577 575	Fully reported

Study/Country	Objective	Subject Age[a]	Design	Vaccines or Vaccine Sequence Administered	Number of Subjects Vaccinated (as Randomized)	Data Reported in Submission
Studies in Subjects Preimmunized With 23vPS						
6115A1-3000 Germany Sweden United States 5.3.5.2 Adult, 3000	Safety study	≥68 y	Single dose with 6-mo FU	13vPnC	1049	Fully reported
6115A1-3005 Sweden United States 5.3.5.1 Adult, 3005	Subsequent vaccination	≥70 y	2 vaccinations, administered 1 year apart Initial dose (Vaccination 1, Year 0) with 6-mo FU; and Subsequent dose (Vaccination 2, Year 1) with 6-mo FU	**Year 0 / Year 1** 13vPnC / 13vPnC 23vPS / 13vPnC	 463 473	Fully reported

Abbreviations: 13vPnC = 13-valent pneumococcal conjugate vaccine; 23vPS = 23-valent polysaccharide vaccine; 6-mo FU = 6 month follow up telephone contact; TIV = trivalent inactivated influenza vaccine; y = years.
a. Age per protocol entry criteria.
b. For study 004, only data for Cohorts 1 and 2 are included in the submission; data for Cohort 3 (subjects aged 18 through 49 years) are not included.
c. For study 3001, only data collected during the first year of the study (Year 0) are included in the submission.

As listed in Table 6, these data include 4 studies conducted in adults not previously vaccinated with the licensed 23-valent pneumococcal polysaccharide vaccine (23vPS) (naïve subjects) and two studies in adults who had previously received 23vPS (pre-immunised subjects). Safety data from the two supportive studies submitted with this application (studies 6115A1-500 and 6115A1-3009) are not included in this summary of safety because those studies did not use the final commercial formulation of 13vPnC. The studies varied with respect to design and objectives but all used standardized methods for collection of safety data. The safety parameters evaluated in each study included unsolicited adverse events (AEs) and predefined, solicited adverse events (local reactions at the injection site and systemic events). Local reactions included pain, redness, swelling,

and limitation of arm movement. Systemic events included fever, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain and aggravated generalized joint pain. Data regarding medications taken to treat pain and medications taken to treat fever were also collected in all studies, except study 004. Subjects monitored these local reactions, systemic events and medications daily for 14 days after each study vaccination and recorded the information. Data regarding unsolicited adverse events were collected by the investigator based on clinical evaluation of the subject as well as information provided by the subject in response to nonspecific questions. Information was collected for AEs that occurred from each clinic visit at which the vaccine was administered through the post-vaccination visit, approximately one month after vaccination. Approximately 6 months after each vaccination, subjects were to be contacted by phone and were asked to report any newly diagnosed chronic medical conditions (including autoimmune and neuroinflammatory diseases) and any serious adverse events that had occurred since the last study visit, and this information was to be recorded on the AE case report form. Three of the six primary adult studies compared 13vPnC with 23vPS.

Patient exposure

In the 6 primary studies, the safety populations comprise a total of 6198 subjects, of which 4213 (68.0%) were naïve to 23vPS and 1985 (32.0%) were pre-immunised (Table 7). Overall, 49.4% of vaccinated subjects were between 50 and 64 years of age at enrollment (per protocol), and 50.6% were ≥65 years of age (Table 8).

Table 7: Number (%) of subjects who received at least one 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 enrolment, per protocol.
b. The numbers in this row are used as the denominators for percentages.

Table 8: Number (%) of subjects who received at least one dose of study vaccine, by age per protocol

Age per Protocol[a] Study Vaccine Group (as Randomized)	Number (%) of Subjects
TOTAL[b]	6198 (100.0)
50-64 y	3061 (49.4)
50-59 y	1515 (24.4)
004	
13vPnC (50-59 y)	404 (6.5)
3001	
13vPnC+TIV/placebo	551 (8.9)
Placebo+TIV/13vPnC	560 (9.0)
60-64 y	1546 (24.9)
004	
13vPnC (60-64 y)	417 (6.7)
23vPS (60-64 y)	414 (6.7)
3010	
13vPnC/13vPnC	177 (2.9)
13vPnC/23vPS	301 (4.9)
23vPS/13vPnC	237 (3.8)
≥65 y	3137 (50.6)
3000*	
13vPnC	1049 (16.9)
3005*	
13vPnC/13vPnC	463 (7.5)
23vPS/13vPnC	473 (7.6)
3008	
13vPnC+TIV/placebo	577 (9.3)
Placebo+TIV/13vPnC	575 (9.3)

* = study in pre-immunised subjects.
Abbreviation: y = years.
a. Age cohort or age at enrollment, per protocol.
b. The numbers in this row are used as the denominators for percentages.

Total number of subjects vaccinated with 13vPnC or 23vPS at any time

During the Studies

The number of subjects vaccinated with 13vPnC or 23vPS at any time during the six primary studies is summarized by study and vaccine actually administered in Table 9 and Table 10. In these tables, for studies 3001 and 3008, the total for 13vPnC includes subjects who received Dose 1 of 13vPnC+TIV/placebo and subjects who received Dose 2 of placebo+TIV/13vPnC. For studies 3010 and 3005, subjects who received both 13vPnC and 23vPS (administered one year apart) are counted once in each column, while subjects who received two doses of 13vPnC are counted only once for 13vPnC. The safety of initial and subsequent study doses of pneumococcal vaccine administered one year apart was evaluated in studies 3010 and 3005. The number of subjects who received Vaccination 2 in a sequence of two pneumococcal vaccines in these studies is shown in Table 11.

Table 9: Number (%) of subjects vaccinated with 13vPnC or 23vPS at any time during the study, by vaccination status

	Vaccine Group (As Administered)	
	13vPnC	23vPS
Study (Age per Protocol)[a]	Number (%) of Subjects	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.

Table 10: Number (%) of subjects vaccinated with 13vPnC or 23vPS at any time during the study, by age per protocol

	Vaccine Group (As Administered)	
Age per Protocol * Study	13vPnC Number (%) of Subjects	23vPS Number (%) of Subjects
TOTAL[b]	5667 (100.0)	1391 (100.0)
50-64 y	2616 (46.2)	918 (66.0)
50-59 y	1498 (26.4)	N/A
004	404 (7.1)	N/A
3001	1094 (19.3)[c]	N/A
60-64 y	1118 (19.7)	918 (66.0)
004	417 (7.4)	414 (29.8)
3010	701 (12.4)[d]	504 (36.2)[d]
≥65 y	3051 (53.8)	473 (34.0)
65-74 y	1785 (31.5)	206 (14.8)
65-69 y	646 (11.4)	N/A
3000*	151 (2.7)	N/A
3008	495 (8.7)[c]	N/A
70-74 y	1139 (20.1)	206 (14.8)
3000*	412 (7.3)	N/A
3005*	385 (6.8)[d]	206 (14.8)[d]
3008	342 (6.0)[c]	N/A
≥75 y	1266 (22.3)	267 (19.2)
75-80 y	760 (13.4)	158 (11.4)
3000*	289 (5.1)	N/A
3005*	289 (5.1)[d]	158 (11.4)[d]
3008	182 (3.2)[c]	N/A
≥80 y	506 (8.9)	109 (7.8)
3000*	197 (3.5)	N/A
3005*	193 (3.4)[d]	109 (7.8)[d]
3008	116 (2.0)[c]	N/A

* = study in pre-immunised with 23vPS.
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.

Table 11: 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)*	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.

Disposition

Studies in naïve subjects

Table 12 summarizes disposition for the 4 primary studies in naïve subjects (studies 004, 3001, 3008, 3010). For studies 004 and 3010, data are included in this table for Vaccination 1 (Year 0) only. In each of the 4 studies in naïve subjects, ≥99.1% of randomized subjects in each vaccine group received at least one dose of study vaccine (Table 12). In studies 004 and 3010 (Year 0 only), at least 98.0% of subjects in each group completed the one month post-vaccination visit, while in studies 3001 and 3008, at least 95.9% of subjects in each group completed the one month post-vaccination visit after Dose 2. In study 004, 3.3% of subjects were withdrawn from the study after the 6 month follow up contact for Vaccination 1 but before the blood draw at Year 1, while 94.5% of subjects completed the one year blood draw. In study 3010, 7.2% of subjects were withdrawn from the study after the 6 month follow up contact for Vaccination 1 but before Vaccination 2. Overall, 90.3% of randomized subjects received Vaccination 2 and 89.3% of subjects completed the 6 month follow up phone contact after Vaccination 2. Across the 4 studies, the most frequently reported reasons for study withdrawal were subject request and protocol violation. A total of 4 subjects died during the studies in naïve subjects: 2 subjects (1 in each vaccine group) after receiving Dose 2 in study 3008; 1 subject after receiving 13vPnC+TIV in study 3001; and 1 subject after receiving 13vPnC in study 004. None of the deaths were considered related to study vaccine.

Table 12: Disposition of subjects – Vaccination 1 (Year 0) (studies in subjects naïve to 23vPS)

Study	3001		004			3010		3008	
Age per Protocol (years)[a]	50-59 y		50-59 y	60-64 y	60-64 y	60-64 y		≥65 y	
Vaccine Group (as Randomized/Assigned)	13vPnC+TIV/ Placebo n (%)	Placebo+TIV/ 13vPnC n (%)	13vPnC n (%)	13vPnC n (%)	23vPS n (%)	13vPnC n (%)	23vPS n (%)	13vPnC+TIV/ Placebo n (%)	Placebo+TIV/ 13vPnC n (%)
Randomized/assigned[b]	554 (100.0)	562 (100.0)	406 (100.0)	418 (100.0)	417 (100.0)	482 (100.0)	238 (100.0)	580 (100.0)	580 (100.0)
Vaccinated[c]									
Dose 1	551 (99.5)	560 (99.6)	404 (99.5)	417 (99.8)	414 (99.3)	478 (99.2)	237 (99.6)	577 (99.5)	575 (99.1)
Dose 2	538 (97.1)	543 (96.6)	N/A	N/A	N/A	N/A	N/A	560 (96.6)	558 (96.2)
Completed visit for blood draw[d]	536 (96.8)	539 (95.9)	398 (98.0)	416 (99.5)	412 (98.8)	475 (98.5)	237 (99.6)	556 (95.9)	557 (96.0)
Withdrawn before vax 1 blood draw	18 (3.2)	23 (4.1)	6 (1.5)	1 (0.2)	2 (0.5)	3 (0.6)	0 (0.0)	24 (4.1)	23 (4.0)
Reasons for withdrawal									
Subject request	8 (1.4)	10 (1.8)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (2.1)	11 (1.9)
Protocol violation	2 (0.4)	4 (0.7)	3 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	7 (1.2)	8 (1.4)
Lost to follow-up	3 (0.5)	6 (1.1)	2 (0.5)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Other	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.3)
Investigator Request	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failed to Return	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Adverse event	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Completed vax 1, 6-month contact	529 (95.5)	528 (94.0)	392 (96.6)	411 (98.3)	411 (98.6)	468 (97.1)	234 (98.3)	N/A	N/A
Withdrawn after vaccination period but before vax 1, 6-month contact	5 (0.9)	10 (1.8)	6 (1.5)	5 (1.2)	1 (0.2)	7 (1.5)	3 (1.3)	N/A	N/A
Unknown	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A

Study	3001		004			3010		3008	
Age per Protocol (years)[a]	50-59 y		50-59 y	60-64 y	60-64 y	60-64 y		≥65 y	
Vaccine Group (as Randomized/Assigned)	13vPnC+TIV/ Placebo n (%)	Placebo+TIV/ 13vPnC n (%)	13vPnC n (%)	13vPnC n (%)	23vPS n (%)	13vPnC n (%)	23vPS n (%)	13vPnC+TIV/ Placebo n (%)	Placebo+TIV/ 13vPnC n (%)
Reasons for withdrawal									
Subject request	1 (0.2)	4 (0.7)	3 (0.7)	1 (0.2)	1 (0.2)	4 (0.8)	0 (0.0)	N/A	N/A
Lost to follow-up	2 (0.4)	4 (0.7)	2 (0.5)	0 (0.0)	0 (0.0)	3 (0.6)	2 (0.8)	N/A	N/A
Protocol violation	1 (0.2)	2 (0.4)	0 (0.0)	4 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	N/A	N/A
Death	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A
Other	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A

Abbreviations: N/A = not applicable; vax = vaccination; y = years.
a. Age cohort (study 004); or age at enrollment, per protocol.
b. The values in this row are used as the denominators for percentages.
c. Dose 1 includes all studies; Dose 2 refers to the second dose of studies 3001 and 3008 only; for study 004, subject 004-019-002243 was randomized and vaccinated in error without a consent form; the subject is counted as vaccinated in the table.
d. Completed vaccination period: for studies 004 and 3010, completed the visit for the post-vaccination blood draw (28 – 57 days after vaccination); for studies 3001 and 3008, completed the visit for the blood draw after Dose 2 (28 – 57 days after Dose 2); for study 3001, subjects 3001-006-1063 and 3001-007-1207 who competed the visit but had no blood draw after Dose 2 (28 – 57 days after Dose 2) are included.

Studies in Pre-immunised Subjects

Disposition is summarized in Table 13 for the two primary studies in pre-immunised subjects: study 3000, in which all subjects received 13vPnC; and study 3005, in which subjects received either 13vPnC or 23vPS at Vaccination 1. In both study 3000 and study 3005, ≥99.6% of randomized subjects in each vaccine group received at least one dose of study vaccine, ≥99.1% of subjects in each group completed the one month post-vaccination visit and ≥97.7% of subjects in each group completed the 6 month follow up contact after Vaccination 1. The most frequent reasons for withdrawal from the studies through the 6 month follow up contact were subject request in study 3000 and protocol violations in study 3005. In study 3005, 13.0% of subjects were withdrawn from the study after the 6 month follow up contact for Vaccination 1 but before Vaccination 2. The most frequent reason for discontinuation at this point in the study was "other" (6.0%). Most of

these subjects were withdrawn because they no longer qualified for the study, often because of deterioration in health or because of receipt of prohibited medications or blood products. Overall, 84.8% of randomized subjects received Vaccination 2 and 84.1% of subjects completed the 6 month follow up phone contact after Vaccination 2.

A total of 12 subjects died during the studies in pre-immunised subjects: 3 subjects after receiving 13vPnC in study 3000 and 9 subjects in study 3005 (4 after receiving 13vPnC, 4 after receiving 23vPS and one after receiving 13vPnC/13vPnC). None of the deaths were considered related to study vaccine. No subjects were withdrawn from study 3000 because of adverse events while a total of 11 subjects were withdrawn from study 3005 because of adverse events: 4 after receiving 13vPnC; 6 after receiving 23vPS; and one after receiving 13vPnC/13vPnC. None of the adverse events leading to withdrawal were considered related to study vaccine.

Table 13: Disposition of subjects – Vaccination 1 (Year 0) (studies in subjects pre-immunised with 23vPS)

	Study 3000		Study 3005			
Age per Protocol (years)	≥68 y		≥70 y			
Vaccine Group (as Randomized/Assigned)	13vPnC		13vPnC		23vPS	
	n	%	n	%	n	%
Randomized/assigned[a]	1053	100.0	464	100.0	474	100.0
Vaccinated	1049	99.6	463	99.8	473	99.8
Completed 1 month post vaccination visit[b]	1046	99.3	460	99.1	473	99.8
Withdrawn before vax 1 post vaccination visit	7	0.7	3	0.6	0	0.0
Reasons for withdrawal						
Subject request	4	0.4	3	0.6	0	0.0
Protocol violation	2	0.2	0	0.0	0	0.0
Other	1	0.1	0	0.0	0	0.0
Completed vax 1, 6-month follow-up	1040	98.8	455	98.1	463	97.7
Withdrawn after vax 1 post vaccination visit but before vax 1, 6-month follow-up	6	0.6	5	1.1	10	2.1
Reasons for withdrawal						
Death	3	0.3	2	0.4	2	0.4
Protocol violation	0	0.0	3	0.6	4	0.8
Lost to follow-up	3	0.3	0	0.0	1	0.2
Subject request	0	0.0	0	0.0	2	0.4
Adverse event	0	0.0	0	0.0	1	0.2

Abbreviations: vax = vaccination; y = years.
a. The values in this row are used as the denominators for percentages.
b. Completed the post-vaccination visit in study 3000 or completed the post-vaccination blood draw (29 – 43 days after vaccination) visit in study 3005.

Adverse events

Local Reactions

- Local reactions (redness, swelling and pain at the injection site; and limitation of arm movement) were monitored daily by subjects from Day 1 through Day 14 after study vaccine administration and recorded. Subjects measured the actual size of redness or swelling with a caliper.

If pain at the injection site was present, subjects were to record the severity of the pain using the following scale:

- Mild: awareness of sign or symptom, but easily tolerated;
- Moderate: discomfort enough to cause interference with usual activity;
- Severe: incapacitating, with inability to do usual activity

Limitation of arm movement was assessed using the following scale:

- Absent: no limitation of arm movement;
- Mild: some limitation of arm movement;
- Moderate: unable to move arm above head, but able to move arm above shoulder;
- Severe: unable to move arm above shoulder

Pain at the injection site occurring within the first 30 minutes after vaccination was assessed as mild, moderate, severe, using the scale described above and the maximum pain was documented.

Systemic Events

- Systemic events (fever, chills, fatigue, headache, vomiting, decreased appetite, rash, generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain and aggravated generalized joint pain) were monitored daily by subjects from Day 1 through Day 14 after study vaccine administration and recorded as present or absent for each day. Oral temperature was collected daily for 14 days after study vaccine administration.

For summarization, adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).[7]

Solicited Adverse Events

Local Reactions

Table 14 summarises local reactions across ages and studies.

[7] MedDRA = Medical Dictionary for Regulatory Activities

Table 14: 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 Age per Protocol (years)	3001[a] 50-59 y (%)	004 50-59 y (%)	004 60-64 y (%)	3010[b] 60-64 y (%)	3008[a] ≥65 y (%)	3000 ≥68 y (%)	3005[b] ≥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.

