Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

Proprietary Product Name: Prevenar 13

Sponsor: Pfizer Australia Pty Ltd

30 October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
23vPS	23-valent pneumococcal polysaccharide vaccine
AE	Adverse event
CAP	community-acquired pneumonia
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CO	clinical overview
CRM197	cross-reacting material 197 (nontoxic mutant form of diphtheria toxin)
CSR	clinical study report
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
GMCs	geometric mean concentrations
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
LLOQ	lower limit of quantitation
MAA	Marketing Authorisation Application

Abbreviation	Meaning
MAH	Marketing Authorisation Holder
MedRA	Medical Dictionary for Regulatory Activities
NIP	National immunisation program
OPA	opsonophagocytic activity
RCDC	reverse cumulative distribution curve
SAP	statistical analysis plan
SCD	sickle cell disease
SmPC	summary of product characteristics
UK	United Kingdom
VT	vaccine type

1. Clinical rationale

On 02 December 2008, the Marketing Authorisation Holder (MAH) submitted an application to the European Medicines Agency (EMA) for 13-valent pneumococcal conjugate vaccine (13vPnC, Prevenar 13), through the centralised procedure in the EU. A positive opinion was adopted on 24 September 2009 by the Committee for Medicinal Products for Human Use (CHMP). The current adult indication for 13vPnC covers adults aged 50 years and older. The MAH is now submitting a Type II variation in multiple countries to expand the adult indication to include adults aged 18 to 49 years. With this expanded coverage, the adult indication would be extended to cover all adults aged 18 years and older.

The epidemiological data contained in this submission is mainly from Europe and the United States[1, 2]. In these countries, as in Australia, there is still a significant burden of IPD in subjects 18 to 49 years of age. The incidence of IPD, according to population-based data from England and Wales, ranged from $4.7/10^5$ to $11.0/10^5$ in the 2009/2010 season. Available data indicate that about 50% of all cases may be caused by 13vPnC serotypes. It is also true that the incidence of pneumococcal pneumonia in subjects 18 to 49 years is largely underestimated, because valid microbiological tests are not routinely available. Estimates from clinical studies indicate CAP incidences range between $44/10^5$ and $134/10^5$, of which roughly 40% are due to *S. pneumoniae*. Administrative data indicate that hospitalisations for CAP or "all cause-pneumonia" are in the magnitude of $30/10^5$ to $60/10^5$ and roughly 40% are due to *S. pneumoniae*; of these 57% have been identified as 13vPnC serotypes in the only study assessing pneumococcal serotypes in patients with CAP using multiple microbiological methods[3]. Epidemiological data in Australia is similar.[4] Herd protection effects from pneumococcal conjugate vaccines are also seen in the group aged 18 to 49 years.

There are subjects with diverse types of "risks" for severe pneumococcal infections. These risks encompass various types of immune deficiencies (with or without a remaining ability to produce protective antibodies), non-immunologically determined other underlying diseases and conditions, as well as various life style factors. While details may vary for such "risk subjects," pneumococcal vaccination is recommended in virtually all European countries. Currently for adults aged 18 to 49 years only 23vPS is available, although it is well known that the polysaccharide vaccine does not offer high and long lasting protection and hyporesponsiveness is a concern[5]. Subjects aged 18 to 49 years in certain at-risk groups have significant risk for pneumococcal diseases, and 13vPnC has an estimated 60% coverage of serotypes causing IPD in these subjects.

[information redacted]

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

Module 5

- Details of the pivotal efficacy/safety studies.
- Details of the high risk groups efficacy/safety studies.

2.2. Paediatric data

The submission includes paediatric efficacy and safety data.

2.3. Good clinical practice

This submission has compliance with good clinical practice.

3. Pharmacokinetics

Not applicable.

4. Pharmacodynamics

Not applicable.

5. Dosage selection for the pivotal studies

The standard dose of 0.5mL was used.

6. Clinical efficacy

6.1. Indication 1: Active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae* in adults (aged 18 years and older).

6.1.1. Pivotal efficacy study

6.1.1.1. Study 6115A1-004

6.1.1.1.1. Study design, objectives, locations and dates

This was a Phase III, randomised, active-controlled, modified double blind trial evaluating the safety, tolerability, and immunogenicity of a 13vPnC compared to a 23-valent pneumococcal polysaccharide vaccine (23vPS) in adults 60 to 64 years old who are naïve to 23vPS and the safety, tolerability, and immunogenicity of 13vPnC in adults 18 to 59 years old who are naïve to 23vPS.

This was conducted at 25 sites in the United States between 23 February 2009 and 18 June 2010, with final serology on 26 April 2012.

The primary objective of this study with respect to Cohort 3 was:

- To demonstrate that the immune response to the 13 serotypes in the 13vPnC in the 18 to 49 year-old age group is non-inferior to the immune response to 13vPnC in the 60 to 64 year-old age group as measured by serotype specific opsonophagocytic assay (OPA) titres 1 month after vaccination.

The secondary objectives of this study with respect to Cohort 3 were:

- To demonstrate that the proportion of subjects achieving an OPA titer ≥ lower limit of quantitation (LLOQ) in the 18 to 49 year-old age group is non-inferior to the proportion of subjects achieving an OPA titer ≥ LLOQ in the 60 to 64 year-old age group measured 1 month after vaccination.
- To demonstrate that the immune response to the 13 serotypes in the 13vPnC in each subgroup (18-29 years, 30-39 years and 40-49 years) is non-inferior to the immune response to 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific OPA titres 1 month after vaccination.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in the 18 to 49 year-old age group compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype specific fold rise OPA geometric mean titres (GMTs).
- To evaluate the immune responses 1 month after vaccination with 13vPnC in each subgroup (18-29 years, 30-39 years and 40-49 years) compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise OPA GMTs.

The safety objective of this study was:

- To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence of local reactions, systemic events, and adverse events (AEs).

The exploratory objectives of this study with respect to Cohort 3 were:

- To demonstrate that 13vPnC in the 18 to 49 year-old age group is as immunogenic as 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific immunoglobulin G (IgG) antibody concentrations 1 month after vaccination in a subset of 100 subjects.

- To demonstrate that 13vPnC in each subgroup (18-29 years, 30-39 years, and 40-49 years) is as immunogenic as 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific IgG antibody concentrations 1 month after vaccination in a subset of 100 subjects in each (sub) group.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in the 18 to 49 year-old age group compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise IgG GMCs in a subset of 100 subjects in each group.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in each subgroup (18-29 years, 30-39 years, and 40-49 years) compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise IgG GMCs in a subset of 100 subjects in each (sub)group.
- To assess persistence of antibody by IgG and OPA in the 18-49 year old age group and each of the subgroups (18-29 years, 30-39 years, and 40-49 years) 1 year after vaccination in a subset of 100 subjects per subgroup.

In this study, there were three cohorts, Cohort 1 (60-64 years of age), Cohort 2 (50 to 59 years of age), and Cohort 3 (18 to 49 years of age).

Cohort 1 was evaluated using a randomized, active-controlled, modified double-blind trial design to compare the safety, tolerability, and immunogenicity of 13vPnC and 23vPS.

Cohorts 2 and 3 were to receive open-label 13vPnC. Approximately 370 subjects were to be enrolled in the 13vPnC group in Cohort 1 and approximately 370 subjects were to be enrolled in Cohort 2. In the original protocol, approximately 370 subjects were to be enrolled in Cohort 3, but the protocol was amended to increase enrolment in this cohort to 900 subjects (amendment 4). In Cohort 3, subjects were stratified into 1 of 3 age subgroups: subgroup 1 (18 to 29 years of age), subgroup 2 (30 to 39 years of age), and subgroup 3 (40 to 49 years of age), with each subgroup to enrol approximately 300 subjects. Serology was assessed at one month and one year post-vaccination. This report includes data for Cohort 3, with comparison to Cohort 1 immunogenicity data for subjects who received 13vPnC, and with comparisons to Cohort 1 and Cohort 2 safety data for subjects who received 13vPnC. Full details regarding the methods and the complete results for cohorts 1 and 2 were presented in a separate study report.

6.1.1.1.2. Inclusion and exclusion criteria

These are consistent with study design. Subjects were excluded if they had previously been vaccinated with any licensed or experimental pneumococcal vaccine, had a documented *S. pneumoniae* infection within the past 5 years, had any other disorder that in the investigator's opinion precluded them from participating in the study, or had any of the other exclusion criteria specified in the protocol.

6.1.1.1.3. Study treatments

One standard dose (0.5 mL) of 13vPnC was used. The vaccine was to be prefilled into single-dose syringes without preservatives. Study vaccine was administered by intramuscular injection into the deltoid muscle.

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was:

Immunogenicity

For Cohorts 1, 2, and 3, blood samples for immunogenicity assessments were obtained before study vaccine administration at Visit 1 (day 1), approximately 1 month after vaccination (day 29 through day 43), and approximately 1 year after vaccination (day 351 through day 379). For

Cohort 3, blood samples were collected approximately 1 year after study vaccine administration only for subjects who enrolled under a protocol amendment (number 4).

Serum OPA titres for the 13 pneumococcal serotypes contained in 13vPnC were determined for all subjects for blood samples collected at baseline and 1 month post-vaccination.

In addition, OPA titres were determined for blood samples collected at 1 year post-vaccination for randomly selected subsets of 100 subjects in each cohort and vaccine group. Serum concentrations of serotype-specific IgG were determined for each of the 13 pneumococcal serotypes contained in 13vPnC using an enzyme-linked immunosorbent assay (ELISA). IgG concentrations were determined for all 3 blood samples (baseline, 1 month post-vaccination, and 1 year post-vaccination) for the same subsets of 100 subjects selected for the 1-year post-vaccination OPA analyses.