13vPnC in 23vPS naïve and 23vPS pre-immunised subjects across studies

The incidence of redness reported after an initial study vaccination of 13vPnC was similar across all 6 studies, ranging from 10.8% to 20.2%, with no apparent differences among the age groups or between naïve and pre-immunised 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% to 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. 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). 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 naïve and 23vPS pre-immunised subjects

The incidence of most local reactions after vaccination with 13vPnC was similar between 23vPS naïve and 23vPS pre-immunised subjects of similar age (pre-immunised adults ≥68

years of age in studies 6115A1-3000 and 6115A1-3005, and naïve adults ≥65 years of age in study 6115A1-3008). The exception was pain, which was reported more often in pre-immunised subjects (51.0% to 51.7%) than in 23vPS naïve subjects (41.7%).

13vPnC compared with 23vPS in 23vPS naïve subjects

In subjects 60 to 64 years of age and naïve 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%) as shown in Table 15.

Table 15: Subjects reporting local reactions within 14 days after an initial study vaccination - comparison of 13vPnC and 23vPS (subjects naïve 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.

13vPnC compared with 23vPS in 23vPS pre-immunised subjects

In subjects ≥70 years of age who had previously received one 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%). These results indicate that subjects pre-immunised with 23vPS 5 or more years previously have

significantly higher local reactogenicity when revaccinated with another dose of 23vPS, compared to vaccination with 13vPnC.

13vPnC and 23vPS administered in 2 vaccine sequences in 23vPS naïve subjects

In study 6115A1-3010, subjects 60 to 64 years of age naïve to 23vPS received an initial dose of either 13vPnC or 23vPS. Subjects who received 13vPnC were vaccinated one year later with either 13vPnC or 23vPS (vaccine sequences designated as 13vPnC/13vPnC or 13vPnC/23vPS, respectively); and subjects who received 23vPS were vaccinated one year later with 13vPnC (23vPS/13vPnC). For each of the four 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 two 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 four reaction types were reported at statistically significantly higher incidence after 13vPnC/23vPS than after 23vPS alone. Pain and limitation of arm movement were the two 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 three 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/23vPS (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 pre-immunised subjects

In study 6115A1-3005, subjects ≥70 years of age pre-immunised with one 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 one dose of 13vPnC. For each of the four 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 of the four 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% (Table 16). For each type of local reaction, the incidence of severe reports after each vaccination was ≤1.8%.

Table 16: Subjects reporting local reactions within 14 days after an initial study vaccination - comparison of 13vPnC and 23vPS (subjects pre-immunised with 23vPS, ≥70 years of age; study 3005)

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

Note: Data presented are from the Vaccination 1 safety population.
a. N = number of subjects with known values.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference in proportions, [13vPnC] - [23vPS], expressed as a percentage.
e. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, [13vPnC] - [23vPS], expressed as a percentage.

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)

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%. The reactogenicity of a subsequent study vaccination of 13vPnC administered one year after an initial study vaccination of 23vPS (23vPS/13vPnC Vaccination 2) was compared with the reactogenicity of an initial study vaccination of 13vPnC using intergroup comparison methods. These analyses utilized pooled data for all subjects who received 13vPnC at Vaccination 1, including subjects randomized to 13vPnC/13vPnC and subjects randomized to 13vPnC/23vPS. Results of these analyses show that the incidence of local reactions was similar after 13vPnC (Vaccination 1) and 23vPS/13vPnC (Vaccination 2), respectively, for swelling (10.0%, 5.0%), pain (69.2%, 69.8%) and limitation of arm movement (23.5%, 18.5%). The incidence of redness was statistically significantly higher after 13vPnC (Vaccination 1) than after 23vPS/13vPnC (Vaccination 2), respectively, both for any redness (12.2%, 4.3%; p = 0.015) and for moderate redness (6.4%, 0.9%; p=0.016). However, these differences were not considered clinically important. For all four types of local reactions, most reports were mild and the incidence of severe reactions was ≤2.3% after each vaccination.

The reactogenicity of a subsequent study vaccination of 23vPS administered one year after an initial study vaccination of 13vPnC (13vPnC/23vPS Vaccination 2) was compared with the reactogenicity of an initial study vaccination of 23vPS using intergroup comparison methods. Results of these analyses show that, for each of the four reaction types, the incidence was statistically significantly higher after 13vPnC/23vPS (Vaccination 2) than after 23vPS (Vaccination 1) (p<0.001). The incidence of local reactions was as follows for 23vPS (Vaccination 1) and 13vPnC/23vPS (Vaccination 2), respectively: redness (11.2%, 27.8%), swelling (10.4%, 25.8%), pain (58.3%, 85.7%) and limitation of arm movement (28.2%, 53.4%). After both vaccinations, most reports of local reactions were mild. The incidence of severe reactions after 23vPS (Vaccination 1) was ≤2.3% for each type of local reaction, whereas after 13vPnC/23vPS (Vaccination 2), the incidence of severe reactions ranged from 6.1% (for severe swelling) to 12.9% (for severe pain).

Comparisons between subsequent vaccinations of 13vPnC or 23vPS

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

Vaccination 2	Vaccination 2
13vPnC/13vPnC versus	13vPnC/23vPS
13vPnC/13vPnC versus	23vPS/13vPnC
13vPnC/23vPS versus	3vPS/13vPnC

After Vaccination 2, for each of the four types of local reactions, the incidence was highest in the 13vPnC/23vPS vaccine group and lowest in the 23vPS/13vPnC group. In pairwise comparisons, the incidence of each type of reaction was statistically significantly higher in the 13vPnC/23vPS vaccine group than in either the 13vPnC/13vPnC group or the

23vPS/13vPnC group. Each of the four types of local reactions was reported more frequently after administration of 13vPnC/13vPnC than after 23vPS/13vPnC, although the differences between the groups were statistically significant only for redness and for swelling. In all 3 groups, most reports of local reactions after Vaccination 2 were mild. Severe reactions were reported most frequently in the 13vPnC/23vPS group, ranging from 6.1% for severe swelling to 12.9% for severe pain. For all four reaction types, the lowest incidence of severe reports was observed in the 23vPS/13vPnC group (0.0% for severe redness and severe swelling; 0.9% for severe pain; and 1.7% for severe limitation of arm movement).

13vPnC with concomitant administration of trivalent influenza vaccine (TIV)

For each type of local reaction, in subjects 50 to 59 years of age naïve to 23vPS (study 6115A1-3001), the incidence of reports after concomitant administration of 13vPnC+TIV was similar to the incidence after 13vPnC administered alone. The two 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 naïve 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 of 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.

Systemic events

13vPnC in 23vPS naïve and 23vPS pre-immunised subjects across studies

The incidence of systemic events reported within 14 days after an initial study vaccination of 13vPnC was assessed in 6 studies (Table 17). The incidence of fever 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). Results of the *post hoc* analyses showed that, after an 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.

The incidence of most systemic events was similar between naïve and pre-immunised subjects of similar age (naïve subjects ≥65 years in study 6115A1-3008; pre-immunised 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-immunised subjects in study 6115A1-3005 (36.8%) than among naïve subjects in study 6115A1-3008 (23.4%). However, the incidence in pre-immunised subjects in study 6115A1-3000 (25.3%) was similar to that in naïve subjects.

Table 17: Subjects reporting systemic events within 14 days after an initial study vaccination of 13vPnC, by immunization status and age

Study Number	Naive to 23vPS					Preimmunized With 23vPS	
	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 >40C after Vaccination 1 were confirmed to be the result of e-diary data entry errors.

13vPnC compared with 23vPS in 23vPS naïve subjects

In subjects 60 to 64 years of age and naïve 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 18).

Table 18: Subjects reporting systemic events within 14 days after an initial study vaccination - comparison of 13vPnC and 23vPS (subjects naïve 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 pre-immunised subjects

In subjects ≥70 years of age who had previously received one 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 19).

Table 19: Subjects reporting systemic events within 14 days after an initial study vaccination – comparison of 13vPnC and 23vPS (subjects pre-immunised with 23vPS, ≥70 years of age; study 3005)

	Vaccine Group (as Administered)										
	13vPnC				23vPS						
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])	p-Value[e]
Fever											
Any (≥38°C)	299	3	1.0	(0.2, 2.9)	309	13	4.2	(2.3, 7.1)	-3.2	(-6.2, -0.7)	0.013
Mild (≥38°C but <38.5°C)	299	3	1.0	(0.2, 2.9)	303	6	2.0	(0.7, 4.3)	-1.0	(-3.4, 1.2)	0.535
Moderate (≥38.5°C but <39°C)	297	0	0.0	(0.0, 1.2)	301	0	0.0	(0.0, 1.2)	0.0	(-1.2, 1.3)	>.999
Severe (≥39°C but ≤40°C)	297	0	0.0	(0.0, 1.2)	301	1	0.3	(0.0, 1.8)	-0.3	(-1.8, 0.9)	0.509
Potentially life threatening (>40°C)[f]	297	0	0.0	(0.0, 1.2)	307	6[f]	2.0	(0.7, 4.2)	-2.0	(-4.2, -0.5)	0.015
Fatigue	350	119	34.0	(29.0, 39.2)	367	159	43.3	(38.2, 48.6)	-9.3	(-16.4, -2.2)	0.011
Headache	329	78	23.7	(19.2, 28.7)	331	86	26.0	(21.3, 31.1)	-2.3	(-8.9, 4.3)	0.510
Chills	305	24	7.9	(5.1, 11.5)	312	35	11.2	(7.9, 15.3)	-3.3	(-8.1, 1.3)	0.162
Rash	303	22	7.3	(4.6, 10.8)	323	53	16.4	(12.5, 20.9)	-9.1	(-14.3, -4.0)	<.001
Vomiting	300	5	1.7	(0.5, 3.8)	304	4	1.3	(0.4, 3.3)	0.4	(-1.9, 2.7)	0.808
Decreased appetite	317	33	10.4	(7.3, 14.3)	313	36	11.5	(8.2, 15.6)	-1.1	(-6.1, 3.9)	0.688
New generalized muscle pain	345	127	36.8	(31.7, 42.1)	358	160	44.7	(39.5, 50.0)	-7.9	(-15.2, -0.6)	0.034
Aggravated generalized muscle pain	320	66	20.6	(16.3, 25.5)	334	92	27.5	(22.8, 32.7)	-6.9	(-13.6, -0.3)	0.039
New generalized joint pain	310	39	12.6	(9.1, 16.8)	323	48	14.9	(11.2, 19.2)	-2.3	(-7.7, 3.1)	0.413
Aggravated generalized joint pain	310	36	11.6	(8.3, 15.7)	322	53	16.5	(12.6, 21.0)	-4.8	(-10.3, 0.6)	0.081
Use of medication to treat pain	327	72	22.0	(17.6, 26.9)	342	91	26.6	(22.0, 31.6)	-4.6	(-11.2, 1.9)	0.169
Use of medication to treat fever	304	9	3.0	(1.4, 5.5)	308	19	6.2	(3.8, 9.5)	-3.2	(-6.8, 0.2)	0.059

a. N = number of subjects with known values.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference in proportions, [13vPnC] – [23vPS], expressed as a percentage.
e. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, [13vPnC] – [23vPS], expressed as a percentage.

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 naïve to 23vPS. Subjects received an initial dose of either 13vPnC or 23vPS. 13vPnC recipients were vaccinated one year later with either 13vPnC or 23vPS. 23vPS recipients were vaccinated one 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 one 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, which was reported 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 one case of severe fever (≥39°C but ≤40°C) after 13vPnC alone. 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. The most frequently reported types of systemic events after 23vPS and 13vPnC/23vPS were fatigue, headache and new generalized muscle pain. 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 sequences, with 2.5% after 13vPnC/13vPnC, 3.1% after 13vPnC/23vPS, and 0.9% after 23vPS/13vPnC.

13vPnC and 23vPS administered as a 2 vaccine sequence in 23vPS pre-immunised subjects

In study 6115A1-3005, systemic events were assessed in adults ≥70 years of age pre-immunised with 23vPS at least 5 years previously. 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, one subject reported severe fever (≥39°C but ≤40°C) and one subject had a confirmed report of a temperature of 40°C on Day 2 after vaccination. The most frequently reported systemic events after both 13vPnC 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. 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.

Comparisons between subsequent vaccinations of 13vPnC

The incidence of systemic events reported after the subsequent vaccination of 13vPnC was similar in the 13vPnC/13vPnC and 23vPS/13vPnC groups. This was true for all types of systemic events as well as for the use of medication to treat fever and pain. Although the incidence of vomiting was statistically significantly higher in the 23vPS/13vPnC group (3.1%) than in the 13vPnC/13vPnC group (0.4%) (p=0.032), the actual difference in the percentage of subjects reporting the event was small and was not considered clinically meaningful.

13vPnC with concomitant administration of trivalent influenza vaccine (TIV)

After concomitant administration of 13vPnC+TIV in subjects 50 to 59 years of age (study 6115A1-3001), the frequencies of all systemic reactions were similar to those observed after 13vPnC administered alone, except for a statistically higher frequency of headache after 13vPnC+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 groups. 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 (58.1% and 52.4%). The incidence of fever was similar in both groups, with 3.4% after 13vPnC+TIV and 1.5% after TIV alone, and with slightly more moderate fever (≥38.5°C but <39°C) after 13vPnC+TIV (1.5%) than after TIV alone (0%).

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.

The incidence of systemic events can also be compared between the different age groups (50 to 59 years in study 6115A1-3001 and ≥65 years in study 6115A1-3008). After administration of 13vPnC+TIV, the incidence of each type of systemic event was higher in the younger age group (study 6115A1-3001) than in the older age group (study 6115A1-3008), except for fever, which was reported at similar incidence in both studies.

Unsolicited adverse events

Adverse events after 13vPnC across studies

The incidence of AEs reported within one 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. 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 naïve 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. Across the studies, the types of AEs reported most frequently were in the System Organs Classes (SOCs) of *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 six 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 *General Disorders and Administration Site Conditions*. 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 (for example, *Cardiac Disorders* and *Musculoskeletal and Connective Tissue Disorders*). 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 AEs reported at the 6 month follow up contact were considered related to study vaccine: one case of arthralgia, bursitis, and tendonitis, and one case of Guillain-Barré syndrome.

Adverse events in 23vPS naïve subjects

In 23vPS-naïve subjects 60 to 64 years of age (study 6115A1-004 [Cohort 1] and study 6115A1-3010), the overall incidence of AEs as well as the types of AEs reported within one month after administration of 13vPnC were similar to those observed after administration of 23vPS and the incidence and types of AEs reported at the 6 month follow up contact were also generally similar after 13vPnC and 23vPS. In study 6115A1-3010, the incidences and types of AEs reported within one month after the second vaccination were similar among the 3 vaccine sequence groups, with overall incidence ranging from 13.8% to 19.1% and the most frequently reported types of AEs being *Infections and Infestations* (4.0% to 7.5% of subjects). AEs considered related to study vaccine were reported in ≤1.9% of subjects in each sequence group. The incidences of AEs reported at the 6 month follow up after Vaccination 2 were also similar among the sequence groups and none of the AEs reported at the 6 month follow up after vaccination were considered vaccine related. After each initial and subsequent vaccination, the types of AEs reported most frequently were *Infections and Infestations* (4% to 13.1%). The incidences of vaccine related AEs were also similar between Vaccination 2 and Vaccination 1 of the regimens compared.

Adverse events in 23vPS pre-immunised subjects

In study 6115A1-3005, subjects ≥70 years of age who had received 23vPS at least 5 years before study entry received 2 vaccinations administered one year apart: 13vPnC/13vPnC or 23vPS/13vPnC. The overall incidence and types of AEs and related AEs reported within one month after the initial study vaccination of 13vPnC were similar to those reported after 23vPS and the most frequently reported types of AEs in both vaccine groups were *Infections and Infestations* (4.1% and 5.3%, respectively). AEs reported at the 6 month follow up were also similar between the vaccine groups and none were considered related to study vaccine. The incidence and types of AEs and related AEs reported within one month after Vaccination 2 were similar between the two groups and were also similar to those reported after Vaccination 1 of 13vPnC. The types of AEs most frequently reported within one month after 13vPnC/13vPnC or 23vPS/13vPnC Vaccination 2 were *Infections and Infestations* (3.3% and 4.5%), and AEs considered related to study vaccine were reported in 2.6% and 1.5% of subjects, respectively. The incidences of AEs reported at the 6 month follow up contact after Vaccination 2 were also similar between the 2 vaccine regimens and were similar to those observed at the 6 month follow up after Vaccination 1.

Adverse events after 13vPnC with concomitant administration of trivalent influenza vaccine (TIV)

AEs reported within one month after administration of 13vPnC+TIV were compared with those reported after 13vPnC alone or after TIV alone. In 50 to 59 year old subjects (study 6115A1-3001), the incidence of AEs reported after 13vPnC+TIV (16.7%) was statistically significantly higher than the incidence after 13vPnC alone (11.8%), whereas in subjects ≥65 years of age (study 6115A1-3008), the incidence of AEs was similar between the two groups (13% and 15.8%). In both age groups, the incidence of AEs reported after 13vPnC+TIV was similar to the incidence after TIV alone. In both age groups, the most frequent types of AEs after 13vPnC+TIV, 13vPnC alone or TIV alone were *Infections and Infestations* (3.5% to 7.7% of subjects). In both age groups, AEs considered related to study vaccine were reported in ≤3.1%of subjects after any vaccination. The most frequently reported related AEs were events associated with vaccine administration (for example, erythema, myalgia, headache).

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 six 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 *General Disorders and Administration Site Conditions*. In naïve subjects 60 to 64 years old and in 23vPS-pre-immunised subjects ≥70 years old, the incidence of related AEs after an initial study vaccination of 13vPnC was similar to the incidence after 23vPS. In both 23vPS naïve and 23vPS pre-immunised 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. AEs reported at the 6 month follow up contact after vaccination were seldom considered related to study vaccine. One 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 one case of cutaneous lupus erythematosus after vaccination with 23vPS, one case of injection site nodule after 13vPnC+TIV, one case of erythema after 23vPS/13vPnC and one case of idiopathic thrombocytopenic purpura (ITP) after 23vPS/13vPnC ongoing at the 6 month follow up contact.

Conclusions: Systemic Events

After an Initial Study Vaccination of 13vPnC

- Fever was reported at similar incidence and severity across studies, regardless of subject age.
- Other than 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 naïve subjects and pre-immunised subjects.
- Mild systemic events such as fatigue, muscle pain and headache were very common in all groups, more common after a second study vaccine (of either type).

After an Initial Study Vaccination of 13vPnC or 23vPS

In subjects 60 to 64 years of age and naïve 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-immunised 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 naïve 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.
- 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.

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 comparisons showed no statistically significant differences between the groups in the incidence of any systemic event.

In pre-immunised 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.

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 two 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%).
- 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 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 of age), 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 alone for all systemic events except headache, which was reported at statistically higher incidence after administration of 13vPnC+TIV than after 13vPnC alone.
- Among older subjects (≥65 years of age), six types of systemic events were reported at statistically higher incidence after administration of 13vPnC+TIV than after 13vPnC alone (fatigue, headache, chills, decreased appetite, new joint pain and aggravated joint pain).
- Among younger subjects (50 to 59 years of age), most types of systemic events were reported at statistically significantly higher incidence after administration of 13vPnC+TIV than after TIV alone; the exceptions were fever, fatigue, vomiting and aggravated joint pain, which were reported at similar incidence in the two groups.
- Among older subjects (≥65 years of age), all systemic events were reported at similar incidence between the two groups, except for chills, rash and new muscle pain, which were reported at statistically higher incidence after 13vPnC+TIV than after TIV alone.

Serious adverse events and deaths

Deaths

During the study period, death occurred in 16 subjects in the 6 studies. Nine 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.

Serious adverse events

Overall, the incidence of serious adverse events (SAEs) reported within one 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 naïve and 23vPS pre-immunised subjects. In both naïve and in pre-immunised subjects, the incidence and types of SAEs reported within one month after 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 one 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 one month after 13vPnC+TIV were similar to those reported after 13vPnC alone and after TIV. 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 of the SAEs were considered by the investigator to be at least possibly related to the study vaccine. In the first case, a 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). In the second case, a male subject was diagnosed with idiopathic thrombocytopenic purpura (ITP) 133 days after receiving Vaccination 2 in the vaccination sequence 23vPS/13vPnC.

Serious adverse events after concomitant administration of 13vPnC and TIV

In study 3001 (subjects 50 to 59 years of age), SAEs were reported in 4 subjects (0.7%) after 13vPnC+TIV, 6 subjects (1.1%) after 13vPnC alone and 5 subjects (0.9%) after TIV alone. In study 3008, SAEs were reported in 4 subjects (0.7%) after 13vPnC+TIV, 5 subjects (0.9%) after 13vPnC alone and in no subjects after TIV alone. The difference in the incidence of SAEs reported after 13vPnC+TIV and after TIV alone was statistically significant (p=0.045).

Adverse drug reactions (ADRs)

ADRs determined for 13vPnC adult

The frequencies summarized in this section for ADRs represent the highest frequency noted after any dose of 13vPnC in any of the six studies as classified using the Council for International Organizations of Medical Sciences (CIOMS) category for each of the events was the same in naïve and in pre-immunised 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 two vaccines.

Adverse drug reactions are listed in Table 20 in CIOMS frequency categories: very common: ≥10%, common: ≥1% and <10%, uncommon: ≥0.1% and <1%, rare: ≥0.01% and <0.1% and very rare: <0.01%

Table 20: 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.

Safety in special populations

High risk populations

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. Safety and reactogenicity patterns were similar in these high-risk adults compared to the overall adult population.

Age subgroups

Three studies enrolled subjects ≥65 years of age: study 6115A1-3008 in naïve subjects and studies 6115A1-3000 and 6115A1-3005 in pre-immunised subjects. Safety was descriptively evaluated among subjects ≥65 years of age in four age subgroups: 65 to 69 years, 70 to 74 years, 75 to 79 years and ≥80 years of age. After an initial study vaccination of 13vPnC, incidences of local reactions, systemic events, related AEs, and SAEs showed no apparent trends related to subject age. A 2 vaccine sequence (13vPnC/13vPnC and 23vPS/13vPnC) was assessed in 23vPS pre-immunised subjects ≥70 years of age (study 6115A1-3005). Incidences of local reactions, systemic events, related AEs, and serious AEs were generally similar among the age subgroups 70 to 74 years, 75 to 79 years, and ≥80 years.

Sex

The safety and tolerability of 13vPnC were evaluated separately for males and females, using data for naïve subjects 60 to 64 years of age (study 004) and for pre-immunised subjects ≥70 years of age (study 3005). The results show that after an initial vaccination of 13vPnC:

- In both studies, all four types of local reactions were generally reported at higher incidence in females than in males.

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

Safety of 13vPnC in subjects at increased risk of pneumococcal disease

The safety and tolerability of 13vPnC were evaluated in subsets of subjects with chronic conditions that could potentially put them at increased risk of invasive pneumococcal disease (high risk subjects). Data were evaluated for subjects who had diagnoses in five high-risk disease categories: chronic cardiovascular diseases, chronic liver diseases including alcoholic liver disease and alcoholism, diabetes mellitus, chronic pulmonary diseases or renal disorders. Results showed that although the numbers of subjects within each of the disease categories were low in most of the studies (especially in studies enrolling younger subjects), data for local reactions, systemic events, related AEs and serious AEs in groups of subjects with these high risk conditions were generally similar to the data observed for the full safety populations in the respective studies. There were no findings to suggest any special concerns with respect to administration of 13vPnC in subjects with these high risk diagnoses.

Discontinuation due to adverse events

Withdrawals

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 one had received TIV+placebo. The type of AE most often resulting in withdrawal from the studies was cancer. Sixteen 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.

Evaluator's overall conclusions on clinical safety

Based on the results of these clinical studies, the reactogenicity profile of 13vPnC has been shown to be acceptable and comparable to 23vPS in 23vPS naïve subjects. In subjects pre-immunised with 23vPS, greater reactogenicity was observed after vaccination with 23vPS than after 13vPnC. Overall, safety and reactogenicity data indicate that subjects naïve to 23vPS can be safely vaccinated with 13vPnC. Even a second dose of 13vPnC given at a stringent one year interval does not increase reactogenicity (13vPnC/13vPnC). In contrast, administration of a study dose of 23vPS to adults ≥70 years of age previously immunised at least 5 years earlier with 23vPS, or administration of 13vPnC followed by 23vPS one year later (13vPnC/23vPS) in younger adults showed higher local reactogenicity and an increase for some systemic events. In fact, there has recently been a recall of an entire batch of 23-valent polysaccharide vaccine in NSW because of an extremely high incidence of local reactions (in previously immunised patients. The common feature for each of these immunisation regimens is receipt of 23vPS with its high pneumococcal polysaccharide load (25 μg for each polysaccharide) in a setting of preexisting 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 preexisting antibody titres have been associated with increased reactions after 23vPS

whether present at the time of initial vaccination or at revaccination.[8] Subjects vaccinated with 23vPS followed one year later by 13vPnC (23vPS/13vPnC) showed an acceptable safety profile, indicating subjects vaccinated with 23vPS could be safely vaccinated with 13vPnC, even at a stringent one 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 one year interval. Overall, subjects pre-immunised with 23vPS had significantly fewer local and systemic events when vaccinated with 13vPnC compared to revaccination with 23vPS. The evaluator believed it was important for both healthcare providers and consumers to know that mild reactions (both local and systemic) are very common, even more common if there has been previous immunisation with the polysaccharide pneumococcal vaccine. It was also shown that pre-immunised 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. Coadministration of 13vPnC with TIV is safe, although somewhat more local and systemic events were observed in the younger subjects (50-59 years) compared to older subjects (≥65 years).

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. There were no questions from the clinical evaluator.

Clinical Summary and Conclusions

Clinical aspects

Clinical efficacy

As mentioned earlier in this AusPAR, a large clinical trial is necessary to assess the epidemiological impact of this vaccine and is currently being carried out in the Netherlands (CAPITA) in which 84,496 subjects aged ≥65 years of age have been enrolled. Subjects have been randomly assigned in a 1:1 ratio to receive either 13vPnC or placebo. The study will provide important information on the efficacy and safety of 13vPnC in these subjects. The major question about efficacy relates to the translation of OPA titres into clinical (and epidemiological) benefit.

The current Phase III studies have shown immunogenicity using OPA as the surrogate for clinical efficacy. Extrapolating from the study data submitted, it would appear that 13vPnC is likely to provide better protection than 23vPS against IPD and vaccine type community acquired pneumonia (VT-CAP) in older 23vPS pre-immunised adults, due to serotypes in common as well as serotype 6A. Overall the results suggest that 13vPnC will be preferred to 23vPS for improvement of protection against serious pneumococcal disease. OPA responses are higher for each serotype and persist longer, and protection against serotypes responsible for disease is likely to be more comprehensive for individual subjects after administration of 13vPnC. Based on observations after one or two doses, 13vPnC is almost certainly for initial immunisation and for repeat immunisation in 23vPS pre-immunised subjects.

Another major issue in relation to the use of this vaccine is the gathering of efficacy data in special groups for which pneumococcal vaccination is currently recommended (and currently undertaken with the polysaccharide vaccine). This includes groups such as immunocompromised, asplenics and other haematological disorders (including post bone

[8] Jackson LA, Benson P, Sneller VP et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999; 281: 243-248.

marrow transplant) and people with HIV. There are current Phase III trials being undertaken in these groups (in HIV and in bone marrow transplant recipients) but groups like asplenics still need to be addressed in relation to the efficacy of this vaccine. These data are particularly important, given that the administration of 13vPnC prior to the administration of the polysaccharide vaccine may also be important in these groups to maximise efficacy.

Clinical safety

What the data in this submission shows convincingly, is that essentially, there is similarity in the incidence of both local and systemic side effects between the two vaccines, hence acceptability (given that the comparator is already licensed and in national recommendations). In fact, the incidence is lower for a second vaccination with 13vPnC, whichever initial vaccine was used, than with a second vaccination using 23vPS. There is still additional safety information collected for analysis from ongoing clinical trials of a second dose of 13vPnC administered at 5 years (6115A1-3001) and at 3 to 4 years after the initial dose (6115A1-004 extension). Coadministration of 13vPnC does seem to cause an increased incidence of mild systemic reactions (particularly in the younger age groups) but this may well still be acceptable, given the greater level of compliance expected if both vaccines are given at the same time. The collection of ongoing postmarketing data will also be important to further examine all these issues. This will be particularly important in relation to the fact that many people suitable for this vaccine, have already been vaccinated with the pneumococcal polysaccharide vaccine.

Benefit risk assessment

Benefits

There is already well established safety and immunogenicity data for the licensed 13vPnC for infants and the known efficacy of 23vPS against IPD in adults. Of the eight 13vPnC clinical trials in this submission, five included 23vPS as an active comparator, two studies assessed the concomitant use of 13vPnC with trivalent influenza vaccine and one added additional safety information in 23vPS pre-immunised subjects. Irrespective of age or 23vPS immunization status, the five Phase III and two Phase II trials have demonstrated that 13vPnC provides at least an equivalent, and in many cases, an enhanced functional immune response to the 12 serotypes in common as well as a strongly enhanced response to serotype 6A. The two pivotal non-inferiority trials, one in 23vPS naïve subjects, and one in 23vPS experienced subjects, achieved primary non-inferiority objectives and demonstrated statistically significantly greater OPA responses to most serotypes in common and serotype 6A. Submitted data showed that sequential administration of 13vPnC first is preferred to administration of 23vPS first, because administration of 23vPS is associated with a negative immunologic consequence for subsequent 13vPnC immunisation. There appeared to be no impediment to immunological response to either vaccine if TIV and 13vPnC were administered concurrently. Additional studies are underway to further evaluate the interval for re-immunisation with 13vPnC to best maintain functional OPA and the best overall sequence of vaccinations, that is, 13vPnC/13vPnC or 13vPnC/23vPS.

Risks

The total safety database from the six Phase III studies supports an acceptable safety profile for administration These include four studies conducted in adults not previously vaccinated with the licensed 23vPS (naïve subjects) and two studies in adults who had previously received 23vPS (pre-immunised subjects).

Conclusions

Invasive pneumococcal disease is recognised by the World Health Organization (WHO) to be a major cause of mortality at both ends of life. In 2007, WHO issued a position paper regarding the need to introduce and implement pneumococcal conjugate vaccination in all countries of the world (at that time using a PCV-7 which was licensed in children).[9] The use of the 7-valent vaccine had shown a significant impact on IPD, pneumonia and even otitis media in children, despite a limited increase in IPD caused by non-vaccine serotypes.[10] Although there is not yet sufficient clinical data to show the impact of the 13vPnC (either in children or adults), the submission contains good modelling data to suggest the use of the 13-valent conjugate vaccine will be even more successful in reducing invasive pneumococcal disease.[11] The evaluator supported the application for the registration of Prevenar 13 in adults.

Conditions for registration

Registration needs to be conditional on the undertaking to/and subsequent submission of, further data following the completion of the trials included in this submission, as well as the major trial of clinical impact in adults (CAPITA). There are a number of other trials already started (in special populations) and these will hopefully be available soon to provide data regarding the use of 13vPnC in these groups – both efficacy and safety.

In addition, it is important to have the follow up data from the trial included in this submission and other studies being undertaken to determine if re-vaccination is needed.

As well as these formal trials, the sponsor needs to continue to do postmarketing surveillance. The Risk Management Plan adapted from that being used in the European market should be adopted.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The summary of the Ongoing Safety Concerns, as specified by the sponsor, is shown in Table 21.

[9] WHO, Pneumococcal conjugate vaccine for childhood immunization—WHO position paper, WER 2007; 82, pp. 93–104.

[10] Bechini, A., Boccalini, S., Bonanni, P. Immunization with the 7-valent conjugate pneumococcal vaccine: Impact evaluation, continuing surveillance and future perspectives. Vaccine 2009; 27: 3285-3290.

[11] Gladstone RA, Jefferies JM, Faust SN, Clarke SC. Continued control of pneumococcal disease in the UK - the impact of vaccination. J Med Microbiol 2011; 60: 1-8.

Table 21: Summary of ongoing safety concerns

Important identified risks	No important identified risks requiring further follow-up have been identified.
Important potential risks	a) Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC. b) Vaccine failure in subjects who are fully vaccinated according to local recommendations.
AEs not associated with 13vPnC in clinical trials or with 7vPnC in post-authorisation observational safety studies, but are included in the Prevenar SmPC	Infants/children a) Wheezing diagnoses b) Apnea c) Convulsions/seizures d) Anaphylaxis/hypersensitivity
Important missing information	a) Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC vaccine (infants/children). b) Effectiveness of 13vPnC (adults). c) Long-term vaccine effectiveness. d) Potential changes in the epidemiology of nonvaccine *S pneumoniae* serotypes that may occur (infants/children). e) Safety and immunogenicity in high risk populations: i) HIV-infected subjects ii) Premature infants born at <37 weeks of gestational age. iii) Immunocompromised subjects including those with bone marrow transplant and sickle cell disease f) Age group (>5 to <50 years). g) Impact of 13vPnC on nasopharyngeal carriage, including monitoring replacement with non-vaccine serotypes and non-pneumococcal bacteria in the nasopharyngeal flora of children. h) 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). i) Immunogenicity of 1 booster dose of 13vPnC against the 6 additional serotypes after a primary series of 7vPnC (infants/children). j) 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). k) Pediatric transition plan. l) Effect of antipyretics on immune response to vaccination (infants/children). m) Safety of more than 1 dose of 13vPnC in adults administered >1 year apart. n) Vaccine exposure during pregnancy and lactation.

a: Applicable to both infants/children and adult populations, unless specified.
Abbreviations: CRM = cross-reactive material; HIV = human immunodeficiency virus.

The OPR reviewer noted that the sponsor's identification and classification of important safety concerns in the table are unusual. Nevertheless, the table does encompass the majority of adverse events expected to be addressed in the pharmacovigilance (PV) plan, including identifying unanticipated safety signals.

The separation of the group "*AEs not associated with 13vPnC in clinical trials or with 7vPnC in post-authorisation observational safety studies, but are included in the Prevenar SmPC*"

from the expected three levels of ongoing safety concerns is unusual. The sponsor indicated that this is based on the original Risk Management Plan (RMP) for the paediatric approval where some of the 13vPnC safety profile was based on the profile for the 7vPnC product. This group identifies 4 specific AEs which are being monitored as a group in ongoing trials and Periodic Safety Update Reports (PSURs). This is acceptable and will be monitored as a separate group of safety concerns.

The clinical evaluation report did not find any significant additional safety concerns that needed addressing. However, it did highlight several concerns that postmarketing data would be important to monitor. These concern the following safety aspects of Prevenar 13:

- Coadministration with other vaccines, notably influenza. This is supported by preliminary data from the US Vaccine Safety Datalink (VSD)[12], which identified a small but significantly increased risk for febrile seizures amongst children aged 12-23 months who received Fluzone and Prevenar 13 concomitantly in an analysis of data from a large managed care database.
- When administered with other pneumococcal vaccines.
- As a second dose in adults: this issue is identified as missing

The OPR reviewer noted that reactions and systemic events were very common; however this category is missing from the summary of ongoing safety concerns. In infant studies, the frequency of any local adverse event was 47 to 56% of the population and fever was reported in 25 to 50% of subjects. In adults both local and systemic reactions were frequently above 10%. While the clinical significance of these minor yet very common adverse events may not be great, the public health implications are potentially very high - for example on the widespread acceptance and hence uptake of the vaccine. The sponsor argued that these adverse events do not reach a level needing duplication in the RMP and that these events are common to many vaccines and addressed via routine PV practices. The evaluator did not fully agree with this assessment, as many of the ongoing safety concerns identified in the summary table are common to many vaccines and addressed with routine PV practices.