6.1.1.1.5. Randomisation and blinding methods

In Cohort 3, the vaccination was open label.

6.1.1.1.6. Analysis populations

The evaluable immunogenicity population included all subjects who were randomized, received the vaccine to which they were randomised and had at least 1 valid and determinate assay result for antibody response to any pneumococcal serotype as well as a pre-vaccination blood drawn on the same day as the day of vaccination or within 15 days prior to day 1, and had no other major protocol violation.

All-available immunogenicity population

The all-available immunogenicity population included all subjects who had at least 1 valid and determinate assay result related to the proposed analysis.

6.1.1.1.7. Sample size

Sample size rationale

Cohort 1:

Sample size estimates were based upon the observed OPA geometric mean titres and standard deviations for the antibody titres in each vaccine group from Wyeth Study 6097A1-508 and Study 6096A1-002. With 350 evaluable subjects per group, a difference of at least 15% in the proportion of subjects responding could be detected with at least 90% power and with a 2-sided, type I error rate of 0.05.

Cohorts 2 and 3:

Sample sizes of 350 evaluable subjects per vaccine group in Cohort 1 and 350 evaluable subjects in cohorts 2 and 3 will provide at least 90% overall power to declare non-inferiority for all 13 pneumococcal antigens using a 2-fold non-inferiority criterion. Assuming a dropout rate of no more than 5% in this study, an overall sample size of approximately 1480 enrolled subjects (370 per group) should achieve 350 evaluable subjects per group.

The sample size in Cohort 3 was increased as part of Amendment 4 of the protocol, such that 274 evaluable subjects in each of the subgroups aged 18 to 29, 30 to 39, and 40 to 49 years within Cohort 3 would provide approximately 80% power to declare non-inferiority between each subgroup and the 60 to 64 year group. Assuming a dropout rate of approximately 9% in each of the subgroups, a total of 900 subjects (300 subjects in each subgroup) were to be enrolled in Cohort 3.

6.1.1.1.8. Statistical methods

Analysis Criteria: For Cohort 3, the primary immunologic comparisons were the serotype specific OPA responses to the 13 pneumococcal serotypes contained in 13vPnC measured 1 month after study vaccine administration in Cohort 3 (subjects 18 to 49 years of age) relative to

the responses among subjects vaccinated with 13vPnC in Cohort 1 (subjects 60 to 64 years of age).

- The primary endpoint for the Cohort 3 and Cohort 1 comparison was the serotype-specific OPA GMTs 1 month after vaccination. Non-inferiority was declared if the lower limit of the 2-sided, 95% confidence interval (CI) for the ratio of GMTs (GMT for Cohort 3/GMT for Cohort 1) was greater than 0.5 (2-fold criterion). Statistical significance was demonstrated if the lower limit of the 2-sided, 95% CI for the ratio of GMTs (GMT for Cohort 3/GMT for Cohort 1) was >1.
- The secondary endpoint for the Cohort 3 and Cohort 1 comparison was the proportion of subjects achieving an OPA titer ≥LLOQ for each serotype 1 month after vaccination. Non-inferiority for a given serotype was demonstrated if the lower limit of the 2-sided, 95% CI for the difference in proportions (Cohort 3–Cohort 1) was greater than -0.10.

Analysis Methods: Serotype-specific OPA titres were logarithmically transformed for analysis. For each of the 13 serotypes contained in 13vPnC, OPA GMTs were calculated at pre-vaccination and the post-vaccination time points; 2-sided, 95% CIs on the GMTs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. Fold rises in OPA titres from the pre-vaccination to the post-vaccination time point were summarized by geometric means (that is, geometric mean fold rise, GMFR) and 95% CIs, also computed using the logarithmically transformed assay results. For the primary analysis comparing the GMTs 1 month after vaccination between Cohort 3 and Cohort 1, the 2-sided, 95% CIs on the ratio of GMTs (GMT for Cohort 3/GMT for Cohort 1) were calculated using the Student t distribution for the mean difference of the measures on the natural log (ln) scale (Cohort 3 relative to Cohort 1). Secondary analyses comparing the GMTs 1 month after vaccination between age subgroups of Cohort 3 (18 to 29, 30 to 39, and 40 to 49 groups) and Cohort 1 were performed in the same manner. For the 13 serotypes contained in 13vPnC, the proportion of subjects in cohorts 1 and 3 achieving an OPA titer ≥LLOQ 1 month after vaccination was evaluated with corresponding exact, 2 sided 95% CIs based on the Chan and Zhang procedure. The difference in proportions between cohorts 1 and 3 was computed with corresponding exact 2 sided 95% CIs.

6.1.1.1.9. Participant flow

A total of 899 people aged between 18-49 years (Cohort 3) were vaccinated. There was an age breakdown as follows: 18-29 – 300, 30-39- 298, 40-49 – 301. Of the 900 subjects assigned to Cohort 3, the majority were vaccinated (99.9%), completed the 1-month blood draw (98.1%) and completed the 6-month contact (94.9%). Of the 854 subjects (94.9% of the subjects assigned to Cohort 3) who completed the 6-month contact, 352 subjects (39.1% of the subjects assigned to Cohort 3) were not scheduled to have a 1-year visit and 502 subjects (55.8% of the subjects assigned to Cohort 3) were scheduled to have a 1-year visit. There were 469 subjects who completed the 1-year blood draw in Cohort 3 (52.1% of the 900 subjects assigned to Cohort 3, 93.4% of the 502 subjects who completed the 6-month contact and were scheduled to have a 1-year visit). Similar results were seen for the Cohort 3 age subgroups (18 to 29, 30 to 39, and 40 to 49 year-olds).

6.1.1.1.10. Major protocol violations/deviations

There were no major issues. Most common deviation was due to blood draw omission.

6.1.1.1.11. Baseline data

In Cohort 3, the majority of subjects were White (85.9%) and non-hispanic and non-latino (91.2%), and 58.2% of the subjects were female. In this cohort, age at vaccination ranged from 18 to 49 years, with a mean age of 34.0 years. The percentages of subjects were similar in each of the age subgroups, with 33.4% of the Cohort 3 subjects in the 18 to 29 year-old age subgroup, 33.1% of the Cohort 3 subjects in the 30 to 39 year-old age subgroup, and 33.5% of the Cohort 3

subjects in the 40 to 49 year-old age subgroup in the safety population. In the evaluable population, the demographic characteristics of the 3 age subgroups were similar with respect to race and ethnicity. The percentage of female subjects was lower in the 18 to 29 year-old age subgroup (50.5%) than in the 30 to 39 year-old (58.7%) or 40 to 49 year-old (65.5%) age subgroups.

6.1.1.1.12. Results for the primary efficacy outcome

OPA titres were assessed on Day 1 before vaccination and 1 month after vaccination. In addition, OPA titres were determined in blood samples collected at 1 year post-vaccination for randomly selected subsets of 100 subjects in Cohort 1 and in each age subset of Cohort 3. Serum concentrations of serotype-specific IgG antibodies, using the enzyme-linked immunosorbent assay (ELISA), were also determined for all 3 blood samples (baseline, 1 month post-vaccination, and 1 year post-vaccination) for the same subset of 100 subjects selected for the 1-year post-vaccination OPA analyses.

The evaluable immunogenicity population for Cohort 1 and Cohort 3 comprised a total of 1285 subjects (97.5%): 411 (98.3%) in Cohort 1 and 874 (97.1%) in Cohort 3. The demographic characteristics of the evaluable immunogenicity population were similar to those in the overall population.

Immune responses after 13vPnC administration to subjects aged 18 to 49 years in Cohort 3 were non-inferior to those of subjects aged 60 to 64 years in Cohort 1, as measured by serotype-specific OPA GMTs 1 month after vaccination (the 2-fold non-inferiority criterion was a lower limit of the 95% CI for the ratio [Cohort 3 GMT/Cohort 1 GMT] of >0.5) as shown in Table 1.

Table1. Comparison of Pneumococcal OPA GMTs 1 Month After Vaccination in subjects Aged 18 to 49 Years (Cohort 3) and 60 to 64 Years (Cohort 1) – Evaluable Immunogenicity Population

	18-49 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	866	353	404	146	2.4	(2.03, 2.87)
3	860	91	394	93	1.0	(0.84, 1.13)
4	849	4747	359	2062	2.3	(1.92, 2.76)
5	836	386	392	199	1.9	(1.55, 2.42)
6A	855	5746	401	2593	2.2	(1.84, 2.67)
6B	865	9813	371	1984	4.9	(4.13, 5.93)
7F	859	3249	394	1120	2.9	(2.41, 3.49)
9V	844	3339	367	1164	2.9	(2.34, 3.52)
14	860	2983	375	612	4.9	(4.01, 5.93)
18C	850	3989	379	1726	2.3	(1.91, 2.79)
19A	855	1580	392	682	2.3	(2.02, 2.66)
19F	841	1533	377	517	3.0	(2.44, 3.60)
23F	851	1570	375	375	4.2	(3.31, 5.31)

Abbreviations: GMT=geometric mean titer; CI=confidence interval. a. n = Number of subjects with a determinate OPA titer to the given serotype. b. Geometric mean titres (GMTs) were calculated using all subjects with available data for the specified blood draw. c. Ratio of GMTs, Cohort 3 to Cohort 1, is calculated by back transforming the mean difference between cohorts on the logarithmic scale. d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Cohort 3 – Cohort 1).