Pharmacovigilance Plan

The pharmacovigilance plan contains many additional or ongoing activities that address safety as well as a combination of efficacy and immunogenicity factors.

The two main studies identified by the sponsor to address the potential safety concerns of "unanticipated safety signals" and "vaccine failure" are:

- 6090A1-4002: Post-approval observational evaluation of 13vPnC Administered in Routine Use to Infants and Children (ongoing), and
- 6115A1-3006: A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community- Acquired Pneumonia and Invasive Pneumococcal Disease (adults).

In addition, for vaccine failure follow up questionnaires will be used to ascertain whether serotype information was collected in vaccine failure reports.

The remaining ongoing studies and activities will be used by the sponsor to address aspects of the "missing information" safety concerns.

[12] presented at the Feb 23 meeting of the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

The OPR reviewer noted that the sponsor's routine pharmacovigilance activities are consistent with the pharmacovigilance guidance in volume 9A of the European guidelines. The pharmacovigilance plan overall appears to be a comprehensive combination of studies or activities assessing safety as well as effectiveness and immunogenicity in the post market period.

The combination of a postmarket study each in children and adults with specific follow up of vaccine failures seeking serotype information through questionnaires, are acceptable PV activities for managing the risks of identifying unanticipated safety signals and monitoring vaccine failure. Updates, interim and final reports will be expected as outlined in the RMP.

The clinical evaluator highlighted three issues that need to be monitored in the post-market period.

1. The safety of a second dose in adults. Two ongoing studies intend to further explore this and given the current indication being sought is for one vaccination only this was currently considered adequate.
2. When administered with other pneumococcal vaccines. The pharmacovigilance activity most likely to contribute to this issue in children is a Phase III trial (6096A1-3011) evaluating the safety (as well as tolerability and immunogenicity) of 13vPnC in healthy children (aged 15 months to 17 years) previously immunized with 7vPnC. There is no activity which will be able to monitor this issue in adults. Due to the limitations of routine PV in monitoring this issue in adults, the OPR recommended that the sponsor supplements routine PV with specific efforts to determine the past immunisation history of adverse events, including local reactions, and specifically address this issue in PSURs.
3. When it is co-administered with other vaccines, notably influenza vaccine. There is no activity in the PV plan which will be monitoring this issue, however this information is much better captured in routine PV reporting. It was recommended that this specifically be reported on in the PSURs.

It was also noted that local reactions are a frequent adverse side effect of the vaccine. As previously stated, the OPR evaluator did not completely agree with the argument provided by the sponsor to not include local reactions and therefore specifically to address them in PV activities. However, the OPR would accept not including local reactions in the summary of safety concerns table if local reactions from routine PV and ongoing studies which collect this information are reported on specifically in PSURs.[13]

The Advisory Committee on the Safety of Medicines (ACSOM) was approached specifically for advice on the adequacy of the proposed PV plan to monitor safety in infants, in the context of 13vPnC being delivered as part of the NIP this year. ACSOM agreed with the evaluator that, in general, the plan as presented appeared adequate for this population group.

[13] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

ACSOM Advice

The ACSOM noted that an RMP was not reviewed at the time of the original registration of Prevenar 13, because it preceded the requirement for RMPs. Although the current indication sought extension of the indication to an adult population, the OPR evaluator considered it appropriate to consider the adequacy of the RMP in the infant population because Prevenar 13 was being added to the National Immunisation Program (NIP), for children at 2, 4 and 6 months of age and would replace Prevenar 7. In addition, a catch up program would provide a single dose of Prevenar 13 for children aged 12 to 35 months who had already received three doses of Prevenar 7. Advice was sought from ACSOM regarding whether the outlined pharmacovigilance plan was adequate to address and monitor the safety concerns in infants. The OPR evaluator noted there were limited details available on the post-approval safety study in infants.

The committee noted that it was expected that the Australian Technical Advisory Group on Immunisation (ATAGI) and the Pharmaceutical Benefits Advisory Committee (PBAC) would review a submission for inclusion of Prevenar 13 in the NIP for adults and that if it were successful, anticipated use in the adult population would be high.

The committee noted that, in support for transitioning from Prevenar 7 to Prevenar 13, the sponsor had provided details for a proposed 'Paediatric Transition Plan'.

The committee noted that it had recently been reported that reactogenicity (febrile convulsion risk) increased slightly in preliminary postmarketing data from the US Vaccine Safety Datalink when Prevenar 13 was given concomitantly to young children with inactivated influenza vaccination. However, the committee agreed that established risk minimisation practices were sufficient to mitigate this risk given that immunisation providers were already aware of the possibility of fever and injection-site reactions. In addition, communication materials regarding inclusion of Prevenar 13 on the NIP would note this issue.

The committee noted that the data presented from 6 studies of Prevenar 13 in adults did not appear to raise any specific safety concerns about the extension of indication in adults, although the data were not reviewed in detail for this meeting. Although there had been an elevated incidence of severe injection site reactions, particularly associated with the second dose of Pneumovax 23, this may not be an issue for Prevenar 13 as a second was not recommended. Members agreed that they would be happy to provide advice about use of Prevenar 13 in adults in future, if the TGA required it.

The committee agreed that the pharmacovigilance plan appeared adequate to address and monitor the safety concerns in infants, and that no additional pharmacovigilance activities would be required other than those routinely associated with inclusion in the National Immunisation Programme because:

- Prevenar 13 had been registered in Australia for children under 5 years of age since March 2010; and
- Prevenar 13 appeared to have a similar safety profile to that of Prevenar 7, which has been in use in the National Immunisation Program since 2005, and there was no evidence of safety issues associated with inclusion of the additional serotypes.

The committee noted the areas of the submission for which the OPR evaluator sought clarification from the sponsor, and agreed that the questions from the evaluator were appropriate. The committee particularly noted the need for clarification on the proposed plan for the transition in Australia from Prevenar 7 to Prevenar 13.

Risk minimisation activities

The sponsor proposed that the important potential risks (unanticipated safety signals and vaccine failure) can be adequately handled through routine risk minimisation activities.[14] Of the missing information, the sponsor stated that routine activities are *not* adequate for the paediatric transition plan and effect of antipyretics on immune response to vaccination.

The OPR reviewer noted that the use of routine risk minimisation activities for potential risks was acceptable.

The RMP provides information on the paediatric transition plan, however there is no further reference to an additional risk minimisation activity for the effect of antipyretics. It is assumed that this is an error and the sponsor is referring to the additional PV activity. The sponsor provided further information on the PV activity but did not address the risk minimisation activity.

There is no additional risk minimisation activity proposed for the extension of indication to adults. The paediatric transition plan described below does incorporate information about the 'catch up' dose change requested in the PI. This transition plan was therefore evaluated as a whole.

The goals of the 'Paediatric Transition Plan' are outlined below, along with some information on how these will be achieved in Australia.

1. To ensure the uninterrupted supply of Prevenar or 13vPnC, there has been close collaboration with State and Territory Government agencies over the last 6 months to ensure adequate stock of Prevenar 13 (which was rolled out on July 1 2011).
2. To communicate to health care providers about the transition, there has been collaboration with State and Territory Government, educational materials and a medical information call service for health care professionals.
3. To avoid confusion among health care providers during the transition period, governments have actively reduced stock of Prevenar 7.
4. To ensure potential AE reports can be unambiguously linked to the type of vaccine administered, the packaging has different colours, there are different batch numbers and the Australian Childhood Immunisation Register has a unique identifier for Prevenar 13.

The OPR reviewer noted that the differentiating physical features are clear, and appear to provide a good visual way to distinguish between the two different Prevenar vaccines.

Prevenar 13 was rolled out as part of the NIP in all states except the Northern Territory, on July 1 2011. An update regarding any serious or significant issues or concerns with the transition that the sponsor becomes aware should be communicated to the TGA.

The OPR reviewer also made a number of recommendations concerning the PI but these are beyond the scope of this AusPAR.

Summary of recommendations

1. The EU Risk Management Plan for 13-Valent Pneumococcal Conjugate Vaccine (13vPnC), version 4.0, date of report 18 November 2010 should be imposed as a condition of registration in Australia with the following considerations.
2. The clinical evaluator highlighted the need to monitor the safety of 13vPnC with respect to several issues. For one of the issues, that is the safety of 13vPnC when

[14] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

administered with other pneumococcal vaccines, there is an ongoing trial that will provide further information regarding this concern in children. However, there is no specific activity that will provide further information in adults. Given that routine PV has significant limitations in its ability to monitor this concern, the OPR recommended that the sponsor supplements routine PV with specific efforts to determine the past immunisation history of adverse events, including local reactions, and specifically address this issue in PSURs.

3. A second issue highlighted by the clinical evaluator was the need to monitor the safety of 13vPnC when co-administered with other vaccines, notably influenza vaccine. While there is no activity in the PV plan which will specifically monitor this, this information is much better captured in routine PV reporting. Therefore, it was recommended that this specifically be reported on in the PSURs.
4. Local reactions are a frequent adverse side effect of this vaccine. While the clinical significance of these minor yet very common adverse events may not be great, the public health implications are potentially very high, for example on the widespread acceptance and hence uptake of the vaccine. The OPR did not completely accept the argument provided by the sponsor to not include local reactions and therefore specifically to address them in PV activities. However, the OPR would accept not including local reactions in the summary of safety concerns table if local reactions from routine PV and ongoing studies which collect this information are reported on specifically in PSURs.

List of Questions

The OPR reviewer had a number of questions for the sponsor.

Summary of Ongoing Safety Concerns

The identification and classification of important safety concerns are unusual. While the table does identify unanticipated safety signals in the potential risk section, which would encompass the majority of serious adverse events we would expect to be addressed in the PV plan, there are two concerns for which further information is requested.

The statement "AEs not associated with 13vPnC in clinical trials or with 7vPnC in post-authorisation observational safety studies, but are included in the Prevenar SmPC" does not appear to directly fit into any of the expected 3 levels of ongoing safety concerns (identified, potential and missing information).

Information was requested to justify this statement as a stand-alone in the table, rather than being incorporated into the 'unanticipated safety signals' risk.

Sponsor response

The description of the classification in the left-hand column is a historical artefact from the initial submission of the Risk Management Plan (RMP) for 13vPnC, which applied to contemporaneous circumstances. At that time, a portion of the 13vPnC safety profile within the initial paediatric approval was based upon the established extensive safety profile of the 7vPnC product. This included some events that had been incorporated in the labeling based solely on 7vPnC postmarketing reports.

The group of AEs listed in this row of the table are wheezing diagnoses, apnoea, convulsions/seizures, and anaphylaxis/hypersensitivity. It was deemed important to mention these AEs as a stand-alone group because they are pre-specified endpoints that are being monitored in the ongoing post-authorization observational safety trial for 13vPnC, Study 6096A1-4002, and are also being tracked as pre-specified topics in the

Periodic Safety Update Reports (PSURs) for 13vPnC. As such, they do not represent "unanticipated safety signals."

Local reactions

In the body of the RMP, it is reported that local reactions and systemic events were very common. In infant studies, the frequency of any local adverse event was 47 to 56% of the population, and fever was reported in 25 to 50% of subjects. In adults both local and systemic reactions were frequently above 10%. While the clinical significance of these minor yet very common adverse events may not be great, the public health implications are potentially very high - for example on the widespread acceptance and hence uptake of the vaccine. Given that the EU guidelines for RMPs state that identified risks "include those that are serious OR frequent", it is therefore surprising that these are not acknowledged as an identified risk in the table of ongoing safety concerns.

Information was requested from the sponsor to adequately justify why this has not been included as an identified risk.

Sponsor response

The RMP included in the adult submission is based upon the EU RMP approved by the European Medicines Agency (EMA) for the 13vPnC paediatric indication. In that RMP, risks that were both identified and sufficiently listed within the Summary of Product Characteristics (SmPC) were not included in the list of "ongoing safety concerns" requiring further follow up. The commonly occurring adverse events observed with 13vPnC (such as local reactions and systemic events) were not felt to rise to the level of requiring duplication within the RMP. Such events are common to many vaccines and are addressed via routine pharmacovigilance practices.

Paediatric post-approval observational study.

The pharmacovigilance plan states that it is using study 6090A1-4002: Post-approval observational evaluation of 13vPnC Administered in Routine Use to Infants and Children (ongoing) to address the potential safety concern of 'unanticipated safety signals'. The information provided in the main body of the RMP identifies a cohort study that will be used to test the hypothesis "Given that a child has received medical care for any reasons, the incidence rates are no greater that the resultant diagnosis has occurred in a post-vaccination risk window than in a control period temporally unrelated to vaccination". The analysis will involve both incidence rate analysis based on the case-crossover method, and a historical comparison analysis.

However, the synopsis and protocol provided for this study is inconsistent with the above information. Further information was requested from the sponsor regarding study 6096A1-4002, and it's relevance to addressing safety concerns and adverse events. This may involve an updated or corrected study protocol.

Sponsor response

This issue was satisfactorily addressed by the sponsor.

Missing Information – Safety of more than 1 dose of 13vPnC in adults

As identified above, local reactions are a frequent adverse side effect of the vaccine. There are also concerns of increased frequency, and possibly severity, of local reactions to the second dose of pneumococcal vaccines in adults.

The sponsor was requested to provide further information about how this issue will be explored in the studies planned to evaluate the safety of a second dose of 13vPnC (that is study 6115A1-3001 and 6115A1-004).

Sponsor response

The reactogenicity of a second dose of 13vPnC administered 1 year after an initial study dose of 13vPnC was assessed in Study 6115A1-3010, conducted in subjects 60 to 64 years of age naïve to 23vPS, and in Study 6115A1-3005, conducted in subjects ³ 70 years of age who had previously been vaccinated with 23vPS. Information regarding local reactions was collected for 14 days after each vaccination using electronic diaries (e-diaries).

In both studies, local reactogenicity after the second dose of 13vPnC was comparable to the reactogenicity seen after the first dose of 13vPnC. This indicates that 13vPnC recipients can be safely revaccinated with 13vPnC even at a stringent interval of 1 year, if needed.

In Study 6115A1-004 (Amendment 6), subjects aged 60 to 64 years and naïve to 23vPS received a second dose of 13vPnC 3 to 4 years (mean 3.7 years) after their first dose of 13vPnC. Information regarding local reactogenicity was collected for 14 days after vaccination using e-diaries. Data from this study have recently been reported and are currently being evaluated. The clinical study report (CSR) summarizing the results of immunogenicity and safety data obtained after the second dose of 13vPnC in this study is expected to be available in 4Q 2011.

The initial part of Study 6115A1-3001 assessed the compatibility of 13vPnC when given concomitantly with a seasonal trivalent inactivated influenza vaccine (TIV) (Fluarix). As part of the study, subjects 50 to 59 years of age at the time of enrolment are being followed up for 5 years with yearly blood draws to measure antibody responses over time. Subjects will be revaccinated with a second dose of 13vPnC 5 years after the first 13vPnC dose. Local reactions will be collected by e-diary for 14 days after the second 13vPnC vaccination. The study is ongoing, with data expected in 2013.

Routine risk minimisation activities - Effect of antipyretics

The RMP identifies that routine risk minimisation activities are not adequate to address the missing information safety concern for the effect of antipyretics on immune response to vaccination. However, there is no further reference to an additional risk minimisation activity for the effect of antipyretics in the RMP.

The sponsor was requested to provide an updated table confirming that there is no additional activity for this concern, or provide details on the intended risk minimisation activity.

Sponsor response

Study 6096A1-4027 is designed to assess the impact of prophylactic paracetamol or ibuprofen administration on the immunogenicity of 13vPnC measured 1 month after completion of the infant series. The protocol for this study has now been finalized following review by the EMA. This is a randomized, open label study, in which all subjects receive 13vPnC and Infanrix Hexa at approximately 2, 3, 4, (infant series) and 12 (toddler dose) months of age. Subjects will be randomized into 5 groups in a 10:10:10:10:12 ratio. The study will be conducted in Poland, and the first subject first visit is expected in August 2011. The final protocol for Study 6096A1-4027 was provided.

Medication Errors

The discussion in this section of the RMP makes generalised statements to support the conclusion that the majority of these reports or AEs were not a problem. However there is a lack of clarity about the minority or non-general aspects of medication errors. For example, it is not clear how big a problem medication errors are and what the AE was in the 'minority' of cases.

The sponsor was requested to provided information on the size of the problem (number (or rate) of reports of medication errors) and follow on with an assessment of whether there is a need for additional risk minimisation activities to reduce these errors. In addition, information is needed on whether any of the medication errors have been associated with a serious AE or serious outcome.

Sponsor response

In order to provide the most up-to-date information for this response, the safety database was searched cumulatively for medically confirmed spontaneous reports of medication error in which Prevenar 13 was the reported or suspect vaccine using the MedDRA high level group term (HLGT) *Medication Errors.*

The search identified a total of 346 medically confirmed reports (12 serious, 334 non-serious) in which at least one of the preferred terms (PTs) was contained in the search strategy. The medication error PTs coded for these reports were summarized. Thirty reports contained two medication error preferred terms and one report contained 3 medication error preferred terms. The sponsor provided an analysis of the search.

Notably, in 314 (91%) of the 346 reports, no adverse event was reported in addition to the medication error. In the remaining 32 cases the reported adverse events included adverse events reported either did not appear to have a causal link to the medication error itself (for example, the medication error reported was merely coincidental to the other adverse events being reported) or were known adverse events associated with the product (vaccination site local reactions/pain/fever).

Overall, no adverse events were reported in 91% of reports of medication errors. In the remaining reports, no new safety concern has been identified from the limited number of adverse events reported with erroneous administration. The sponsor will continue to monitor and report on medication errors in the next PSUR.

Paediatric Transition Plan

The transition plan described in the RMP will (or has been) implemented in each European country. However, there is no information on the use of the transition plan in Australia. This is particularly relevant given the recent decision in Australia to include 13vPnC on the National Immunisation Programme.

The sponsor was requested to provide information about the intention to implement the plan in Australia. If the plan is not to be used in Australia, a justification was required. If it is then further information was required on its suitability and appropriateness, and how this will be implemented here in this context (including identification and liaison with relevant stakeholders).

Sponsor response

The essential principles contained in the European transition plan are being applied and adapted for the planned introduction of Prevenar 13 in Australia. The essential elements of this plan being:

- To ensure the uninterrupted supply of Prevenar or Prevenar 13, this is being achieved through close collaboration with State and Territory Government agencies to manage the smooth supply transition from Prevenar to Prevenar 13. Pfizer has been working with State and Territory Governments over the past 6 months to ensure minimal wastage of Prevenar and ensuring adequate stock of Prevenar 13, including safety stock.

- To communicate to healthcare providers (HCPs) about the transition, Pfizer has been working closely with State and Territory Governments to ensure HCPs know about the transition to Prevenar 13. Pfizer is providing information to State and Territory Governments that will be supplied in each order to HCPs from the State and Territory warehouses.
- Materials have been developed by Pfizer that are being provided directly to HCPs as part of education about the transition. In addition, there is a medical information service provided within Pfizer that HCPs can call directly.
- To avoid confusion among HCPs during the transition period State and Territory Governments are actively reducing the stock of Prevenar in anticipation of Prevenar 13 being available from 1 July 2011.
- To ensure potential adverse event reports can be unambiguously linked to the type of vaccine being administered, the packaging of Prevenar and Prevenar 13 in Australia are distinguishable:
    - Outer packaging is different;
    - Syringe plungers have different colours;
    - Tip caps have different colours.
    - The different vaccines have different batch numbers.
    - The Australian Childhood Immunisation Register (ACIR) that records immunisation for the National Immunisation program has a unique identifier for Prevenar 13.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Included with the submission was a study on the effect of aluminium phosphate and polysorbate 80 on the stability of the drug product in syringes. Aluminium phosphate and polysorbate 80 provided additive effects to protect against loss of antigenicity with agitation. The vaccine formulation evaluated in the initial submission for Prevenar 13 included polysorbate 80.

Nonclinical

A combined fertility and embryofetal development study was submitted. Female rabbits were administered a human IM dose, or adjuvant, on Days 17 and 3 before mating and on gestation Days 10 and 24. There were no treatment related effects of vaccine or adjuvant on mating, fertility, pregnancy, parturition, fetal gross external, soft tissue and skeletal alterations, and pup survival and growth. There were no nonclinical objections to the proposed extension of indications to include adults 50 years and older.

Clinical

Efficacy

Prevenar 13 (13v PCV) was assessed for efficacy in 8 clinical studies in subjects 50 years of age or older. Two pivotal non-inferiority trials were conducted in which 13vPCV response was compared to 23vPPV immune response, one in naïve subjects 50-64 years of age (6115A1-004) and one in 23vPPV pre-immunised subjects ≥ 70 years of age (6115A1-

3005). A third Phase II non-inferiority trial comparing 13vPCV and 23vPPV in naïve subjects ≥ 65 years of age provided supportive data (6115A1-500). This supportive study also included a comparison of 13vPnC with and without aluminium phosphate ($AlPO_4$) as a co-primary objective. 6115A1-3009 was a follow on study to 6115A1-500. Study 6115A1-3010 was designed to evaluate sequential administration of 13vPCV and 23vPPV in 23vPS naïve subjects 60 to 64 years of age. Studies 6115A1-3001 (adults 50-59 years of age) and 6115A1-3008 (adults ≥65 years of age) were conducted in the USA and Europe, respectively, to demonstrate the compatibility of 13vPCV given concomitantly with influenza vaccine.

Study 6115A1-004 was a Phase III, randomised, modified double blind study in pneumococcal vaccine naïve adults ≥ 50 years of age. The original cohort of adults 60-64 years of age was randomised to receive a single dose of 13vPCV or 23vPPV. In a protocol amendment additional cohorts were added who received open label a single dose of 13vPCV. The second cohort was aged 50 to 59 years and the third cohort aged 18 to 49 years. The primary objectives were to demonstrate OPA response to 13vPCV is non-inferior to 23vPPV measured one month after vaccination and that proportion with a fourfold rise in anti-6A OPA titer is superior in the 13vPCV group.

Table 1 shows OPA response at 1 month after 13vPCV and that it was non-inferior to response after 23vPPV for the 12 serotypes in common with serotype specific GMRs in range 0.9 to 5.2 and lower bound on 95% CI exceeding 0.5 for all 12 serotypes. A statistically greater OPA response was shown for 6A in the 13vPCV group with 6A unique to 13vPCV. 13vPCV showed statistically superior response to 23vPPV for 8 of the common serotypes (1, 4, 6B, 7F, 9V, 18C and 23F). The difference in proportion of subjects with OPA ≥ LLOQ ranged from 0.9% to 23% with lower bound of 95% CI >-10% for all serotypes. All primary and secondary objectives were achieved for Cohort 1.

An exploratory analysis assessed persistence of antibody by IgG and OPA one year after vaccination in a subgroup. OMA GMTs for all serotypes in both vaccine groups were generally lower at one year after vaccination compared to one month after vaccination but higher at one year after vaccination compared to baseline. For 6 serotypes, point estimates of titres at one year remained higher in the 13vPCV compared to 23vPPV groups but 95% CI were overlapping. IgG responses showed similar results.

In Cohort 2 of the 406 enrolled subjects, 404 received vaccine. Table 1 shows that OPA response at one month after 13vPCV was non-inferior in the 50-59 year group compared to response to 13vPCV in the 60-64 year group. Serogroup specific GMRs ranged for 1.0 to 1.7. The protocol did not specify a superiority analysis but for 8 common serotypes if the same criteria are applied as in Cohort 1 then statistically higher response was seen in the 50-59 year group compared to 60-64 year group. For each of the 13 serotypes the proportion of subjects with OPA ≥ LLOQ in the 50-59 year group was non-inferior to the 60-64 year group measured one month after vaccination.

In exploratory analysis, serotype specific IgG concentrations measured one month after vaccination in a subset of 100 subjects were as high in the 50-59 years group as in the 60-64 year group. At one year after vaccination OPA GMTs for all serotypes were generally lower than at one month after vaccination but higher at one year after vaccination than at baseline. Point estimates for one year OPA values were higher for all serotypes in the 50-59 year group compared to 60-64 year group and for 5 serotypes 95% CI did not overlap (Serotypes 4, 6B, 9V, 14, 19A). Primary objective and secondary objectives for Cohort 2 were achieved.

Study 6115A1-3005 was a Phase III, randomised, modified double blind study in healthy subjects ≥ 70 years of age who had received 23vPPV at least 5 years before study

enrolment. The primary objectives were to demonstrate OPA response to 13vPCV is non-inferior to 23vPPV measured one month after vaccination and that the proportion with a fourfold rise in anti-6A OPA titre is superior in the 13vPCV group.

Table 2 shows that OPA response at one month after 13vPCV was non-inferior to response after 23vPPV for the 12 serotypes in common with serotype specific GMRs in a range 1.1 to 3.7 and the lower bound on 95% CI exceeding 0.5 for all 12 serotypes. The lower limit of the 2 sided 95% CI was > 1 for 10 of 12 serotypes in common (1, 4, 5, 6B, 7F, 9V, 18C, 19A, 19F, 23F). A statistically significant increase in OPA response for 6A was seen the 13vPCV group compared to 23vPPV (71.1% vs 27.3%).

The immune response to a second dose of 13vPCV administered one year after the initial study dose is non-inferior to immune response to the initial dose of 13vPCV. Serotype specific GMRs ranged from 0.8 for serotypes 4, 5 and 7F to 1.9 for serotype 23F. The lower bound of 2 sided 95% CI for GMR exceeded 0.5 for all 13 serotypes. The immune response to a second dose of 13vPCV is non-inferior to the immune response to 23vPPV (Year 0) for the 12 serotypes in common. For those who received 23vPPV as first dose and 13vPCV as second dose, point estimate OPA GMFR were lower than after 13vPCV two doses, and statistically lower for 6 of 13 serotypes. Study 3005 met all primary and secondary objectives for both years.

Study 6115A1-3010 was a Phase III, randomised, modified double blind study which assessed sequential 13vPCV and 23vPPV administration in pneumococcal vaccine naïve adults aged 60-64 years. The primary objective of this study was to assess non-inferiority of OPA response to 23vPPV administered one year after an initial study dose of 13vPCV (13vPCV/23vPPV) relative to OPA response after an initial study dose of 23vPPV for the 12 serotypes common to both. A co-primary objective was to assess non-inferiority of immune response to 23vPPV administered one year after an initial study dose of 13vPCV (13vPCV/23vPPV) relative to OPA response to 13vPnC administered one year after an initial study dose of 23vPS (23vPS/13vPnC) for the 12 common serotypes.

Table 3 shows OPA GMTs and GMFRs for all vaccine groups. For the primary objective, the immune response to 23vPPV administered one year after an initial study dose of 13vPCV is as immunogenic as the immune response to an initial study dose of 23vPPS for the 12 serotypes in common as measured by serotype specific OPA titres obtained one month after vaccination. For 6 of the 12 serotypes the immune response to 23vPS administered one year after an initial study dose of 13vPCV was superior (3,5,6B,7F,19F,23F) based on lower bound of 2 sided 95% CI >1.

For the co-primary objective, immune response to 13vPnC/23vPS relative to 23vPS/13vPnC after the second vaccination, the immune responses were non-inferior for the 12 serotypes in common. For 11 of the 12 serotypes, 13vPCV/23vPPV elicited statistically significantly greater responses (exception serotype 4).

Study 6115A1-500 was a Phase II study of two different 13vPCV formulations in pneumococcal vaccine naïve adults aged 65 years and older. The study also assessed 23vPPV and 13vPCV sequential administration given one year after an initial dose. The results indicated that 13vPCV formulated with or without AlPO4 showed non-inferior IgG values for all 13 serotypes. The selected 13vPCV formulation + AlPO4 was as immunogenic as 23vPPV, measured by OPA and IgG concentrations. 13vPCV formulation + AlPO4 given before 23vPPV enhanced the immune response to most serotypes in common.

Study 6115A1-3009 was an open label single arm study in subjects who had participated in Study 500 to assess OPA responses to the 3 vaccine sequence 13vPCV/23vPPV/13vPCV given at one year intervals compared to 13vPCV after Vaccination 1. Point estimates for OPA GMTs for all serotypes tended to be lower after Vaccination 3 compared to

Vaccination 1 and for 10 of 13 serotypes (all except 3, 6B, 23F) were statistically significantly lower. Point estimates for OPA GMTs were also lower after Vaccination 3 compared to Vaccination 2 for 10 of 13 serotypes and were statistically significantly lower for 8 serotypes (serotypes 1, 3, 5, 7F, 9V, 14 , 19A and 19F). The study concluded that 13vPCV administered one year before 23vPPV does not prevent the negative effect of 23vPPV on immune response to subsequent 13vPCV.

Study 6115A1-3001 and Study 6115A1-3008 assessed concomitant administration of 13vPCv with trivalent inactivated influenza vaccine (TIV) in adults naïve to pneumococcal vaccine. Study 3001 involved adults aged 50-59 years was conducted in USA and Study 3008 involved health adults aged 65 years and older was conducted in Europe. In study 3001 predefined non-inferiority criterion were met for all three antigens in TIV when administered concomitantly with 13vPCV compared to being given with placebo and non-inferiority criterion were met for all serotypes for concomitant administration of 13vPCV +TIV compared to 13vPCV given alone. In Study 3008 concomitant administration of 13vPCV and TIV missed the non-inferiority criteria for A/H3N2 strain by a small margin (-10.8% vs criterion of >-10% for 4 fold rise in HAI titre). For 13vPCV given with TIV compared to 13vPCV alone, all serotypes met the non-inferiority criterion , except for serotype 19F for which lower limit of 95% CI of 0.49 compared to GMFR criterion >0.5. It was concluded that 13vPCV could be administered concomitantly with TIV.

Safety

In 6 primary studies considered that contributed safety and tolerability data, a total of 6198 adult subjects aged ≥ 50 years received the study vaccine of whom 4213 were naïve to 23vPPV and 1985 had previously received 23vPPV. A total of 5667 subjects received at least one dose of 13vPCV and 1391 received a study dose of 23vPPV. Tables 6-10 summarise the numbers who received study vaccine by study, age and prior 23vPPV status. Safety data from studies 500 and 3009 were not included in the sponsor's combined safety analysis, as these studies involve vaccine formulations that differed from final commercial formulation.

Disposition of subjects is summarised in Table 12 for subjects naïve to 23vPPV and in Table 13 for subjects who had prior vaccination with 23vPPV. Across studies 96% to 99.5% completed the blood draw visit after the first dose with subject request and protocol violations the most frequent reasons for withdrawal. Few subjects (0% to 0.2%) withdrew due to adverse events. Among subjects withdrawn for an AE, 6 had received 13vPCV, 9 had received 23vPPV and 1 TIV+placebo. The type of AE most often resulting withdrawal was cancer. A total of 4 naïve subjects and 12 pre-immunised subjects died during the studies. Nine of the deaths occurred in study 3005 which enrolled subjects ≥ 70 years of age. No deaths were considered related to study vaccine.

Local adverse reactions comparison of initial dose 13vPCV and 23vPPV in subjects naïve to 23vPPV are shown in Table 15. Pain was more frequent in the 13vPCV group in both study 004 (80.1% vs 73.4%) and 3010 (66.1% vs 58.3%) with some excess in frequency of redness and swelling in 13vPCV group only in Study 004. Table 16 shows local reactions comparison of 13vPCV and 23vPPV in subjects who had received 23vPPV at least 5 years previously. Redness, swelling, pain and limitation of arm movement were seen at higher frequencies in the 23vPPV group with pain (51.7% vs 58.5%) the most frequently reported reaction. 13vPCV /13vPCV sequences in 23vPPV naïve subjects were associated with similar incidences of local reactions after each vaccination.

Systemic events within 14 days of after initial 13vPCV are presented by age and immunisation status in Table 17. In comparison of initial 13vPCv and initial 23vPPV, systemic events occurred at similar incidences, except decreased appetite, aggravated

muscle pain and new generalised joint pain, which were reported more frequently after 23vPPV (Table 18). In comparison between 13vPCV and 23vPPV in subjects who had previously received 23vPPV at least five years previously, systemic events occurred at similar incidences, except fatigue, rash, aggravated muscle pain and new generalised muscle pain, which were reported more frequently after 23vPPV (Table 19). 13vPCV/13vPCV sequences showed similar incidences of systemic events after each vaccination. When 13vPCV was administered concomitantly with TIV in subjects 50-59 years old, incidence of headache was higher than after 13vPCV alone (65.9% vs 50.9%). When 13vPCV was administered concomitantly with TIV in subjects ≥ 65 years of age, higher incidences were seen in concomitant group for fatigue (37.4% vs 28.5%), headache (32.6% vs 24.7%), chills (13.8% vs 9.1%), decreased appetite (16.9% vs 11.3%), new joint pain (16.2% vs 11.5%) and aggravated generalised joint pain (15.7% vs 8.6%).

Unsolicited adverse events within one month after vaccination were reported in 11.4% to 19.2% across studies and were generally reflective of the types of diseases and conditions observed in these age groups. AEs occurring after initial 13vPCV and considered possibly study vaccine related were reported in 1.1% to 3.1% of subjects, regardless of age or 23vPPV status, and were similar to incidence after 23vPPV. Overall incidence of AEs related to 13vPCV+TIV were low but one case of Guillain Barré syndrome developed on Day 123 after 13vPCV and was ongoing at 6 month contact. Other events reported at 6 months were one case of cutaneous lupus erythematosis after 23vPPV, one case of injection site nodule after 13vPCV + TIV and one case of idiopathic thrombocytopenic purpura (ITP) after 23vPPV/13vPCV.

The incidence of serious adverse events reported within one month of initial 13vPCV vaccine ranged between 0.2% and 1.1%, with no apparent differences between age groups and 23vPPV status. The incidence of SAEs at 6 months was 1.2% to 1.8% in subjects 50-59 years, 2.9% to 3.1% in subjects 60-64 years and was 3.9% to 5.8% in subjects ≥ 65 years of age. Two SAEs were considered possibly related to study vaccine. A female with Guillain Barré syndrome had other possible risk factors of TIV administered on Day 29 after 13vPCV, and suspected varicella zoster. A male had ITP diagnosed 133 days after receiving the second vaccine in the sequence 23vPPV/13vPCV. For studies involving concomitant 13vPCV +TIV in study 3008, SAEs were reported in 0.7% after 13vPCV+TIV, 0.9% after 13vPCV and no subjects after TIV alone, with the difference between 13PCv+TIV and TIV of statistical significance.

Conclusion of clinical evaluator

The five Phase III and two Phase II clinical studies have demonstrated that 13vPCV provides at least an equivalent, and in many cases an enhanced OPA response to the 12 serotypes in common. In the pivotal non-inferiority studies significantly greater OPA responses were achieved to most serotypes in common. A strong response to serotype 6A was also achieved. Sequential administration of 13vPCV followed by 23vPPV was shown to be preferable, because administration of 23vPPV before 13vPCV reduces antibody response to 13vPCV. TIV and 13vPCV could be administered concomitantly without significant impairment of immune response to either. The safety profile from 6 Phase III studies was considered acceptable. The incidence of local and systemic effects was considered comparable for 13vPCV and 23vPPV in 23vPPV naïve subjects. In subjects who received 23vPPV five or more years previously, 23vPPV was associated with higher incidences of local adverse reactions and some systemic events than 13vPCV. 13vPCV concomitantly administered with TIV was associated with an increase in systemic events (headache) in subjects aged 50-59 years compared to 13vPCV administered alone, and in subjects > 65 years with increase in the incidence of the systemic events fatigue, headaches, chills, decreased appetite, new joint pain and aggravated joint pain. The

clinical evaluator considered safety profile of concomitant administration of 13VPCV and TIV may be acceptable as the increase in systemic events were generally of mild to moderate severity and with higher vaccine uptake with concomitant administration. A large clinical study (85,496 subjects) is in progress to assess protective efficacy of 13vPCV in subjects ≥ 65 years of age. The clinical evaluator recommended registration of Prevenar 13 supported by submitted immunogenicity and safety data.