In addition, in each age subgroup of Cohort 3 (18 to 29 years, 30 to 39 years and 40 to 49 years) the OPA GMTs for the 13vPnC serotypes were non-inferior to those of Cohort 1 when measured 1 month after vaccination. In Cohort 3 overall and in each age subgroup, OPA GMTs for all serotypes except serotype 3, at 1 month after vaccination, were statistically significantly higher than those in the 13vPnC group of Cohort 1 (that is, the lower limit of the of 95% CI for the ratio was >1) (Table 1 and Table 2). Among the age subgroups, the OPA GMTs were generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup at 1 month after vaccination and 1 year after vaccination, indicating a lower immune response with

increasing age. The serotype-specific geometric mean fold rise (post-vaccination OPA GMT/pre-vaccination OPA GMT) was generally similar or higher in the 18 to 49 year old group) relative to that of the 60 to 64 year old group, at 1 month and 1 year after vaccination.

Table 2. Comparison of Pneumococcal OPA GMTs 1 Month After Vaccination in Subjects Aged 18 to 29 Years, 30 to 39 Years, and 40 to 49 Years (Cohort 3) to OPA GMTs of Subjects Aged 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

18 to 29 Years vs 60 to 64 Years						
	18-29 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	289	409	404	146	2.8	(2.22, 3.52)
3	287	112	394	93	1.2	(1.00, 1.45)
4	288	7152	359	2062	3.5	(2.73, 4.40)
5	279	567	392	199	2.8	(2.18, 3.70)
6A	288	8476	401	2593	3.3	(2.55, 4.18)
6B	290	14134	371	1984	7.1	(5.51, 9.21)
7F	289	3741	394	1120	3.3	(2.55, 4.38)
9V	282	5086	367	1164	4.4	(3.35, 5.71)
14	287	4452	375	612	7.3	(5.52, 9.59)
18C	281	5240	379	1726	3.0	(2.37, 3.89)
19A	287	2162	392	682	3.2	(2.64, 3.81)
19F	276	2251	377	517	4.4	(3.35, 5.66)
23F	285	2954	375	375	7.9	(5.85, 10.62)
30 to 39 Years vs 60 to 64 Years						
	30-39 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	288	353	404	146	2.4	(1.91, 3.04)
3	287	93	394	93	1.0	(0.82, 1.22)
4	279	4589	359	2062	2.2	(1.72, 2.88)
5	278	375	392	199	1.9	(1.39, 2.55)
6A	284	6131	401	2593	2.4	(1.82, 3.07)
6B	285	10180	371	1984	5.1	(3.93, 6.70)
7F	285	3276	394	1120	2.9	(2.23, 3.84)
9V	276	3208	367	1164	2.8	(2.06, 3.70)
14	283	2919	375	612	4.8	(3.58, 6.35)
18C	281	3841	379	1726	2.2	(1.70, 2.91)
19A	283	1504	392	682	2.2	(1.83, 2.66)
19F	278	1507	377	517	2.9	(2.20, 3.85)
23F	282	1606	375	375	4.3	(3.16, 5.81)
40 to 49 Years vs 60 to 64 Years						
	40-49 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	289	305	404	146	2.1	(1.62, 2.67)
3	286	72	394	93	0.8	(0.64, 0.96)
4	282	3229	359	2062	1.6	(1.20, 2.04)
5	279	271	392	199	1.4	(1.01, 1.84)
6A	283	3626	401	2593	1.4	(1.07, 1.83)
6B	290	6571	371	1984	3.3	(2.52, 4.35)
7F	285	2792	394	1120	2.5	(1.88, 3.30)
9V	286	2292	367	1164	2.0	(1.46, 2.65)
14	290	2049	375	612	3.4	(2.51, 4.46)
18C	288	3171	379	1726	1.8	(1.42, 2.39)
19A	285	1209	392	682	1.8	(1.46, 2.15)
19F	287	1076	377	517	2.1	(1.57, 2.75)
23F	284	814	375	375	2.2	(1.54, 3.08)

Abbreviations: GMT=geometric mean titer, CI=confidence interval. a. n = Number of subjects with a determinate OPA titre to the given serotype. b. Geometric mean titres (GMTs) were calculated using all subjects with available data for the specified blood draw. c. Ratio of GMTs, Cohort 3 to Cohort 1, is calculated by back transforming the mean difference between cohorts on the logarithmic scale. d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Cohort 3 – Cohort 1).

The proportion of subjects achieving an OPA titer ≥LLOQ in Cohort 3 was non-inferior to that of Cohort 1 for all 13 serotypes at 1 month after vaccination and was statistically significantly greater in Cohort 3 for all serotypes except serotype 3. With regard to the persistence of the antibody response, a decrease in OPA GMTs was observed from 1 month to 1 year after vaccination, but titres at 1 year remained higher than titres before vaccination for both cohorts 3 1. Antibody response curves for Cohort 3 were higher than those for Cohort 1 for all serotypes except for serotype 3. In general the OPA antibody response curves were highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup. Reverse cumulative distribution curves (RCDCs) for Cohort 3 were higher across the full range of OPA titres than the curves for Cohort 1, with the exception of serotype 3 at 1 month after vaccination. At 1 year after vaccination the Cohort 3 curves were higher than the Cohort 1 curves for all serotypes. The RCDCs for each of the 3 age subgroups of Cohort 3 were also generally higher than the curves for Cohort 1 at 1 month and at 1 year after vaccination. The RCDCs for the 40 to 49 year old subgroup were generally the lowest of the Cohort 3 age subgroups, and in some cases were similar to the Cohort 1 curves.

IgG results supported those of the OPA analysis (Table 3). In Cohort 3, IgG GMCs for all serotypes in 13vPnC were noninferior (and for most serotypes statistically significantly higher) to those of Cohort 1, measured 1 month after vaccination. The same pattern of response was observed for each age subgroup. Among the age subgroups in general the IgG GMCs were highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup.

Table 3. Pneumococcal IgG GMCs (µg/mL) at Dose 1 and Dose 2 for 13vPnC – Evaluable Immunogenicity Population (6096A1-3014)

Serotype	Sampling Time	n[a]	GMC[b]	(95% CI[c])
7vPnC				
4	Before Dose 1	136	1.01	(0.80, 1.27)
	After Dose 1	138	6.85	(5.55, 8.44)
	Before Dose 2	136	2.77	(2.20, 3.35)
	After Dose 2	137	5.09	(4.38, 6.04)
6B	Before Dose 1	138	5.79	(4.89, 6.87)
	After Dose 1	137	27.25	(22.09, 33.61)
	Before Dose 2	138	13.67	(11.23, 16.63)
	After Dose 2	137	24.52	(20.48, 29.35)
9V	Before Dose 1	138	3.01	(2.56, 3.53)
	After Dose 1	138	9.31	(7.83, 11.07)
	Before Dose 2	136	5.19	(4.41, 6.09)
	After Dose 2	136	7.46	(6.46, 8.61)
14	Before Dose 1	138	6.30	(4.78, 8.30)
	After Dose 1	138	34.63	(27.77, 43.18)
	Before Dose 2	138	21.07	(17.29, 25.67)
	After Dose 2	137	26.19	(22.11, 31.03)
18C	Before Dose 1	137	1.40	(1.14, 1.73)
	After Dose 1	138	7.83	(6.42, 9.56)
	Before Dose 2	138	3.73	(3.10, 4.49)
	After Dose 2	137	5.44	(4.64, 6.38)
Serotype	**Sampling Time**	**n[a]**	**GMC[b]**	**(95% CI[c])**
19F	Before Dose 1	134	4.46	(3.60, 5.53)
	After Dose 1	138	20.40	(16.03, 25.95)
	Before Dose 2	137	10.34	(8.32, 12.85)
	After Dose 2	136	20.56	(17.13, 24.63)
23F	Before Dose 1	138	2.80	(2.38, 3.30)
	After Dose 1	137	18.25	(14.52, 22.93)
	Before Dose 2	137	8.07	(6.63, 9.83)
	After Dose 2	135	16.18	(13.27, 19.73)
Additional				
1	Before Dose 1	129	1.57	(1.26, 1.95)
	After Dose 1	138	5.24	(4.30, 6.39)
	Before Dose 2	137	2.65	(2.21, 3.19)
	After Dose 2	137	4.51	(3.83, 5.32)
3	Before Dose 1	133	1.02	(0.83, 1.25)
	After Dose 1	138	2.04	(1.78, 2.38)
	Before Dose 2	135	1.27	(1.06, 1.52)
	After Dose 2	134	1.67	(1.42, 1.97)
5	Before Dose 1	138	4.14	(3.58, 4.78)
	After Dose 1	138	7.19	(6.19, 8.35)
Serotype	**Sampling Time**	**n[a]**	**GMC[b]**	**(95% CI[c])**
	Before Dose 2	137	4.91	(4.26, 5.66)
	After Dose 2	139	6.31	(5.58, 7.17)
6A	Before Dose 1	132	4.42	(3.91, 5.46)
	After Dose 1	138	17.81	(14.16, 21.91)
	Before Dose 2	135	9.05	(7.48, 10.95)
	After Dose 2	136	16.17	(13.65, 19.64)
7F	Before Dose 1	137	2.16	(1.80, 2.59)
	After Dose 1	138	9.46	(8.17, 10.94)
	Before Dose 2	138	4.09	(3.52, 4.74)
	After Dose 2	137	7.06	(6.20, 8.04)
19A	Before Dose 1	138	8.16	(7.03, 9.48)
	After Dose 1	138	28.82	(22.16, 32.48)
	Before Dose 2	139	15.13	(12.73, 17.98)
	After Dose 2	137	22.19	(18.94, 25.90)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype. b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

6.1.2. Other efficacy studies – data from these to be included in PI

6.1.2.1. Study 6096A1-4001 in preterm infants

6.1.2.1.1. Study design, objectives, locations and dates

Study 6096A1-4001 was an open-label, Phase IV, multicentre, parallel-group study that compared the safety, tolerability, and immune response to 4 doses of 13vPnC in preterm infants to that of infants born at term. The 2 study groups were defined as follows: Group 1 – preterm infants aged <37 weeks of gestation; Group 2 - term infants aged ≥37 weeks of gestation. In addition, Group 1 was divided into the following preterm subgroups: Group 1A- 32≤ GA <37 weeks, Group 1B - 29≤ GA <32 weeks; Group 1C - GA <29 weeks. All subjects in each group were to receive 13vPnC at 2, 3, 4, and 12 months of age.

Objectives:

The primary objective was to describe the pneumococcal immune response induced by IM administration of 13vPnC when measured 1 month after the infant series in preterm infants compared to that of infants born at term.

A secondary objective was to describe the pneumococcal serotype-specific immune response induced by 13vPnC when measured 1 month after the toddler dose in preterm infants compared to term infants (≥ 37 weeks of gestation).

Other objectives were to describe the immune response to 13vPnC when measured 1 month after the infant series and before (at 12 months) and 1 month after (at 13 months) the toddler dose in the 3 preterm subgroups Groups 1A, 1B, and 1C (defined above).

The safety objective was to evaluate the safety profile of 13vPnC when administered at 2, 3, 4, and 12 months of age to preterm and term infants, as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

The study was conducted between 19 October 2010 and 23 February 2012 with the final serology date of 22 June 2012. The study was conducted at 6 sites in Spain and 5 sites in Poland.

6.1.2.1.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria are detailed in Table 4.

Table 4. Inclusion and exclusion criteria for Study 6096A1-4001

Inclusion criteria
Group 1: Preterm Infant 1. Male or female infant born at <37 weeks of gestation 2. Chronological age ≥42 to ≤98 days (approximately 2 months) at the time of enrolment 3. Otherwise healthy preterm infant as determined by medical history, physical examination, and judgment of the investigator 4. Parent/legal guardian was able to complete all relevant study procedures during study participation 5. Available for the entire study period and whose parent/legal guardian could be reached by telephone *Group 2: Term Infant*

1. Male or female infant born at ≥37 weeks of gestation (GA as determined by the investigator)
2. Chronological age ≥42 to ≤98 days (approximately 2 months) at the time of enrolment
3. Healthy infant as determined by medical history, physical examination, and judgment of the investigator
4. Parent/legal guardian was able to complete all relevant study procedures during study participation
5. Available for the entire study period and whose parent/legal guardian could be reached by telephone

Exclusion Criteria

Subjects were ineligible to participate in this study if any of the following criteria were met:

1. Previous vaccination with licensed or investigational pneumococcal vaccine, Hib conjugate vaccine, meningococcal type C conjugate vaccine, or diphtheria, tetanus, pertussis, or poliovirus vaccines.
2. A previous anaphylactic reaction or allergy to any vaccine or vaccine-related component
3. Contraindication to vaccination with any routine paediatric vaccines
4. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection
5. History of culture-proven invasive disease caused by *S.pneumoniae.*
6. Known or suspected immune deficiency or immune suppression
7. Major known congenital malformation or serious chronic disorder
8. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorder
9. Receipt of any other investigational vaccines, drugs, or medical devices from 28 days before inclusion and the first study vaccination until the end of the study. (Note: participation in purely observational studies was acceptable.)
10. Infant who was a direct descendant (eg, child or grandchild) of the study personnel
11. Major illness or conditions that, in the investigator's judgment, substantially increased the risk associated with the subject's participation in, and completion of, the study, or precluded the evaluation of the subject's response

6.1.2.1.3. Study treatments

Subjects received 1 dose (0.5 mL) of 13vPnC at each vaccination visit (visits 1, 2, 3, and 5).

6.1.2.1.4. Efficacy variables and outcomes

The main efficacy outcome was:

· Immune response 1 month after the primary infant series in preterm infants.

Other efficacy outcomes included:

· The immune response one month after the toddler dose given at 12 months to the preterm infants.

6.1.2.1.5. Randomisation and blinding methods

This was an open label study.

6.1.2.1.6. Analysis populations

Immunogenicity analyses were performed for 2 populations. The primary immunogenicity population was the evaluable immunogenicity population, which consisted of eligible subjects who received all the assigned vaccinations, had blood drawn within required time frames, had at least 1 valid and determinate assay result for the proposed analysis, received no prohibited vaccines, and had no major protocol violations. The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate assay result for the proposed analysis. All subjects who received at least 1 dose of 13vPnC were included in the safety population.

6.1.2.1.7. Sample size

Sample size estimation was based on the proportion of subjects achieving IgG concentration ≥0.35 μg/mL in the 13vPnC group from Wyeth Study 6096A1-3007. With 80 evaluable subjects per group, the study allowed estimation of the proportion for each serotype to be within ± 7.6% precision with a 2-sided 95% confidence interval (CI). Assuming a dropout rate of at most 20%, 200 subjects were enrolled to ensure that 160 subjects were evaluable.

6.1.2.1.8. Statistical methods

The immunogenicity analyses are described by summary statistics, that is, GMCs, GMTs, or GMFRs along with 95% CIs by group. For each of the pneumococcal serotypes, the proportion of the subjects achieving IgG concentration ≥0.35 μg/mL measured 1 month after the infant series was calculated along with an exact, 2-sided 95% CI. The difference in the proportion between the 2 groups was computed along with exact, unconditional, 2-sided 95% CI, with the standardized test statistics. For the assay results 1 month after the toddler dose, immunogenicity analyses were performed similarly. In addition, the serotype-specific fold rise in antibody concentration from the pre-toddler dose to 1 month after the toddler dose was derived for each subject and summarized using GMFR along with 2-sided 95% CI. The 2 groups were compared by computing the ratio of the GMFR along with 2-sided 95% CI.

For the 3 subgroups in Group 1 (32≤ GA <37 weeks, 29≤ GA <32 weeks, GA <29 weeks), the above descriptive statistics are summarized by subgroup following the infant series and the toddler dose.

Serum OPA was described by GMT along with 2-sided 95% CI for each serotype. The OPA results following the infant series and the toddler dose were analysed in the same manner as IgG concentration. Proportions of the subjects achieving OPA titres ≥ lower limit of quantitation (LLOQ) for the assay were derived. Proportions were compared between groups in a manner similar to what was done for the IgG proportions.

6.1.2.1.9. Participant flow

Of the 200 total subjects (100 in each group) assigned to receive study vaccine, all (100.0% both groups) were vaccinated at each dose of the infant series. Ninety-nine (99%) preterm infants in Group 1 and 97 (97%) term infants in Group 2 were vaccinated at the toddler dose.

6.1.2.1.10. Major protocol violations/deviations

There were approximately 15 patients who were excluded from analyses, mostly for not having serology drawn during study window (4 were not eligible for study or missed vaccinations).

6.1.2.1.11. Baseline data

In Group 1, 52% of preterm infants were males, and in Group 2, of infants born at term, 45% were males. All subjects (100%) in each group were categorised as White. The mean

chronological age at first vaccination was 1.8 months in preterm infants and 1.5 months in term infants. The mean GA in Group 1 was 30.8 weeks (range 26.0 to 36.3 weeks) and in Group 2 was 39.4 weeks (range 37.0 to 42.0 weeks). Mean weight at birth was 1.6 kg (range 0.7 to 3.2 kg) in Group 1 and 3.3 kg (range 2.0 to 4.5 kg) in Group 2. Distributions by race and sex were not notably different for each dose.

6.1.2.1.12. Results for the primary efficacy outcome

For assessment of immunogenicity, blood samples (approximately 15 mL) were collected from all subjects at 3 time points, that is, 1 month after the third dose (at approximately 5 months of age), just before the toddler dose (at approximately 12 months of age), and 1 month after the toddler dose (at approximately 13 months of age). This study is ongoing and 2 additional blood samples will be obtained at 12 months (approximately 24 months of age) and 24 months (approximately 36 months of age) after the toddler dose. Serum concentrations of serotype-specific IgG antibodies were measured by the enzyme linked immunosorbent assay (ELISA), and serotype-specific OPA titres were measured by the OPA assay for the 13 pneumococcal serotypes in each blood sample.

The evaluable immunogenicity population, the primary analysis population, comprised a total of 99 (99%) subjects in Group 1 and 98 (98%) subjects in Group 2 at the infant series. At the toddler dose, 88 subjects in each group (88%) were included in the evaluable immunogenicity population. The primary immunogenicity endpoint of Study 6096A1-4001 was the percentage of subjects in each group achieving a pre specified IgG antibody concentration of ≥0.35 µg/mL at 1 month after the infant series for each serotype. The same endpoint (that is, proportion with IgG concentrations ≥0.35 µg/mL) was assessed at 1 month after the toddler dose.

IgG results

Proportion of Subjects Achieving IgG Concentrations ≥0.35 µg/mL:

The proportions of subjects (that is, responders) achieving serotype-specific IgG antibody concentrations ≥0.35 µg/mL were generally similar in preterm infants (Group 1) and in term infants (Group 2) for 10 of 13 serotypes. For serotypes 6B, 5, and 6A the proportion of responders in Group 1 was statistically significantly lower (upper limit of 95% CI <0) than in Group 2. The proportion of responders was not notably different in each of the age subgroups, that is, Group 1A - birth at ≥32 weeks and <37 weeks (that is, 32≥ GA <37); Group 1B - birth at ≥29 weeks and <32 weeks (that is, 29≥ GA <32); Group 1C - birth at<29 weeks (that is, GA <29), although the highest proportions were consistently observed in Group 1A.