Risk Management Plan

A RMP was not reviewed at the time of the original registration of Prevenar 13, because it preceded the requirement for RMPs in Australia. Although the current indication sought extension of the indication to an adult population, the OPR evaluator considered it appropriate to consider the adequacy of the RMP in the infant population because Prevenar 13 was recently added to the National Immunisation Program (NIP), for children at 2, 4 and 6 months of age, and would replace Prevenar 7. ACSOM noted that the data presented from 6 studies of Prevenar 13 in adults did not appear to raise any specific safety concerns about the extension of indication in adults.

Risk Benefit Analysis

Delegate Considerations

In addition to the extension of indications into the adult population, the submission refers to a change in dosage in children to allow for children up to 5 years of age who have completed vaccination with Prevenar (7-valent) to receive Prevenar 13 to elicit immune responses to the six addition serotypes. The Delegate proposed to approve a statement along the lines of "Children aged 12 months to 5 years of age who have completed primary infant vaccination with Prevenar may receive one dose of Prevenar 13 to elicit immune responses to the six additional serotypes". Twelve months of age was the youngest age at which sequential 7vPCV primary series followed by 13vPCV was assessed in submitted clinical studies. Two clinical studies were submitted to support the recommendation.

Prevenar 7 has been included in the NIP for all children aged up to 2 years from 2005. Australian data show a substantial reduction in 7vPCV serotypes causing IPD among adults aged ≥ 65 years since 2005. Based on NNDSS in adults ≥ 65 years in 2007-2009 the composition of serotypes causing IPD was 24% for 7vPCV serotypes, 35% for 13v-non7v serotypes and 20% for 23v-non13v serotypes. The introduction of 13vPCV into the childhood NIP in 2011 may be expected to lead to a further reduction in proportion of IPD caused by 13v serotypes among people aged ≥ 65 years and a further increase in proportion of 23v-non13v serotypes in adults. The introduction of 13vPCV and the potential for increase in disease by replacement by non-vaccine serotypes is currently an area of uncertainty. The draft PI for Prevenar 13 refers to Australian serotype surveillance data for adults ≥ 65 years causing IPD that reports 81.9% were 13vPCV serotypes. The PI should be updated to reflect the much lower proportion (59%) of 13vPCV coverage in more recent surveillance data. If Prevenar 13 were registered for use in adults consideration of sequential administration of a 13vPCV/23vPCV regimen would appear appropriate in adults ≥ 65 years given the recently demonstrated extent of 23v-non13v serotypes causing IPD in this age group in Australia.

The adult 13vPCV clinical developmental program is based on immunogenicity and safety comparison of 13vPCV and 23vPPV. Clinical efficacy studies of PPV were first undertaken in the 1970s. Multiple meta-analyses of vaccine effectiveness of PPV have been published including a Cochrane Review published in 2008 that reported PPV vaccine efficacy of 74% (95% CI: 56 to 85%) in protection against IPD based on randomised controlled trials. The Cochrane Review concluded efficacy of PPV against all cause pneumonia was inconclusive

and PPV was not associated with substantial reduction in all cause mortality. This application proposes the indications:

Active immunisation for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older.

This submission has provided no efficacy data. It was considered unacceptable for "(including pneumonia and invasive disease)" when these are not included in the indications for Pneumovax 23.

There was also uncertainty about the effectiveness of 23vPCV in adults. The Joint Committee on Vaccination and Immunisation in UK (JCVI) on 16 March 2011 issued a recommendation for discontinuation of the routine pneumococcal vaccination program for adults aged 65 years and older after review of cumulative data on invasive pneumococcal disease suggested that 23vPPV effectiveness was poor in those 65 years and older (overall VE of 23%; 95% CI: 3 to 36%) following the introduction of a vaccination programme. JCIV have subsequently issued a 20 July 2011 statement that concluded that 23vPPV may provide some short term protection against IPD to those aged 65 years and older with possibly longer lasting protection in the youngest age cohorts.

The clinical evaluator noted the lack of 13vPCV efficacy data in groups with underlying medical conditions predisposing to IPD, such as immunocompromised, asplenics and other haematological disorders and people with HIV.

Data on persistence of antibody response after 13vPCV administration to adults are of short duration currently and do not allow a recommendation on the need or timing of subsequent doses of 13vPCV.

The Delegate considered the efficacy has not been adequately supported to support the extension of indications of Prevenar 13 for use in adults 50 years and older. This is based on the reliance on immunogenicity comparison with 23vPPV. For 23vPCV randomised controlled trial data support limited efficacy against IPD caused by serotypes in the vaccine, inconclusive efficacy against all cause pneumonia and lack of substantial reduction in all cause mortality. The Delegate considered the current application was premature when the CAPITA placebo controlled protective efficacy clinical study is underway and fully recruited in the Netherlands, which will allow reliable assessment of efficacy in subjects $\geq$ 65 years of age. The Delegate proposed to reject the application. The grounds for rejection were inadequate demonstration of efficacy in adults aged 50 years and older with associated uncertainty in the risk/benefit ratio of the product.

Response from Sponsor

The sponsor noted that the Delegate proposed to reject Pfizer's application to extend the indication of Prevenar 13 to include use in adults 50 years and older on the grounds of inadequate demonstration of efficacy with associated uncertainty in the benefit/risk ratio of the product.

The sponsor maintained that Prevenar 13(13vPnC) is an effective vaccine with an acceptable safety profile for use in this population.

In pneumococcal vaccine naïve adults, there exists an unmet medical need for an effective vaccine to prevent pneumococcal disease (PD) beginning at 50 years of age when an increase in the incidence of PD is seen in the general population. In addition, for individuals who have received the currently licensed 23-valent "free" (unconjugated) pneumococcal polysaccharide vaccine (23vPS), there is an unmet need to extend protection against PD for their entire lifetime of risk.

While 23vPS has demonstrated efficacy against IPD in controlled clinical trials, the vaccine has a number of limitations. The 23vPS vaccine fails to generate immunologic memory with consequent poor durability of protection; only one or two doses are recommended for adults ≥65 years of age thereby limiting the ability to maintain protection. In addition, the demonstration of 23vPS efficacy against all cause community-acquired pneumonia (CAP) (which includes non-invasive pneumonia) has been inconsistent. By contrast, polysaccharide protein conjugate vaccines induce immunologic memory, permit maintenance of antibody response by revaccination, and have shown consistent efficacy against IPD and CAP in children and HIV infected adults.

The best measurable immune response associated with the efficacy of pneumococcal vaccines is OPA. Therefore, the proposed licensure of 13vPnC is based on studies demonstrating the non-inferiority of the functional anti-pneumococcal immune response elicited by 13vPnC to that elicited by 23vPS.

Importantly, as demonstrated by sequential immunisation studies, 13vPnC induces immunologic memory, thereby permitting revaccination to maintain protection over the age span of adult risk. This attribute contrasts with the negative immunologic impact of 23vPS on subsequent 13vPnC immunisation, and the inability to achieve optimum 13vPnC response if 23vPS is given first. Hence, the sponsor agreed with the clinical reviewer's assessment that 13vPnC should be given first if use of both 13vPnC and 23vPS are considered.

The Phase III data support the view that the 13vPnC label indication should at a minimum reflect that of the 23vPS comparator. The TGA approved Pneumovax 23 indication in the Product Information (PI), dated 13 January 2010, included:

> "……Pneumovax 23 is indicated for immunisation only against pneumococcal disease caused by those pneumococcal types included in the vaccine. **Effectiveness of the vaccine in the prevention of pneumococcal pneumonia and pneumococcal bacteraemia has been demonstrated.** Pneumovax 23 will not prevent disease caused by capsular types of pneumococcus other than those contained in the vaccine."

The CAPiTA study, which is ongoing, is expected to confirm efficacy against CAP; however, results may not be available until 2013. Given this timing, the pressing medical need and the observed immunologic advantages of 13vPnC to establish and maintain functional anti-pneumococcal antibody responses in both pneumococcal vaccine naïve and 23vPS experienced adults (outcomes not possible with 23vPS), waiting for results of the CAPiTA study is not in the best interests of Australian public health. The available data already support the position that 13vPnC is likely to be at least as effective as 23vPS, but with the described immunological advantages.

The sponsor responded to the Delegate's specific comments:

Vaccine effectiveness of PPV

Controlled clinical trials and observational studies support the efficacy of 23vPS against pneumococcal pneumonia and IPD, and these indications are included in the current Pneumovax 23 PI, thereby affirming the use of 23vPS as an appropriate comparator. Immunogenicity comparisons with 23vPS are based on the quantitative and qualitative assessment of functional anti-pneumococcal opsonising antibodies, as measured by OPA. These antibody measurements are well accepted surrogates of vaccine mediated protection against pneumococcal disease.

Proposed Indications

The sponsor maintained that it is appropriate for the proposed indication to include "prevention of pneumococcal disease (including pneumonia and invasive disease)," based on the qualitative and quantitative immunologic advantages that 13vPnC affords compared to 23vPS and that the approved indication for Pneumovax 23 does include a statement of efficacy against IPD and pneumococcal pneumonia (pneumococcal pneumonia and pneumococcal bacteraemia).

In addition, the Cochrane review quoted by the Delegate notes the established effectiveness of 23vPS for invasive disease of 74% (95% CI: 56%-85%). Although the Delegate points out that the Cochrane report determined that efficacy of 23vPS against all cause pneumonia was inconclusive, the authors of the Cochrane meta-analysis note: "the meta-analysis is inadequately powered to exclude a protective efficacy less than 48%. This has been a consistent criticism of previous meta-analyses that remains valid in this updated review."[15]

Hence, given that 30%-40% of all cause pneumonia is due to pneumococcus, it is unlikely that the Cochrane meta-analysis would identify all cause pneumonia efficacy, even if 23vPS efficacy was 100% against vaccine-type pneumococcus.

It is important to note that the Cochrane review includes analyses of vaccine efficacy against definitive pneumococcal pneumonia and definitive vaccine type pneumococcal pneumonia. The respective efficacies for these were 74% and 87%. Efficacy against vaccine type pneumococcal pneumonia (87%), rather than efficacy against all cause pneumonia, is the most relevant outcome for the indication sought.

The WHO reaches the following conclusion in a 2008 position paper based on evaluation of meta-analyses and a review of randomized controlled trials (RCTs): "On balance, as shown in the meta-analyses, the results of the RCTs of PPV23 are consistent with a protective effect against IPD and all-cause pneumonia among generally healthy young adults and, to a lesser extent, protection against IPD in the general population of elderly people.",[16],[17] In the same WHO position paper, now limited to an analysis of the observational studies, the conclusion was: "…observational studies of the effectiveness of PPV23 generally have shown that the vaccine is 50%–80% effective in preventing IPD among immunocompetent adults and individuals with various underlying illnesses who are not severely immunosuppressed. Furthermore, among recipients of PPV23 who nevertheless develop pneumonia, the severity of their illness and their risk of dying may be reduced."[16]

Importantly, 13vPnC demonstrates a quantitative and qualitative superior immune response compared to 23vPS in both pneumococcal vaccine naïve and 23vPS experienced adults. The nature of the 13vPnC elicited response as well as its local reactogenicity profile compared with that of 23vPS permit the use 13vPnC to both establish and maintain an optimal anti-pneumococcal immune state. Accordingly, 13vPnC would satisfy an existing unmet medical need in that it (1) can be used to protect against pneumococcal disease (caused by the most important disease associated pneumococcal serotypes) in adults ≥50 year of age coincident with the increased risk of pneumococcal disease and (2) can be

[15] Moberley SA, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2008;(1):CD000422.

[16] 23-valent pneumococcal polysaccharide vaccine, WHO position paper. Weekly Epidemiological Record. WHO 2008; 42(83): 373–84.

[17] Huss A, Scott P, Stuck AE, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ 2009;180:48-58.

used to establish an immune state that will permit maintenance of the protective immunity through revaccination.

The ongoing CAPiTA efficacy trial is a blinded event driven study that is not likely to achieve its endpoint for a few more years. This trial will provide confirmation of 13vPnC's protective efficacy for vaccine serotype specific CAP. Nonetheless, there is a current existing need for a vaccine that can elicit optimum protective immunity against pneumococcal disease in adults and maintain this high level of immunity. The immunogenicity and safety profiles of 13vPnC both show that 13vPnC can satisfy this medical need; waiting for the final results of the CAPiTA trial should not be a consideration.

To ensure absolute clarity on the indication sought, Pfizer would be willing to amend the proposed adult Indication statement to read:

"Active immunisation for the prevention of pneumococcal disease (including **pneumococcal** pneumonia and invasive **pneumococcal** disease) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older.

The use of Prevenar 13 should be determined by official recommendations, taking into consideration the impact of invasive pneumococcal disease in different age groups as well as variability of serotype epidemiology in different geographical areas."

Uncertainty about the effectiveness of 23vppv [sic] in adults.

The UK Joint Committee on Vaccination and Immunisation (JCVI) ultimately determined that 23vPS in fact does provide protection against invasive pneumococcal disease. Specifically, JCVI came to the following conclusions:

(i) PPV23 may provide some short term protection against IPD to those aged 65 years and older with possibly longer lasting protection in the youngest age cohorts,

(ii) routine universal vaccination of all those aged 65 years and older is likely to be cost effective and

(iii) an alternative risk group based program may be more difficult to implement, be less effective and less cost effective. The committee advised that, based on these observations, the existing routine universal programme for those aged 65 years and older should continue.

In fact, greater efficacy in the youngest cohorts supports the view that adult immunisation against pneumococcal disease may provide the greatest protection at the younger age of 50 years, in contrast to the current recommendation of 65 years. As discussed in the submission, the incidence of pneumococcal disease begins to increase at 50 years.

Safety

The alert noted by the Delegate states: "The TGA is advising health professionals not to administer a second or subsequent dose of Pneumovax 23 vaccine pending the outcome of a review of an apparent increased rate of injection site reactions following administration of the second dose."[18]

[18] Pneumovax 23 - recommendation about revaccination. 2 May 2011 [last update]. Australian Government Department of Health and Aging, Therapeutic Goods Administration. Available: http://www.tga.gov.au/safety/alerts-medicine-pneumovax-110416.htm. 2 Sept 2011.

This alert specifically refers to second or subsequent administration of Pneumovax 23, not to the vaccine's initial use. While the two vaccines demonstrate comparable local reactogenicity upon initial administration, the local reactogenicity profile differs significantly for revaccination. The safety data from study 3010 show that the injection site reactogenicity of 13vPnC is notably lower, when given following a previous dose of 13vPnC or 23vPS, compared to that of 23vPS given after a previous administration of 13vPnC.

The local reactions are likely due to the large quantity of purified pneumococcal polysaccharide in the 23vPS vaccine, resulting in reactivity at the injection site as the polysaccharide forms complexes with the anti-polysaccharide antibodies elicited by the initial vaccination.

The above data support the view that the polysaccharide "load" of 23vPS results in local reactivity in the presence of anti-pneumococcal polysaccharide antibodies whether previously elicited by 23vPS or 13vPnC. By contrast, the much lower polysaccharide "load" of 13vPnC does not mediate a similar reactivity in the presence of anti-polysaccharide antibodies. The safety data provided in the 13vPnC application clearly favour the use of 13vPnC for revaccination. As a conjugated vaccine, 13vPnC is immunogenic despite containing a tenfold lower quantity of polysaccharide compared to 23vPS. Therefore 13vPnC should be preferred to 23vPS for the maintenance of an optimal anti-pneumococcal immune response

Sequential administration

The sponsor agreed with the clinical evaluator's assessment that 13vPnC should be given first, if use of 13vPnC and 23vPS are considered. The Delegate proposed that consideration of sequential administration of 13vPnC then 23vPS appears appropriate in adults ≥65 years, given the 2007-2009 NNDSS data cited where the proportion of 23vPS non13vPnC serotypes causing IPD in this age group in Australia was approximately 20%. While the submission provides data from sequential use studies of 13vPnC and 23vPS, it was not the intent of these studies to fully inform the sequential use of the two vaccines or the time interval to revaccination. These studies were designed specifically to assess and demonstrate important differences in the quality of the immune responses elicited by the vaccines. As noted in the sponsor's *Clinical Overview*, the 13vPnC conjugate vaccine has the potential to elicit an immune memory state that will permit revaccination with either 13vPnC or 23vPS; this is in contrast to 23vPS which elicits a negative immune state that does not allow for the maintenance of optimal anti-pneumococcal immune responses following subsequent administration of pneumococcal vaccine. These data demonstrate that that the conjugate 13vPnC, while containing fewer serotypes than 23vPS, nonetheless establishes an immune response that permits revaccination. 13vPnC therefore provides the potential for establishment and maintenance of a functional anti-pneumococcal immune response in adults against pneumococcal serotypes of particular virulence.

Underlying medical conditions predisposing to IPD

As noted in previous communications with the TGA, clinical studies are ongoing to establish the functional anti-pneumococcal immunogenicity of 13vPnC in populations at high risk of acquiring pneumococcal disease. These studies will take some time to complete given the nature of the medical conditions involved. The results will be communicated to regulatory agencies and recommending bodies as they become available.

Data on persistence of antibody response

The longest interval of observation and revaccination reported in the Phase III studies included in the application is one year. The ability to address the Delegate's question will

necessarily be defined by the passage of time. Studies are ongoing to assess the long term duration of the 13vPnC elicited immune response and to provide data that will inform the determination of the appropriate interval for revaccination. These data will be provided to regulatory agencies and recommending bodies as they become available.