6.1.2.1.13. Results for other efficacy outcomes

IgG GMCs and GMFRs

IgG GMCs were measured 1 month after the infant series, on the day of vaccination before toddler dose administration, and 1 month after the toddler dose. At most time points and for the majority of serotypes, point estimates for IgG GMCs were higher in Group 2 than in Group 1. IgG GMCs were statistically significantly lower (an upper limit of the 95% CI for the ratio [Group 1/Group 2] of <1) in Group 1 for 7 of 13 serotypes after the infant series (6B, 9V, 19F, 23F, 5, 6A, 7F) and after the toddler dose (4, 6B, 9V, 19F, 23F, 5, 6A).

In both groups at the pre-toddler dose time point IgG GMCs were lower than GMCs at 1 month after the infant series, but for most serotypes GMCs remained higher in Group 2 than in Group 1. At 1 month after the toddler dose GMCs for 12 of 13 serotypes (all but serotype 3) rose to higher concentrations than observed at 1 month after the infant series in both groups. In the preterm subgroups IgG GMCs were higher in Group 1A than in Groups 1B or 1C after the infant series and after the toddler dose (and for most serotypes before the toddler dose).

IgG GMCs at 1 month after the toddler dose were higher than at 1 month after the infant series for all serotypes in Groups 1A and 1B (except for serotype 3) and for 10 of 13 serotypes in Group 1C (except for serotypes 4, 18C, and 3).

GMFRs (post toddler GMC dose/pre-toddler GMC) were calculated in subjects with data for both pre-vaccination and post-vaccination time points. In the preterm and term groups, IgG GMCs for all serotypes were notably higher after the toddler dose compared with GMCs before the toddler dose. GMFRs ranged from 3.47 to 10.82 across serotypes in the preterm group and from 3.46 to 12.31 in those born at term. In each preterm subgroup, GMCs were higher at 1 month after the toddler dose than before the toddler dose for all serotypes and, GMFRs were generally highest in Group 1A and lowest in Group 1C.

Proportion achieving OPA titers ≥LLOQ

The proportion of subjects achieving OPA antibody titres ≥LLOQ at 1 month after the infant series was >90% in both groups for 10 of 13 serotypes (all but serotypes 1, 5, and 9V). There were no statistical differences between groups for 12 of 13 serotypes (all but serotype 5: 67.5% preterm, 83.5% term). The proportion of responders in Group 1A was similar to, or higher than, that of the other 2 subgroups.

After the toddler dose, >95% of subjects in Group 1 and Group 2 achieved an OPA antibody titer ≥LLOQ for all serotypes except serotypes 1 (both groups) and 19F (preterm).

OPA GMTs and GMFRs

One month after the infant series, OPA GMTs were comparable in Group 1 and Group 2 for 11 of 13 serotypes (all but serotypes 5 and 18C). The GMT in Group 1 was statistically lower for serotype 5 and higher for serotype 18C. In both groups at the pre-toddler dose time point OPA GMTs were lower than GMTs at 1 month after the infant series, and for most serotypes GMTs were somewhat higher in Group 2 than in Group 1 at this time point. At 1 month after the toddler dose, OPA GMTs rose to higher titres than observed at 1 month after the infant series for 9 of 13 serotypes (all but 4, 14, 18C, 19F) in the Group 1 and for all serotypes in Group 2.

After the toddler dose, OPA GMTs were statistically significantly lower for 6 of 13 serotypes (4, 18C, 1, 5, 6A, 19A) in Group 1 than in Group 2. As with IgG GMCs, OPA GMTs for serotype 3 were similar at each time point in both groups. In the preterm subgroups OPA GMTs for most serotypes were higher in Group 1A than in Groups 1B or 1C after the infant series and before and after the toddler dose. In each subgroup, OPA GMTs after the toddler dose were higher than after the infant series for the majority of serotypes, also for Group 1A (12 of 13 serotypes) and Group 1B (11 of 13 serotypes) than for Group 1C (8 of 13 serotypes).

In Group 1 and Group 2, OPA GMTs for all serotypes were higher after the toddler dose compared with GMTs before the toddler dose. GMFRs (post toddler GMT dose/pre-toddler GMT) ranged from 5.2 to 162.0 across serotypes in Group 1 and from 4.7 to 342.2 in Group 2. The same pattern of response was observed in the preterm subgroups. GMFRs (post toddler GMT dose/pre-toddler GMT) were generally lowest in Group 1C for most serotypes. When GMFRs (post toddler GMC/pre-toddler GMC) in Group 1 and Group 2 were compared, no notable differences were observed for 11 of 13 serotypes. GMFRs were statistically significantly lower in the Group 1 than in Group 2 for serotypes 19F and 1.

Comparison of results in subpopulations: Subjects with risk conditions

In Study 6115A1-004, Cohort 3, the proportion of subjects with risk conditions for pneumococcal disease was generally low with percentages as follows: asthma, 5.2%; cardiac disorders 3.3%; and diabetes mellitus, 2.9%. Because of these low percentages, the responses for risk and non-risk subjects were not compared in Cohort 3.

6.1.3. Other efficacy studies – data from these to be included in PI

6.1.3.1. Study 6096A1-3014 in children and adolescents with sickle cell disease

6.1.3.1.1. Study design, objectives, locations and dates

Study 6096A1-3014 was a Phase III, multicentre, open-label, single-arm study in children with sickle cell disease (SCD) ≥6 to <18 years of age who had been previously immunized with at least 1 dose of 23vPS. The study assessed the immunogenicity and safety of 2 doses of 13vPnC, given approximately 6 months apart. The study was conducted globally, with sites in the United States, the United Kingdom, Italy, Lebanon, Egypt, Saudi Arabia, and France between November 2009 and 05 March 2012. The last 1 month post-vaccination 2 blood draw completed 31 July 2012.

The primary objective of this study was to evaluate the immune response 1 month after 2 doses of 13vPnC, spaced 6 months apart, compared to 1 month after 1 dose of 13vPnC as measured by fold rise in serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) in children with SCD who had previously been immunized with at least 1 dose of 23vPS.

6.1.3.1.2. Inclusion and exclusion criteria

The inclusion criteria required that all subjects be between the ages of ≥6 to <18 years, have a diagnosis of SCD by haemoglobin (Hb) electrophoresis or polymerase chain reaction (PCR) (HbSS, HbSC, HbSD, HbSE, HbSβ-thal); and documentation to show vaccination with 23vPS at least 6 months before enrolment. Subjects with a history of hematopoietic stem cell transplantation were excluded from the study. These are detailed in Table 6.

Table 6. Inclusion and Exclusion criteria for Study 6096A1-3014

Inclusion criteria:
1. Male or female subject aged ≥6 and <18 years.
2. Diagnosis of SCD by haemoglobin (Hb) electrophoresis or polymerase chain reaction (PCR); (HbSS, HbSC, HbSD, HbSE, and HbSβ-thal).
3. Documentation to show 23vPS vaccination at least 6 months prior to enrolment.
4. Available for entire study period and whose parent/legal guardian could be reached by telephone.
5. Subject and/or parent/legal guardian were able to complete all relevant study procedures during study participation.
6. Negative urine pregnancy test for female subjects who were post menarche.
7. All female and male subjects who were biologically capable of having children must have agreed to abstinence or commit to the use of a reliable method of birth control for the duration of the study and for 3 months after the last vaccination.

Exclusion Criteria:

1. History of culture-proven invasive disease caused by *S pneumoniae* within the last year.
2. Subject had/has a major illness or condition that, in the investigator's judgment, substantially increased the risk associated with the subject's participation in, and completion of the study.
3. Subject had a major illness or condition that, in the investigator's judgment, precluded the evaluation of the subject's response to vaccination.
4. History of hematopoietic stem cell transplantation.
5. Previous vaccination with pneumococcal conjugate vaccine.
6. Had a dose of 23vPS recommended between enrolment and the blood draw at visit 6.
7. Previous anaphylactic reaction to any vaccine or vaccine-related component.
8. Contraindication to vaccination with pneumococcal conjugate vaccine.
9. Bleeding diathesis or condition associated with prolonged bleeding time that would have contraindicated intramuscular injection.
10. Receipt of immunoglobulin infusion or injection during the 42 days preceding enrolment.
11. Known or suspected immune deficiency or suppression.
12. Pregnant or breastfeeding female.
13. Participation in another investigational trial from 28 days before enrolment until the end of the study. (Note: participation in purely observational studies was acceptable).
14. Subject was a direct descendant (child or grandchild) of a member of site study personnel or was study personnel.
15. Active hepatitis C infection requiring interferon or ribavirin treatment.

6.1.3.1.3. Study treatments

In this study, subjects received 1 dose of 13vPnC at Visit 1, followed by a second Dose 182 to 224 days later at Visit 3.

6.1.3.1.4. Efficacy variables and outcomes

The primary efficacy outcome was to evaluate the immune response 1 month after 2 doses of 13vPnC, spaced 6 months apart, compared to 1 month after 1 dose of 13vPnC as measured by fold rise in serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) in children with SCD who had previously been immunized with at least 1 dose of 23vPS.

The safety objective was to evaluate the acceptability of the safety profile of 13vPnC, as measured by the incidence rates of local reactions, systemic events, and AEs.

6.1.3.1.5. Randomisation and blinding methods

This was an open-label study.

6.1.3.1.6. Analysis populations

Of the 158 subjects assigned to receive study vaccine, all were vaccinated at Dose 1 and 146 subjects (92.4%) were vaccinated at Dose 2. Of the 158 subjects vaccinated at Dose 1, 146 subjects had previously received 1 dose of 23vPS and 12 subjects had received 2 or more doses of 23vPS.

6.1.3.1.7. Sample size

This study was to enrol about 150 subjects so that at least 80 subjects would be included in the evaluable population. The precision of confidence intervals (CIs) for the primary endpoint, geometric mean fold rise (GMFR) of Dose 2:1, based upon an evaluable sample size of 80 subjects, utilized a 2-sided, type I error of 0.05. Based upon the highest of these estimates of variation for the 7 common Prevenar serotypes and the 6 additional non-Prevenar serotypes, the planned sample size would provide 21% - 37% precision. That is, 95% confidence bounds of the GMFR were expected to fall within 37% of the GMFR.

Precision calculations were not performed for secondary endpoints.

6.1.3.1.8. Statistical methods

Data from all sites were pooled, analysed using standard descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum and maximum. Summary statistics for categorical variables are: n, percentage, and total (N).

6.1.3.1.9. Participant flow

All 158 enrolled subjects received the first dose of 13vPnC and 146 subjects received the second dose of 13vPnC, 12 subjects (7.6%) were withdrawn from the study. Of the 12 subjects (7.6%) who were withdrawn from the study, 5 were lost-to-follow-up, 2 withdrew at the request of a parent or guardian, 2 withdrew upon subject request, 1 withdrew due to an AE (injection site pain and systemic events).

6.1.3.1.10. Major protocol violations/deviations

One subject had a protocol violation (Subject had previous 23vPS vaccine given within 6 months before enrolment), and 1 failed to return.

6.1.3.1.11. Baseline data

Of all vaccinated subjects, slightly more subjects were male (51.9%) and the majority were categorised as Black or African American (42.4%) or White (35.4%); 22.2% were categorised as Other. Mean age at vaccination was 13.3 years (age range 6.0 years to 17.9 years).

6.1.3.1.12. Results for the primary efficacy outcome

For immunogenicity assessment of blood samples were collected from all subjects immediately before and approximately 1 month (28 to 42 days) after each 13vPnC dose. An additional blood sample will be collected approximately 1 year (365 to 425 days) after the second dose. Serum concentrations of serotype-specific IgG antibodies were measured by the enzyme-linked immunosorbent assay (ELISA), and serotype-specific OPA titres were measured by the OPA assay for the 13 pneumococcal serotypes.

The primary immunogenicity endpoint was the GMFR in IgG GMC from 1 month after Dose 1 to 1 month after Dose 2 (GMC Dose 2/GMC Dose 1) along with the 2-sided 95% CI for each serotype. The immunogenicity analysis includes results in subjects with >1 prior dose of 23vPS and in the subset of subjects who had received only 1 previous dose of 23vPS. In the other subset of subjects who received 2 or more previous doses of 23vPS, immunogenicity results were not summarized because there were too few subjects (12 subjects). The evaluable immunogenicity population was the primary analysis population and comprised a total of 138

(87.3%) subjects at vaccination 1. Data from the evaluable immunogenicity population are provided in this variation.

Comparisons between dose 1 and dose 2

The geometric mean fold rise (GMFR) in the IgG GMC from 1 month after Dose 1 to 1 month after Dose 2 (that is, GMC post-Dose 2/GMC post-Dose 1) was assessed for each serotype. IgG GMCs were higher after Dose 1 than after Dose 2 for all serotypes, except for 19F. GMFRs were less than 1 for 12 of 13 serotypes and ranged from 0.70 to 1.05. For 9 of 13 serotypes (all but 6B, 19F, 23F, and 6A) IgG GMCs were statistically significantly lower after Dose 2 than after Dose 1 (that is, upper limit for 95% CI for the GMFR was <1). Comparable results were observed in the subset of subjects who received only 1 previous 23vPS dose.

Comparison of GMFRs

When GMFRs (post-dose/predose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that GMFRs were statistically significantly lower after Dose 2 than after Dose 1 for all serotypes. This result was also observed in the subset of subjects pre-immunised with only 1 dose of 23vPS.

6.1.3.1.13. Results for other efficacy outcomes

OPA GMTs and GMFRs

OPA GMTs after Dose 1 and after Dose 2 were notably higher than the OPA GMTs before each respective 13vPnC dose. GMFRs for Dose 1 (post-Dose 1/preDose 1) ranged from 3.5 to 40.3. GMFRs for Dose 2 (post-Dose 2/preDose 2) ranged from 1.3 to 3.4. OPA GMTs before and after Dose 1 and Dose 2 were not notably different in the subgroup of subjects pre-immunised with 1 23vPS dose.

OPA GMTs rose after each vaccination from pre-vaccination titres. Although OPA GMTs had declined at pre-vaccination 2 from titres achieved after the first vaccination, GMTs remained higher than at baseline (before vaccination 1). In contrast to IgG GMCs, after the second dose of 13vPnC, OPA GMTs were similar to (5 serotypes) or higher (8 serotypes) than titres after Dose 1.

Comparisons between dose 1 and dose 2

The geometric mean fold rise (GMFR) in the OPA GMTs from 1 month after Dose 1 to 1 month after Dose 2 were similar or higher after Dose 2 compared with GMTs after Dose 1. GMFRs (that is, GMT post-Dose 2/GMT post-Dose 1) ranged from 0.9 to 1.4. For 4 of 13 serotypes the lower limit of the 95% CI for the GMFR was >1, indicating that titres for these serotypes (1, 7F, 9V, 23F) were statistically significantly higher after Dose 2 than after Dose 1. Comparable results were observed in the subset of subjects with 1 previous 23vPS dose.

Comparison of GMFRs

When GMFRs (GMT post-dose/ GMT predose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that the fold rise from before vaccination to after vaccination was statistically significantly lower for Dose 2 than for Dose 1 for all serotypes. This result was also observed in the subset of subjects pre-immunised with only 1 dose of 23vPS.

6.1.3.2. Study 6115A1-3017 in adults with HIV infection

6.1.3.2.1. Study design, objectives, locations and dates

This was a Phase III, open-label, single-arm trial in which HIV-infected subjects previously immunized with the 23vPS vaccine received 3 doses of 13vPnC given at 6-month intervals.

Subjects were stratified into 2 groups:

- Previously vaccinated with a single dose of 23vPS
- Previously vaccinated with 2 or more doses of 23vPS

The primary objective of this study was to evaluate the immune response 1 month after 3 doses of 13vPnC compared with 1 month after 2 doses of 13vPnC (doses spaced 6 months apart), as determined by the fold rise (Dose 3 GMC/Dose 2 GMC) in serotype-specific IgG GMCs in HIV-infected subjects previously immunized with at least 1 dose of 23vPS.

The safety objective was to evaluate the acceptability of the safety profile in this population as measured by incidence rates of local reactions, systemic events, and adverse events. This SCS provides the safety data for Study 6115A1-3017.

Approximately 330 subjects (aged 18 years or older) were to participate in the study, 165 subjects who had previously received 1 dose of 23vPS and 165 subjects who had previously received 2 or more doses of 23vPS. Subjects withdrawn from the study were not replaced, regardless of the reason for withdrawal. Subjects participated in the study for approximately 18 months, consisting of Visit 1 through Visit 7. A follow-up telephone call was made approximately 6 months after the last dose of the study vaccine.

6.1.3.2.2. Inclusion and exclusion criteria

These are detailed in Table 7.

Table 7. Inclusion and exclusion criteria for Study 6115A1-3017.

Inclusion criteria
1. Male or female subjects aged 18 years or older at time of enrolment.
2. All female and male subjects biologically capable of having children who agreed and committed to the use of a reliable method of birth control from the signing of the ICF until 3 months after the last dose of investigational product.
3. Documented vaccination with 1 or more doses of 23vPS at least 6 months before study enrolment.
4. CD4+ T-cell count ≥200 cells/μL, obtained on the most recent 2 occasions within 6 months before the first investigational product vaccination.
5. HIV-infected subjects with a viral load of <50,000 copies/mL, obtained on the most recent 2 occasions within 6 months before the first investigational product vaccination.
6. Has received a stable dose of HAART for at least 6 weeks prior to the first investigational product vaccination, or not currently receiving antiretroviral therapy.
7. Was expected to be available for the entire study period (approximately 18 months) and could be contacted by telephone.
8. Was able to complete an electronic diary (e-diary) and complete all relevant study procedures during study participation.
9. Was deemed to be eligible for the study on the basis of medical history, physical examination, and clinical judgment. (Note: Subjects with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease 6 weeks before investigational product vaccination, were eligible).
Exclusion Criteria
1. Active AIDS-related illness, including opportunistic infections or malignancy.
2. Evidence of current illicit substance and/or alcohol abuse that in the investigator's

opinion, precluded the subject from participating in the study or interfered with the evaluation of the study objectives.

3. Receipt of any licensed or experimental PnC prior to enrolment.
4. Contraindication to vaccination with PnC.
5. Previous anaphylactic reaction to any vaccine or vaccine-related component.
6. History of culture-proven invasive disease caused by S. pneumoniae within the last year.
7. Current anticoagulant therapy or a history of bleeding diathesis or any condition associated with prolonged bleeding time that contraindicated intramuscular injection. (Note: Use of antiplatelet drugs, such as aspirin and clopidogrel, was permitted.)
8. Pregnant or breastfeeding women, as defined by history or positive human chorionic gonadotropin (hCG) urine test. All women of childbearing potential had a urine pregnancy test.
9. History of active hepatitis with elevation in pre-treatment aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >5 times the upper limit of normal within the last 6 months.
10. Serious chronic disorder or any other disorder that, in the investigator's opinion, precluded the subject from participating in the study.
11. History of splenectomy.
12. Receipt of any blood products, including immunoglobulin, within 42 days before investigational product vaccination until the last blood draw for the study (approximately 13 months after the first investigational product vaccination).
13. Evidence of dementia or other severe cognitive impairment.
14. Subject who was, in the opinion of the investigator, unable to receive a vaccination in the deltoid muscle of either arm because of insufficient muscle mass.
15. Participation in another study using investigational product from 28 days before study enrolment until the blood draw at Visit 6.
16. Residence in a nursing home, long-term care facility, or other institution or requirement of semiskilled nursing care.
17. Subject who was a direct relative (child, grandchild, parent, or grandparent) of study personnel, or who was the study personnel.