Catch up dose in infants and children

The sponsor noted the Delegate's proposal to approve the change in dosage to allow children who have completed vaccination with Prevenar to receive a supplemental dose of Prevenar 13 and agreed to amend the Dosage and Administration section of the PI with the Delegate's proposed text.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

It was noted that clinical efficacy data had not been presented; however, the surrogate serological endpoints used in the eight clinical studies in adults >50 years, including two pivotal trials, conform to TGA-adopted EU guidelines and are considered acceptable for the extension of vaccine indications.

A Cochrane Review found significant efficacy of 23 valent polysaccharide pneumococcal vaccine (23vPPV) against IPD but no effect on pneumonia was demonstrated. The committee noted the sponsor's pre-ACPM argument that the Cochrane review is underpowered to detect difference in all cause pneumonia, assuming pneumococcal pneumonia contributes only a proportion.

Prevenar 13 in adult trials has met the non-inferiority criteria for shared serotypes when compared to23vPPV.

The change in dosage in children from 12 months of age was also supported by the evidence submitted. The catch up indication for children immunised with PCV7 was considered reasonable and was supported.

Safety

There has been extensive paediatric experience with Prevenar 7 and no safety signals have emerged. The paediatric experience with Prevenar 13, although not as extensive, is also reassuring.

23vPPV (Pneumovax 23) is currently licensed for prevention of pneumococcal disease in adults. TGA advice not to give repeat doses of this vaccine following recent problems with local reactions was noted by the committee.

The reported rate of local reactions was as expected while the rate of systemic reactions was higher if given with influenza vaccine but not different in pre-immunised patients. The single report of Guillain Barré syndrome was noted. The lack of data in subjects who were immune compromised, asplenic or with other haematological disorders and people with HIV was problematical.

The ACPM proposed a simplified indication statement similar to that of 23vPPV and to reflect the lack of clinical outcome data:

Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults aged 50 years and older.

Use should be in accordance with official recommendations….

The ACPM was also of the view that the sponsor should submit the CAPITA clinical trial, currently being conducted, as soon as completed. The results of this trial are expected to provide definitive evidence of clinical efficacy in prevention of pneumonia.

The committee supported the amendments to the Product Information (PI) and Consumer Medicines Information (CMI) put forward by the evaluators and the Delegate but these are beyond the scope of this AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, and in accordance with the official recommendations, in addition to the evidence of safety and efficacy provided for Prevenar 13 would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Prevenar 13 containing pneumococcal polysaccharide conjugate 13 valent vaccine, indicated for:

Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older.

The use of Prevenar 13 should be guided by official recommendations.

Among specific conditions of registration was the implementation in Australia of the Prevenar 13, version 4.0 Risk Management Plan (RMP), dated 18 November 2010, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

Prevenar 13®

NAME OF THE MEDICINE

Prevenar 13
Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

DESCRIPTION

The vaccine is a ready to use homogeneous white suspension for intramuscular injection, supplied as a pre-filled syringe.

Active ingredients

Each 0.5 mL dose contains:
2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F
4.4 µg of pneumococcal purified capsular polysaccharides for serotype 6B.

Each serotype is individually conjugated to non-toxic diphtheria CRM_{197} protein and adsorbed on aluminium phosphate (0.565 mg).

Excipients

Succinic acid, polysorbate 80, aluminium phosphate, sodium chloride in water for injections.

PHARMACOLOGY

Streptococcus pneumoniae is an important cause of morbidity and mortality in persons of all ages worldwide. It is a leading cause of death and illness in infants, among the elderly, and in persons who have certain underlying medical conditions. The organism causes invasive infections, including bacteraemia and meningitis, pneumonia and other lower respiratory tract infections, and upper respiratory tract infections including otitis media and sinusitis.

Infants and children less than 5 years of age

Based on serotype surveillance performed before the introduction of Prevenar, Prevenar 13 is estimated to cover 93.3% of serotypes causing IPD (Invasive Pneumococcal Disease) among children less than 5 years of age in Australia (Watson M. et al., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 92.8 % in New Zealand (Heffernan H.M., et al,. *Epidemiology of Infections* 2007; 1-8.)

Prevenar 13 is estimated to cover over 90% of serotypes causing antibiotic resistant IPD.

Adults

Based on serotype surveillance performed before the introduction of Prevenar, Prevenar 13 is estimated to cover 81.9% of serotypes causing IPD among adults aged 65 years and older in Australia (Watson M. et al., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 77.4 % in New Zealand (Heffernan H.M., et al., *Epidemiology of Infections* 2007; 1-8.).

Following the introduction of Prevenar on to the National Immunisation Program (NIP) for children, Prevenar 13 is estimated to cover 62.2% of serotypes causing IPD among adults aged 65 years and older in Australia, based on National Notifiable Diseases Surveillance System data from 2008.

Pharmacodynamics

Pharmacotherapeutic group: pneumococcal vaccines.

Mode of action

Prevenar 13 contains the 7 pneumococcal capsular polysaccharides that are in Prevenar (7-valent) conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM_{197} carrier protein. B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. The immune response to most antigens is T-dependent and involves the collaboration of CD4+ T-cells and B-cells, recognizing the antigen in a linked fashion. CD4+ T-cells (T-helper cells) provide signals to B-cells directly through cell surface protein interactions, and indirectly through the release of cytokines. These signals result in proliferation and differentiation of the B-cells, and production of high-affinity antibodies. CD4+ T-cell signaling is a requisite for the generation of long-lived B-cells called plasma cells, which continuously produce antibodies of several isotypes (with an IgG component) and memory B-cells that rapidly mobilize and secrete antibodies upon re-exposure to the same antigen.

Bacterial capsular polysaccharides (PSs), while varied in chemical structure, share the common immunological property of being largely T-independent antigens. In the absence of T-cell help, PS-stimulated B-cells predominantly produce IgM antibodies; there is generally no affinity maturation of the antibodies, and no memory B-cells are generated. As vaccines, PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age Conjugation of PSs to a protein carrier overcomes the T-cell–independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of *Streptococcus pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody response and induces immune memory. This has been demonstrated to elicit booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not available for vaccines.

CLINICAL TRIALS

Prevenar 13 immunogenicity clinical trials in infants and children

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide IgG antibody concentration of 0.35 µg/mL using an enzyme-linked immunosorbent assay, measured one month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against IPD. This recommendation is largely based upon the observed correlation between immunogenicity and IPD efficacy from three placebo-controlled trials with either Prevenar or the investigational 9-valent CRM_{197} conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

Immune responses following a three-dose primary infant series

Clinical trials have been conducted in a number of European countries and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL and opsonophagocytic activity (OPA) antibody titers ^{3} 1:8, one month after a three-dose primary series (at 2, 4 and 6 months) and after booster dosing, from representative studies are presented below (Table 1):

Table 1: Percentage of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations ³ 0.35 µg/mL and OPA antibody titer ³ 1:8 following Prevenar 13 administration in a 2, 4, 6 month primary schedule

Serotype		Primary Schedule (2, 4, 6 months)	Booster
		IgG (N=897-924) OPA (N=91-94)	IgG (N=458-479) OPA (N=88-92)
1	IgG ³ 0.35 µg/mL	95.6-99.3%	98.7-100.0%
	OPA Antibody ³ 1:8	98.9%	98.9%
3	IgG ³ 0.35 µg/mL	63.5-90.3%	90.5-92.2%
	OPA Antibody ³ 1:8	96.8%	97.8%
4	IgG ³ 0.35 µg/mL	94.4-98.9%	99.1-99.2%
	OPA Antibody ³ 1:8	97.8%	98.9%
5	IgG ³ 0.35 µg/mL	89.7-97.3%	99.1-99.6%
	OPA Antibody ³ 1:8	92.3%	98.9%
6A	IgG ³ 0.35 µg/mL	96.0-98.2%	99.1-100.0%
	OPA Antibody ³ 1:8	100.0%	98.9%
6B	IgG ³ 0.35 µg/mL	87.3-98.5%	99.6%
	OPA Antibody ³ 1:8	98.9%	98.9%
7F	IgG ³ 0.35 µg/mL	98.4-100.0%	98.8-99.6%
	OPA Antibody ³ 1:8	100.0%	100.0%
9V	IgG ³ 0.35 µg/mL	90.5-99.3%	99.1-100.0%
	OPA Antibody ³ 1:8	100.0%	98.9%
14	IgG ³ 0.35 µg/mL	97.4-98.2%	98.7-100.0%
	OPA Antibody ³ 1:8	100.0%	100.0%
18C	IgG ³ 0.35 µg/mL	96.8-98.1%	98.7-99.6%
	OPA Antibody ³ 1:8	100.0%	98.9%
19A	IgG ³ 0.35 µg/mL	98.4-99.6%	100.0%
	OPA Antibody ³ 1:8	100.0%	97.8%
19F	IgG ³ 0.35 µg/mL	98.0-99.3%	99.6-100.0%
	OPA Antibody ³ 1:8	90.4%	96.7%
23F	IgG ³ 0.35 µg/mL	87.2-94.6%	99.1-99.6%
	OPA Antibody ³ 1:8	98.9%	98.9%

In Prevenar 13 recipients, antipolysaccharide binding antibody for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically active antibody).

Immune responses following a two-dose primary infant series

The immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥ 0.35 mg/mL one month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) and 23F (55.8% to 68.6%). Compared to a three-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a two-dose infant series for most serotypes.

Booster responses following two-dose and three-dose primary infant series

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. Antibody responses to booster doses following two-dose or three-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged from 7 months to 5 years, age appropriate catch-up immunisation schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

Prevenar protective efficacy

The efficacy of Prevenar (7-valent) was evaluated in two major trials – the Northern California Kaiser Permanente (NCKP) trial and the Finnish Otitis Media trial (FinOM). Both trials were randomised, double-blind, active-control trials in which infants were randomised to receive either Prevenar (7-valent) or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a four-dose series at 2, 4, 6, and 12 - 15 months of age. The various efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 2).

Table 2: Summary of efficacy of Prevenar (7-valent)

Test	Study	N	VE*	95% CI
Invasive Pneumococcal Disease (IPD)				
Per-protocol	NCKP	30,258	97%	85, 100
Intent-to-treat		37,866	94%	81, 99
Pneumonia (Per-protocol)				
With bacteraemia			87.5%	7, 99
C*linical pneumonia with abnormal chest X-ray*			20.5%	4.4, 34.0
Acute Otitis Media (AOM)				
Per-protocol (reduction of)	NCKP	37,868		
Total episodes			7%	4, 10
Recurrent AOM (3 episodes in 6 mo. or 4 episodes in 1 yr.)			9%	3, 15
Recurrent AOM (5 episodes in 6 mo. or 6 episodes in 1 yr.)			23%	7, 36
Tympanostomy tube placement			20%	2, 35
Per-protocol (reduction of)	FinOM	1662		
Total episodes			6%	-4, 16
All pneumococcal AOM			34%	21, 45
Vaccine-serotype AOM			57%	44, 67
Intent-to-treat				
Vaccine-serotype AOM			54%	41, 64

*Vaccine efficacy

Prevenar effectiveness

The effectiveness of Prevenar (7-valent) against pneumococcal disease (comprising the protection afforded by vaccination and from herd immunity due to reduced transmission of vaccine serotypes in the population) has been evaluated in routine paediatric immunisation programmes that employ either three-dose or two-dose primary infant series, each with booster doses. This surveillance will continue with Prevenar 13.

Data from several countries is summarised in Table 3. It is important to note that as countries continually update the data from their surveillance systems, values included in this table may change over time.

Table 3. Summary of effectiveness of Prevenar (7-valent) for invasive pneumococcal disease

Country	Year of Introduction	Recommended Schedule	Disease Reduction, %	95% CI
USA	2000	2, 4, 6, 12 - 15 months		
Children <5[a]			Vaccine serotypes: 98% All serotypes: 77%	97, 99% 73, 79%
Persons ≥65[b]			Vaccine serotypes: 76.2% All serotypes: 38.2%	NA
Canada (Quebec)[c]	2004	2, 4 and 12 months	All serotypes: 72.5%	NA
UK (England and Wales)[d]	2006	2, 4 and 13 months	Two doses under age 1: 85%	49, 95%
Australia [e]	2002	2, 4 and 6 months	Vaccine serotypes: 89.6%	NA

[a] 2005 data.
[b] 2004 data.
[c] Children < 5 years of age. 2006 data.
[d] Children <2 years of age. Calculated vaccine effectiveness as of May 2008 (Broome method). Complete effectiveness for routine 2+1 schedule not yet available.
[e] Roche et al., *Communicable Disease Intelligence*. 2008; 32:18-30.

Effectiveness of Prevenar (7-valent) in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42.7%, and prescriptions for AOM by 41.9%, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52.4% and 41.1%, respectively. For those events specifically identified as pneumococcal pneumonia, the observed reductions in hospitalisations and ambulatory visits were 57.6% and 46.9%, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99).

While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar (7-valent) plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Children with sickle cell disease

The immunogenicity of Prevenar (7-valent) has been investigated in an open-label, multicentre study in 49 infants with sickle cell disease. Children were vaccinated with Prevenar (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15 - 18 months. After primary immunisation, 95.6% of the subjects had antibody levels of at least 0.35 μg/mL for all seven serotypes found in Prevenar. A significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

Immunogenicity clinical trials in adults 50 years and over

In adults, an antibody threshold of serotype-specific pneumococcal polysaccharide IgG binding antibody concentration associated with protection has not been defined. For all pivotal clinical trials, a serotype-specific opsonophagocytosis assay (OPA) was used as a surrogate to assess potential efficacy against invasive pneumococcal disease and pneumonia. OPA geometric mean titres (GMTs) measured 1-month after each vaccination were calculated. OPA titres are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50 %.

Pivotal trials for Prevenar 13 were designed to show that functional OPA antibody responses for the 13 serotypes are non-inferior, and for some serotypes superior, to the 12 serotypes in common with the licensed 23-valent pneumococcal polysaccharide vaccine (23vPPV) [1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F]. The response to serotype 6A, which is unique to Prevenar 13, was assessed by demonstration of a 4-fold increase in the specific OPA titre above pre-immunised levels.

Five clinical studies were conducted in Europe and the USA evaluating the immunogenicity of Prevenar 13 in different age groups ranging from 50-95 years of age. Clinical studies with Prevenar 13 currently provide immunogenicity data in adults aged 50 years and older, including adults aged 65 and older previously vaccinated with one or more doses of 23vPPV, 5 years prior to enrolment. Each study included healthy adults and immunocompetent adults with stable underlying conditions known to predispose individuals to pneumococcal infection (i.e., chronic cardiovascular disease, chronic pulmonary disease, renal disorders and diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism).

Immunogenicity and safety of Prevenar 13 has been demonstrated in adults aged 50 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

Adults not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine
In a head-to-head, comparative trial conducted in adults aged 60-64 years, subjects received a single dose of either Prevenar 13 or 23vPPV. In the same study another group of adults aged 50-59 years received a single dose of Prevenar 13.

Table 4 compares the OPA GMTs, 1-month post-dose, in 60-64 year olds given either a single dose of Prevenar 13 or 23vPPV, and in 50-59 year olds given a single dose of Prevenar 13.

Table 4: OPA GMTs in adults aged 60-64 years given Prevenar 13 or pneumococcal polysaccharide vaccine (23vPPV) and in adults aged 50-59 years given Prevenar 13[a,b,c]

	Prevenar 13	Prevenar 13	23vPPV	Prevenar 13, 50-59 Relative to 60-64 Years		Prevenar 13 Relative to 23vPPV, 60-64 Years	
	50-59 Years N=350-384	60-64 Years N=359-404	60-64 Years N=367-402				
Serotype	GMT	GMT	GMT	GM Ratio	(95% CI)	GM Ratio	(95% CI)
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6A†	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] For serotype 6A†, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR being greater than 2.

In adults aged 60-64 years, OPA GMTs to Prevenar 13 were non-inferior to the OPA GMTs elicited to the 23vPPV for the twelve serotypes common to both vaccines. For 8 of the serotypes

in common, the OPA titres were shown to be statistically significantly greater in Prevenar 13 recipients. In addition, OPA GMTs for serotype 6A were statistically significantly greater in Prevenar 13 recipients.

In adults aged 50-59 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years. For 9 serotypes, immune responses were related to age, with adults in the 50-59 years group showing statistically significantly greater responses than adults aged 60-64 years.

In adults aged 60-64 years, antibody levels one year after vaccination were greater after Prevenar 13 compared to antibody levels after 23vPPV for 7 of 12 serotypes in common. In adults aged 50-59 years, antibody levels one year after vaccination with Prevenar 13 were greater for 12 of 13 serotypes compared to vaccination with Prevenar 13 in 60-64 year olds.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine
Immune responses to Prevenar 13 and 23vPPV were compared in a head to head trial in adults aged ≥ 70 years, who had received a single dose of pneumococcal polysaccharide vaccine at least 5 years before study vaccination.

Table 5 compares the OPA GMTs, 1-month post-dose, in pneumococcal polysaccharide vaccinated adults aged ≥ 70 years given a single dose of either Prevenar 13 or 23vPPV.

Table 5 - OPA GMTs in pneumococcal polysaccharide (23vPPV) vaccinated adults aged ≥ 70 years given either Prevenar 13 or 23vPPV[a,b,c]

	Prevenar 13 N=400-426	23vPPV N=395-445	Prevenar OPA GMT Titers Relative to 23vPPV	
Serotype	**OPA GMT**	**OPA GMT**	**Ratio**	**(95% CI)**
1	81	55	1.5	(1.17 , 1.88)
3	55	49	1.1	(0.91 , 1.35)
4	545	203	2.7	(1.93 , 3.74)
5	72	36	2.0	(1.55 , 2.63)
6A†	903	94	9.6	(7.00 , 13.26)
6B	1261	417	3.0	(2.21 , 4.13)
7F	245	160	1.5	(1.07 , 2.18)
9V	181	90	2.0	(1.36 , 2.97)
14	280	285	1.0	(0.73 , 1.33)
18C	907	481	1.9	(1.42 , 2.50)
19A	354	200	1.8	(1.43 , 2.20)
19F	333	214	1.6	(1.17 , 2.06)
23F	158	43	3.7	(2.69 , 5.09)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] For serotype 6A†, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GM ratio greater than 2.

In adults vaccinated with pneumococcal polysaccharide vaccine at least 5 years prior to the clinical study, OPA GMTs to Prevenar 13 were non-inferior to the 23vPPV responses for the 12 serotypes in common. Furthermore, in this study statistically significantly greater OPA GMTs were demonstrated for 10 of the 12 serotypes in common. Immune responses to serotype 6A were statistically significantly greater following vaccination with Prevenar 13 than after 23vPPV.

Additional Immunogenicity data
In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar 13 can be given concomitantly with trivalent inactivated influenza vaccine (TIV). The responses to all three TIV antigens were comparable when TIV was given alone or concomitantly with Prevenar 13.

When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone. The clinical significance of this is unknown. In adults aged 50-59, non-inferiority was met for all serotypes. In adults aged 65 years and over, non-inferiority was met for all serotypes except serotype 19F.

INDICATIONS

Active immunisation for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older.

The use of Prevenar 13 should be guided by official recommendations.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid
- Allergic reaction or anaphylactic reaction following prior administration of Prevenar.

PRECAUTIONS

Do not administer Prevenar 13 intravenously. Do not administer Prevenar 13 intravascularly. Take care to avoid injecting into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area (see Dosage and administration).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

As with other vaccines, the administration of Prevenar 13 should be postponed in subjects suffering from acute moderate or severe febrile illness.

Disease coverage

Prevenar 13 will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other micro-organisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

Blood disorders

As with other vaccines administered intramuscularly, this vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Impaired immune response

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Vaccination in high-risk groups

Limited data have demonstrated that Prevenar (three dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups. Safety and immunogenicity data for Prevenar 13 are not available for individuals in immunocompromised groups (e.g., congenital or acquired splenic dysfunction, HIV infected, malignancy, haematopoietic stem cell transplant, nephrotic syndrome) and vaccination should be considered on an individual basis.

Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 24 months of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Prevenar 13 should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the 13-valent pneumococcal conjugate vaccine (Prevenar 13) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of 23-valent pneumococcal polysaccharide vaccine to unprimed children or to children primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

Risk of apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born £ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Prophylactic antipyretics

Antipyretic treatment should be initiated according to local treatment guidelines.

Prophylactic antipyretic medication is recommended:

- for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions
- for children with seizure disorders or with a prior history of febrile seizures.

Carcinogenicity

Prevenar 13 has not been tested for carcinogenic potential.

Genotoxicity

Prevenar 13 has not been tested for genotoxic potential.

Effects on fertility

Prevenar 13 showed no adverse effects on mating or fertility in a combined fertility and embryofoetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24 (see also Use in pregnancy).

Use in pregnancy

Category B2
Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans.

Prevenar 13 showed no treatment-related effects on mating, fertility, pregnancy, parturition, foetal gross, external, soft tissue and skeletal alternations, and pup survival and growth in a combined fertility and embryofoetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24. Serotype-specific antibodies against each of the 13 vaccine serotypes were detected in does, foetuses, and pups.

Use in lactation

Safety during lactation has not been established. It is not known whether vaccine antigens or antibodies are excreted in breast milk.

In a female rabbit fertility and embryofoetal development study, serotype–specific antibodies against each of the 13 vaccine serotypes were detected in the pups of does administered the vaccine prior to mating and during gestation. There were no adverse findings in these pups.

Geriatric use

Prevenar 13 has been shown to be safe and immunogenic in the geriatric population. Of the 5,667 adults in the 6 studies of the clinical development program who received Prevenar 13, 1,785 (31.5%) were 65 to 74 years of age, and 1,266 (22.3%) were 75 years of age and over. No

clinically significant differences in safety or immunogenicity were observed between 65 to 74 year-old individuals and greater than 75 year-old individuals.

Interactions with other medicines

Different injectable vaccines should always be given at different injection sites.

Infants and children aged 6 weeks to 5 years

Prevenar 13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical trials demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Previously, trials with Prevenar and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in Prevenar and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed if Prevenar 13 is used. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed.

Adults aged 50 years and older

Prevenar 13 may be administered concomitantly with the seasonal trivalent inactivated influenza vaccine (TIV) with no interference with the immune responses to TIV. Concomitant use with other vaccines has not been investigated.

Prevenar 13 is not contraindicated in people who have previously been vaccinated with 23vPPV. Clinical studies have demonstrated Prevenar 13 can be safely given one year after 23vPPV. However, when Prevenar 13 was given 1 year after 23vPPV the immune responses were lower for all serotypes compared to when Prevenar 13 was given to subjects not previously immunised with 23vPPV. The clinical significance of this is unknown (see also Dosage and administration in adults).

Studies in which Prevenar 13 was given to subjects who had 23vPPV at least one year prior have not found an increased incidence of local or systemic side effects.

Effects on ability to drive and operate machinery

Not relevant.

ADVERSE EFFECTS

Adverse reaction frequencies are listed below in CIOMS frequency categories:
Very common: ³ 10%
Common: ³ 1% and < 10%
Uncommon: ³ 0.1% and < 1%
Rare: ³ 0.01% and < 0.1%
Very rare: < 0.01%

These data are from clinical trials in which Prevenar 13 was administered to children simultaneously with other routine childhood vaccines.

Body as a whole	
Very common:	Fever; any injection-site erythema, induration/swelling or pain/tenderness; Injection-site erythema or induration/swelling 2.5 cm –7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39ºC; injection-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm
Digestive system disorders	
Common:	Diarrhoea; vomiting
Immune system disorders	
Rare:	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Metabolic and nutritional disorders	
Very common:	Decreased appetite
Nervous system disorders	
Very common:	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon:	Seizures (including febrile seizures)
Rare:	Hypotonic-hyporesponsive episode
Skin and appendages	
Common:	Rash
Uncommon:	Urticaria or urticaria-like rash
Psychiatric disorders	
Very common:	Irritability
Uncommon:	Crying

Table 6: Percentage of infant and toddler subjects reporting solicited local reactions at the Prevenar 13 or Prevenar (7-valent) injection sites

	Dose 1[a]		Dose 2[a]		Dose 3[a]		Dose 4[b]	
Graded Local Reaction	Prevenar 13 (N[c]=3601-3878)	Prevenar 7 (N[c]=2025-2148)	Prevenar 13 (N[c]=3087-3388)	Prevenar 7 (N[c]=1699-1824)	Prevenar 13 (N[c]=2603-2809)	Prevenar 7 (N[c]=1245-1364	Prevenar 13 (N[c]=1049-1198)	Prevenar 7 (N[c]=654-791)
Tenderness								
Any	46.8	44.9	44.7	43.9	41.0	39.5	52.1	56.0
Significant[d]	8.3	9.3	6.3	8.6*	6.0	5.9	6.2	8.1
Induration								
Any	23.0	21.9	28.0	28.9	30.1	30.3	32.6	33.5
Mild[e]	19.8	20.0	25.6	26.5	27.6	27.9	29.8	29.4
Moderate[e]	6.9*	4.7	7.0	6.1	8.0	7.2	12.0	10.5
Severe[e]	0	0	0.1	0	0	0	0	0
Erythema								
Any	26.3	27.8	35.3	35.1	38.3	37.0	43.6	43.7
Mild[e]	24.7	26.8	33.9	33.9	36.5	35.3	39. 4	40.0
Moderate[e]	2.7*	1.8	3.0	3.1	5.0	5.3	11.8	11.7
Severe[e]	0	0	0.1	0	0	0	0.1	0.2

* Statistically significant difference $p < 0.05$

Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.
b. Toddler dose data are included for the 6 infant studies with toddler dose data.
c. Number of subjects reporting Yes for at least 1 day or No for all days.
d. Significant = present and interfered with limb movement.
e. Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

Table7: Percentage of infant and toddler subjects reporting solicited systemic adverse reactions, fever and antipyretic medications after each vaccination

	Dose 1[a]		Dose 2[a]		Dose 3[a]		Dose 4[b]	
Graded Systemic Events	Prevenar 13 (N[c]=3594-4022)	Prevenar 7 (N[c]=1998-2215)	Prevenar 13 (N[c]=3110-3606)	Prevenar 7 (N[c]=1718-1969)	Prevenar 13 (N[c]=2580-3024)	Prevenar 7 (N[c]=1253-1480)	Prevenar 13 (N[c]=1073-1283)	Prevenar 7 (N[c]=666-873)
Decreased Appetite	38.4	37.2	37.8	41.0	36.6	38.1	42.2	50.2
Irritability	69.2	63.9	68.8	68.1	61.9	60.6	63.4	69.6
Increased Sleep	59.0	57.4	50.9	51.1	41.2	40.7	42.7	52.3
Decreased Sleep	36.4*	33.5	35.3	34.9	34.0	32.8	30.1	33.2
Fever[d]								
Any	25.0*	24.4	32.2	38.4	27.8	32.4	43.0	49.8
Mild	24.1*	23.5	30.7	37.3	26.8	31.3	41.1	48.2
Moderate	1.5	1.2	3.0	2.9	2.9	2.6	6.6	8.3
Severe	0.0	0.2*	0.1	0.1	0.2	0.2	0.3	0.2
Antipyretic Medications								
Treat	45.9	45.9	49.8	55.3	46.1	51.9	43.0	50.4
Prevent	46.5	46.0	48.9	50.9	47.1	51.1	36.1	46.5

* Statistically significant difference $p < 0.05$

Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.

b. Toddler dose data are included for the 6 infant studies with toddler dose data.

c. Number of subjects reporting Yes for at least 1 day or No for all days.

d. "Any" fever = subjects with any temperature ≥38°C; for subcategories of fever by grading, subjects may be included in more than 1 row. Fever grading: mild ≥38°C but ≤39°C, moderate >39°C but ≤40°C, severe >40°C.

Adults aged 50 years and older

Safety was assessed in 6 clinical studies including 6,198 adults ranging in ages from 50 to 95 years, of which 5,667 received Prevenar 13. There were 2,616 (46.2%) adults aged 50 to 64 years and 3,051 (53.8%) adults 65 years and older. Of the Prevenar 13 recipients, 1,916 adults were previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine more than 3 years prior. Adults older than 65 years of age reported fewer events than younger adults, regardless of prior immunisation status. Overall, the frequency categories were similar for both age groups.

Adverse reactions from clinical studies

The following frequencies are based on adverse reactions assessed as related to vaccination with Prevenar 13 in adults:

Gastrointestinal disorders: Very common: Common: Uncommon:	 Diarrhoea Vomiting Nausea
General disorders and administration site conditions Very common**:** Common: Uncommon:	 Chills; fatigue; injection site erythema; injection site induration /swelling; injection site pain/tenderness; limitation of arm movement Fever Lymphadenopathy localized to the region of the injection site
Immune system disorders Uncommon:	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Musculoskeletal and connective tissue disorders Very common	New joint pain/aggravated joint pain; new muscle pain/aggravated muscle pain
Metabolic and nutritional disorders Very common:	Decreased appetite
Nervous system disorders Very common:	Headaches
Skin and subcutaneous tissue disorders Very common:	 Rash

Overall, no significant differences in frequencies of adverse reactions were seen when Prevenar 13 was given to adults previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine or adults not vaccinated with 23-valent pneumococcal polysaccharide vaccine.

Solicited adverse reactions in adult studies with Prevenar 13 and TIV

The safety of concomitant administration of Prevenar 13 with Trivalent Inactivated Influenza Vaccine (TIV) was assessed in two studies in 23vPPV unvaccinated adults. Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥ 65 years were similar after Prevenar 13 was administered with TIV compared to Prevenar 13 administered alone.

Higher frequency of some solicited systemic reactions was observed when Prevenar 13 was administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or Prevenar 13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Table 8: Percentage of adults reporting solicited local reactions at Prevenar 13 injection site within 14 days after vaccination

	- Naïve to 23vPPV -			Pre-immunised with 23vPPV
Age (years)	**50-59**	**60-64**	**≥65**	**≥70**
Number of Subjects	137 - 322	178 - 331	848 - 950	297 - 362
Local Reaction				
Redness[a]				
Any	15.8	20.2	14.4	10.8
Mild	15.2	15.9	12.1	9.5
Moderate	5	8.6	6.1	4.7
Severe	0.7	1.7	0.8	1.7
Swelling[a]				
Any	21.7	19.3	12	10.4
Mild	20.6	15.6	10	8.9
Moderate	4.3	8.2	4.6	4
Severe	0	0.6	0.1	0
Pain[b]				
Any	88.8	80.1	41.7	51.7
Mild	85.9	78.6	36.1	50.1
Moderate	39.5	23.3	17.2	7.5
Severe	3.6	1.7	2	1.3
Limitation of arm movement[c]				
Any	40.7	28.5	14.4	10.5
Mild	38.6	26.9	13.2	10.3
Moderate	2.9	2.2	1.2	0.3
Severe	2.9	1.7	1.6	0.7

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

b. 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.

c. 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.

Table 9: Percentage of adults reporting solicited systemic adverse reactions, use of medication to treat pain and fever within 14 days after vaccination with Prevenar 13

	--- Naïve to 23vPPV ---			Pre-immunised with 23vPPV
Age (years) Number of Subjects	**50-59** 136 - 248	**60-64** 177 - 277	**≥65** 420 - 456	**≥70** 297 - 350
Systemic Event				
Any (≥38°C)	1.5	4.0	3.6	1.0
Mild (≥38°C but <38.5°C)	1.5	4.0	3.1	1.0
Moderate (≥38.5°C but <39°C)	0.0	0.6	1.0	0.0
Severe (≥39°C but ≤40°C)	0.0	0.0	0.0	0.0
Potentially life threatening (>40°C)	0.0	0.0	0.0	0.0
Fatigue	63.3	63.2	28.5	34.0
Headache	65.9	54.0	24.7	23.7
Chills	19.6	23.5	9.1	7.9
Rash	14.2	16.5	6.8	7.3
Vomiting	6.9	3.9	1.7	1.7
Diarrhoea	N/A	N/A	N/A	N/A
Decreased appetite	25.3	21.3	11.3	10.4
New muscle pain	61.8	56.2	23.4	36.8
Aggravated muscle pain	39.9	32.6	15.0	20.6
New joint pain	31.5	24.4	11.5	12.6
Aggravated joint pain	25.6	24.9	8.6	11.6
Use of medication to treat pain	N/A	N/A	9.9	22.0
Use of medication to treat fever	N/A	N/A	5.4	3.0
Abbreviation: N/A = not applicable				

Adverse reactions from Prevenar 13 postmarketing experience

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for Prevenar 13 as they were reported in the postmarketing experience. Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

General disorders and administration site conditions	Injection-site dermatitis; injection-site urticaria, injection-site pruritus
Blood and lymphatic system disorders	Lymphadenopathy localized to the region of the injection-site
Immune system disorders	Anaphylactic/anaphylactoid reaction including shock
Skin and subcutaneous tissue disorders	Angioedema; erythema multiforme

DOSAGE AND ADMINISTRATION

The dose of Prevenar 13 is 0.5 mL given intramuscularly only, with care to avoid injection into or near nerves and blood vessels. The preferred sites are anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in children and adults.

Do not administer Prevenar 13 intravascularly or into the gluteal area. Do not administer Prevenar 13 intravenously, subcutaneously or intradermally, since the safety and immunogenicity of these routes have not been evaluated.

Upon storage, a white deposit and clear supernatant can be observed. The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate

matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. Prevenar 13 is a suspension containing an adjuvant. The vaccine must not be used if it cannot be uniformly suspended.

Prevenar 13 is not to be mixed with other vaccines or products in the same syringe. Prevenar 13 is for single-use in one patient only. The suspension contains no antimicrobial agent. Discard any residue.

Immunisation schedules

Data on the interchangeability of Prevenar or Prevenar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

It is recommended that infants who receive a first dose of Prevenar 13 complete the vaccination course with Prevenar 13.

The immunisation schedules for Prevenar 13 should be based on official recommendations.

Infants aged 6 weeks - 6 months

The primary infant series consists of three doses, each of 0.5 mL, with the first dose usually given at 6 weeks of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose.

Vaccination schedule for infants (6 weeks – 6 months of age)				
Dose:	Dose 1	Dose 2	Dose 3	Dose 4
Age at Dose:	6 weeks	4 months	6 months	12-15 months

Infants and children previously vaccinated with Prevenar

Prevenar 13 contains the same 7 serotypes contained in Prevenar and is manufactured based on the same conjugate technology using the same carrier protein $CRM_{197.}$

Infants and children who have begun immunisation with Prevenar may complete immunisation by switching to Prevenar 13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable. Children aged 12 months to 5 years of age who have completed primary infant immunisation with Prevenar (7-valent) may receive one dose of Prevenar 13 to elicit immune responses to the six additional serotypes. This catch-up (supplemental) dose of Prevenar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevenar (7-valent).

Vaccination schedule for previously unvaccinated children [3] 7 months of age		
Age at first dose	**Total number of 0.5 mL doses**	**Duration between doses**
7-11 months of age	3	Between dose 1 and 2: At least 1 month Between dose 2 and 3: At least 2 months (3rd dose after 12 months of age)
12-23 months of age	2	At least 2 months
24 months to <72 months of age	1	N/A

Adults aged 50 years and older

One single dose in adults 50 years and older including those previously vaccinated with pneumococcal polysaccharide vaccine.

The need for revaccination with a subsequent dose of Prevenar 13 has not been established. Refer to local recommendations.

If sequential administration of Prevenar 13 and 23vPPV is considered, Prevenar 13 should be given first for maximal efficacy and to avoid blunting of the immune response by 23vPPV.

Influence of foods, compatibility with drugs/fluids

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children, there have been reports of overdose with Prevenar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended paediatric schedules of Prevenar 13.

PRESENTATION

Prevenar 13 is presented as a suspension in 0.5 mL pre-filled syringes (Type I glass) in packs of 1 and 10. All syringe components are latex-free.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if the vaccine has been frozen.

POISON SCHEDULE

Prescription Only Medicine (S4)

NAME AND ADDRESS

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® Registered Trade Mark

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