6.1.3.2.3. Study treatments

A dose of 0.5 mL of 13vPnC was administered intramuscularly to all subjects at Visits 1, 3, and 5, each 6 months apart.

6.1.3.2.4. Efficacy variables and outcomes

The primary efficacy outcome was to evaluate the immune response 1 month after 3 doses of 13vPnC, given 6 months apart, compared to response 1 month after 2 doses of 13vPnC, as measured by the fold rise in serotype-specific IgG GMCs in HIV-infected subjects previously vaccinated with at least 1 dose of 23vPS. Also, to evaluate the acceptability of the safety profile of 13vPnC, as measured by the incidence rates of local reactions, systemic events, and adverse events.

Secondary outcomes

· To evaluate the immune response 1 month after 3 doses of 13vPnC, given 6 months apart, compared to response 1 month after 2 doses of 13vPnC, as measured by the serotype

specific IgG GMCs in HIV-infected subjects previously vaccinated with at least 1 dose of 23vPS.

- To evaluate the immune response 1 month after 3 doses of 13vPnC, given 6 months apart, compared to response 1 month after 2 doses of 13vPnC, as measured by serotype-specific OPA GMTs and the fold rise in OPA GMTs in HIV-infected subjects previously vaccinated with at least 1 dose of 23vPS.

6.1.3.2.5. Randomisation and blinding methods

This was an open-label, single-arm study requiring no randomization.

6.1.3.2.6. Analysis populations

Two (2) analysis populations were defined for the immunogenicity analyses:

- Evaluable immunogenicity, and
- All-available immunogenicity

The all-available immunogenicity population included subjects who had at least 1 valid and determinate assay result related to the proposed analysis.

The evaluable immunogenicity population was considered the primary analysis population and included subjects who:

1. Were eligible for the study.
2. Were ≥18 years of age on the day of first vaccination.
3. Received at least 2 doses of 13vPnC in the sequence assigned.
4. Had pre-vaccination blood drawn on the same day as the day of vaccination or 15 days prior to Day 1.
5. Had valid and determinate assay result for at least 1 serotype with blood draw occurring within 27 to 56 days after third vaccination of 13vPnC or after second vaccination of 13vPnC.
6. Received no prohibited vaccines.
7. Had no other major protocol violations within 42 days before investigational product vaccination until the last blood draw for the study.

If at least 1 of the criteria in 4 or 5 was satisfied and all other criteria were met, the subject was included in the evaluable immunogenicity population. However, the assay results that did not meet the criteria in 4 and 5 were excluded from analysis.

6.1.3.2.7. Sample size

A sample of 200 evaluable subjects in the study provided precision of at least 0.237 on the 2-sided 95% CI for IgG mean fold rise among the 13 serotypes. Allowing for a rate of approximately 39% for drop-outs and exclusions from the evaluable population due to protocol violations during the initial 13 months of the study (Visit 1 through Visit 6), a total of 330 enrolled subjects provided at least 200 evaluable subjects in the study.

6.1.3.2.8. Statistical methods

An estimation approach was used to assess primary, secondary, and exploratory endpoints in this study. The sample size for this study was based on the precision of the 2-sided 95% confidence interval (CI) for the IgG mean fold rise. The study was stratified by number of previous vaccinations of 23vPS such that approximately 50% each of subjects enrolled was previously vaccinated with a single dose of 23vPS or previously vaccinated with 2 doses or

more of 23vPS. The precision of the 2-sided 95% CI for the IgG mean fold rise in each of these groups was at least 0.335.

6.1.3.2.9. Participant flow

Of the 331 subjects (aged 18 years or older) assigned to receive study vaccine, 329 subjects (99.4%) were vaccinated at Dose 1; 300 subjects (90.6%) were vaccinated at Dose 2, and 279 (84.3%) were vaccinated at Dose 3. Of all subjects vaccinated at Dose 1, 160 subjects had previously received 1 dose of 23vPS and 169 subjects had received 2 or more doses of 23vPS.

6.1.3.2.10. Major protocol violations/deviations

One of the protocol deviations was major and led to exclusion of all subjects at one site from evaluable immunogenicity analyses. Thirty-eight (38) subjects at a site received at least 1 vaccination of 13vPnC that was stored below the recommended storage range of 2 to 8^0C, at a range of -1 to 1^0C. These subjects were excluded from the immunogenicity analysis.

6.1.3.2.11. Baseline data

The majority of subjects were male (79.9%) and were categorised as White, 66.6%; 25.2% were Black or African American; 0.3% were Asian; 1.2% were American Indian or Alaska Native; and 6.7% were categorised as Other. Mean age at vaccination was 47.3 years (age range 19 years to 73 years). Distributions by race, sex and age were not notably different between the 2 groups based on 23vPS pre-immunisation status (that is, 1 previous dose versus 2 or more previous doses of 23vPS). Overall, the subjects in the 2 subgroups (1 previous dose of 23vPS and ≥2 previous doses of 23vPS) were similar with respect to HIV status at baseline. The majority of subjects contracted HIV through sexual contact (87.5%) and were receiving HAART at baseline (95.4%). The mean length of time since the HIV diagnosis was 13.0 years. The mean CD4+ cell counts at the first and second baseline assessments were 599.0/mm^3 and 604.5/mm^3, respectively. The mean viral load at the first and second baseline assessments was 463.0 copies/mL and 630.3 copies/mL, respectively.

6.1.3.2.12. Results for the primary efficacy outcome

The evaluable immunogenicity population was the primary analysis population and comprised a total of 138 (87.3%) subjects at vaccination 1.

IgG GMCs and GMFRs

IgG GMCs before and after Dose 1 and before and after Dose 2 and the corresponding GMFRs (post-dose/preDose) are presented for subjects in the evaluable immunogenicity population in the SCE, 2.7.3, Table 10 and 11, respectively. IgG GMCs 1 month after Dose 1 and 1 month after Dose 2 were notably higher than the IgGs GMCs before each respective 13vPnC dose.

GMFRs (post-dose/preDose) for Dose 1 (1 month post-Dose 1/preDose 1) ranged from 1.74 to 6.91.GMFRs for Dose 2 (1 month post-Dose 2/preDose 2) ranged from 1.24 to 2.08. Results for Dose 1 and Dose 2 were not notably different in the subgroup of subjects pre-immunised with only 1 prior 23vPS dose. IgG GMCs had declined at pre-vaccination 2 from levels achieved after the first vaccination, GMCs but remained higher than baseline levels (before vaccination 1). IgG GMCs rose from pre-vaccination levels after each dose; however GMCs after Dose 2 were similar to or slightly lower than the GMCs after Dose 1 for all serotypes.

Comparisons between dose 1 and dose 2

The geometric mean fold rise (GMFR) in the IgG GMC from 1 month after Dose 1 to 1 month after Dose 2 (ie, GMC post-Dose 2/GMC post-Dose 1) was assessed for each serotype. IgG GMCs were higher after Dose 1 than after Dose 2 for all serotypes, except for 19F. GMFRs were less than 1 for 12 of 13 serotypes and ranged from 0.70 to 1.05. For 9 of 13 serotypes (all but 6B, 19F, 23F, and 6A) IgG GMCs were statistically significantly lower after Dose 2 than after Dose 1 (ie, upper limit for 95% CI for the GMFR was <1). Comparable results were observed in the subset of subjects who received only 1 previous 23vPS dose.

Comparison of GMFRs

When GMFRs (post-Dose/preDose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that GMFRs were statistically significantly lower after Dose 2 than after Dose 1 for all serotypes. This result was similar in the subset of subjects pre-immunised with only 1 dose of 23vPS.

OPA GMTs and GMFRs

OPA GMTs after Dose 1 and after Dose 2 were notably higher than the OPA GMTs before each respective 13vPnC dose. GMFRs for Dose 1 (post-Dose 1/preDose 1) ranged from 3.5 to 40.3. GMFRs for Dose 2 (post-Dose 2/preDose 2) ranged from 1.3 to 3.4. OPA GMTs before and after Dose 1 and Dose 2 were not notably different in the subgroup of subjects pre-immunised with 1 23vPS dose. For each serotype, OPA GMTs rose after each vaccination from pre-vaccination titres. Although OPA GMTs had declined at pre-vaccination 2 from titres achieved after the first vaccination, GMTs remained higher than at baseline. In contrast to IgG GMCs, after the second dose of 13vPnC, OPA GMTs were similar to (5 serotypes) or higher (8 serotypes) than titres after Dose 1.

6.1.3.2.13. Results for other efficacy outcomes

Comparisons between dose 1 and dose 2

The geometric mean fold rise (GMFR) in the OPA GMTs from 1 month after Dose 1 to 1 month after Dose 2 was assessed for each serotype. OPA GMTs were similar or higher after Dose 2 compared with GMTs after Dose 1. GMFRs (that is, GMT post-Dose 2/GMT post-Dose 1) ranged from 0.9 to 1.4. For 4 of 13 serotypes the lower limit of the 95% CI for the GMFR was >1, indicating that titres for these serotypes (1, 7F, 9V, 23F) were statistically significantly higher after Dose 2 than after Dose 1. Similar results were observed in the subset of subjects with 1 previous 23vPS dose.

Comparison of GMFRs

When GMFRs (GMT post-dose/ GMT preDose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that the fold rise from before vaccination to after vaccination was statistically significantly lower for Dose 2 than for Dose 1 for all serotypes. This result was also seen in the subset of subjects pre-immunised with only 1 dose of 23vPS.

6.1.4. Analyses performed across trials (pooled analyses and meta-analyses)

Nil.

6.2. Evaluator's conclusions on clinical efficacy

6.2.1. For active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae* in adults (aged 18 years and older).

In Study 6115A1-004 Cohort 3 the primary immunological comparisons were the serotype-specific OPA GMTs for the 13 pneumococcal serotypes contained in 13vPnC, when measured 1 month after study vaccine administration in subjects 18 to 49 years of age in Cohort 3 relative to those in subjects 60 to 64 years of age in Cohort 1. The results demonstrated that all 13 serotypes elicited immunologic responses in Cohort 3 that were non-inferior to those in Cohort 1 and were statistically significantly higher in Cohort 3 for all serotypes except serotype 3.

In addition the immune response in each of the 3 age subgroups of Cohort 3 was statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3, which elicited a non-inferior response. Among the age subgroups, OPA GMTs were

generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.

The serotype-specific geometric mean fold rise (post-vaccination OPA GMT/pre-vaccination OPA GMT) was generally similar or higher in the 18 to 49 year old group relative to that of the 60 to 64 year old group, at 1 month and 1 year after vaccination.

After vaccination, the proportion of subjects achieving a serotype-specific OPA titer ≥LLOQ in Cohort 3 was non-inferior to that of Cohort 1 for all 13 serotypes and was statistically significantly greater for all serotypes, except for serotype 3.

A high antibody response in Cohort 3 was still present 1 year after vaccination. Except for serotype 3, the OPA GMTs were higher for Cohort 3 than for Cohort 1 one year after vaccination and were still well above baseline (pre-vaccination) levels.

6.2.2. For use in preterm infants

Most preterm subjects (Group 1) and those born at term (Group 2) achieved IgG antibody concentrations ≥0.35 μg/mL 1 month after the infant series (>85%) and 1 month after the toddler dose (>97%) for at least 10 serotypes. After the infant series, IgG concentrations elicited by 13vPnC were somewhat lower in preterm infants compared with term infants, although OPA GMTs were similar in the 2 groups indicating that the immune response is likely to be adequate to provide protection against disease. While post-toddler dose responses varied by serotype and with gestation age, there is good evidence of adequate priming among preterm infants given 13vPnC in a 2, 3, and 4 month schedule when compared with that of infants born at term.

6.2.3. In children and adolescents With SCD

Children and adolescents between 6 and 18 years of age with SCD who were previously immunized with 23vPS had significant increases in both IgG binding and functional antibody (OPA) after both 1 dose and 2 doses of 13vPnC. The addition of a second dose of 13vPnC given 6 months after the first dose resulted in IgG GMCs that were similar to or lower than those seen after Dose 1. Serotype-specific OPA responses after the second 13vPnC dose were comparable or higher than those after the first dose, suggesting a potential positive impact on maturation of functional antibody response for at least some serotypes after the second dose but the differences were modest and the clinical significance is uncertain. Overall these data suggest that a 2-dose regimen of 13vPnC given 6 months apart does not enhance pneumococcal immune responses beyond those of a single dose of 13vPnC.

6.2.4. For adults with HIV-infection

HIV-infected subjects previously immunized with 23vPS responded to 13vPnC at each of 3 vaccine doses and immune responses remained above initial baseline levels (before Dose 1) throughout the study. The immune response after vaccine Dose 3 was either stable or increased relative to the response after Dose 2 or Dose 1. However, the clinical significance of the increased immune response (statistically significant for most serotypes) after Dose 3 is unknown. The number of previous 23vPS doses had no impact on the immune response.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

- Study 6115A1-004 – all cohorts.

7.1.1. Pivotal efficacy studies

In the pivotal efficacy Study 6115A1-004, the following safety data was evaluated by the following methods:

- AEs of particular interest were assessed by electronic diaries (e-diary) on Days 1-14 after vaccination. Specific local reactions included pain, redness, and swelling at the injection site, and limitation of arm movement. Systemic events of interest included fever, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalised muscle pain, aggravated generalised muscle pain, new generalised joint pain, and aggravated generalised joint pain.
- In addition, AEs were to be reported and recorded in the case report form from the signing of the informed consent form (ICF) through day 29 (Visit 2). At the 6 month follow-up contact, any newly diagnosed chronic medical conditions and any serious adverse event (SAE) that occurred since the last study visit were to be reported and recorded.
- Investigators collected information regarding unsolicited AEs based on observations made during study visits as well as information provided by the subject in response to nonspecific questioning. Investigators were to characterise each AE as related or not related to study vaccine and categorise the event's severity as mild, moderate, severe, or life-threatening. Safety data were evaluated for all subjects who received at least 1 dose of 13vPnC (safety population).

7.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.2. Patient exposure

The data supporting age expansion are from 899 subjects vaccinated in Study 6115A1-004. The most relevant information for this age extension submission is for Cohort 3 (ages ≥18 years to 49 years [up to the 50th birthday) of a single trial, Study 6115A1-004.

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

7.3.1.1. Pivotal studies

The percentage of subjects reporting any AEs within approximately 1 month after vaccination was similar in Cohort 3 (14.3%), in Cohort 2 (11.4%) and in the 13vPnC group in Cohort 1 (17.0%). Most AEs were the types of diseases and conditions commonly observed among adults in these age groups and were similar across the three cohorts. In Cohort 3, the most frequently occurring types of AEs were Infections and infestations (4.4% of subjects) and gastrointestinal disorders (2.6%). The most frequently reported individual AEs in Cohort 3 were nausea (12 subjects, 1.3%), upper respiratory tract infection (11 subjects, 1.2%), nasopharyngitis (7 subjects, 0.8%), and diarrhoea (6 subjects, 0.7%). In Cohort 2, the most frequently occurring types of AEs were Infections and infestations (4.2% of subjects), General disorders and Administration site conditions (2.5%), and Musculoskeletal and connective tissue disorders (2.0%). Sinusitis was reported for 4 subjects (1.0%) and arthralgia was reported for 3 subjects (0.7%). All other AEs were reported for ≤2 subjects each. In Cohort 1, the most frequently occurring types of AEs were Infections and infestations (7.7% of subjects) and Musculoskeletal and connective tissue disorders (4.1%). The most frequently reported individual AEs in Cohort 1 were nasopharyngitis (7 subjects, 1.7%), sinusitis (6 subjects, 1.4%); myalgia (5 subjects, 1.2%); and upper respiratory tract infection, cough, and gastroenteritis (each in 4 subjects, 1.0%). The percentage of subjects reporting any AEs within approximately 1 month after vaccination was similar in the 18 to 29 year old (13.0%), the 30 to 39 year old (14.4%), and the

40 to 49 year old (15.6%) age subgroups in Cohort 3 (Table 8). The percentages of subjects reporting individual AEs were also similar among the age subgroups.

Table 8. Subjects Reporting Local Reactions Within 14 Days After Vaccination With 13vPnC by Age Groups, Ages 18-29 Years, 30-39 Years, and 40-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Age Group (Years)											
	18-29 Years Old				30-39 Years Old				40-49 Years Old			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Redness[d]												
Any	62	31	50.0	(37.0, 63.0)	104	29	27.9	(19.5, 37.5)	100	21	21.0	(13.5, 30.3)
Mild	60	29	48.3	(35.2, 61.6)	101	24	23.8	(15.9, 33.3)	97	15	15.5	(8.9, 24.2)
Moderate	41	5	12.2	(4.1, 26.2)	90	12	13.3	(7.1, 22.1)	96	10	10.4	(5.1, 18.3)
Severe	38	1	2.6	(0.1, 13.8)	82	3	3.7	(0.8, 10.3)	91	2	2.2	(0.3, 7.7)
Swelling[d]												
Any	73	41	56.2	(44.1, 67.8)	118	48	40.7	(31.7, 50.1)	111	30	27.0	(19.0, 36.3)
Mild	68	36	52.9	(40.4, 65.2)	116	46	39.7	(30.7, 49.2)	109	27	24.8	(17.0, 34.0)
Moderate	51	15	29.4	(17.5, 43.8)	92	14	15.2	(8.6, 24.2)	95	7	7.4	(3.0, 14.6)
Severe	38	1	2.6	(0.1, 13.8)	81	1	1.2	(0.0, 6.7)	90	1	1.1	(0.0, 6.0)
Pain[e]												
Any	268	267	99.6	(97.9, 100.0)	265	257	97.0	(94.1, 98.7)	254	237	93.3	(89.5, 96.1)
Mild	242	238	98.3	(95.8, 99.5)	245	226	92.2	(88.2, 95.3)	234	208	88.9	(84.1, 92.6)
Moderate	150	135	90.0	(84.0, 94.3)	164	126	76.8	(69.6, 83.1)	153	99	64.7	(56.6, 72.3)
Severe	48	12	25.0	(13.6, 39.6)	93	17	18.3	(11.0, 27.6)	97	9	9.3	(4.3, 16.9)
Limitation of arm movement[f]												
Any	187	170	90.9	(85.8, 94.6)	165	119	72.1	(64.6, 78.8)	147	86	58.5	(50.1, 66.6)
Mild	173	153	88.4	(82.7, 92.8)	151	103	68.2	(60.1, 75.5)	142	77	54.2	(45.7, 62.6)
Moderate	56	23	41.1	(28.1, 55.0)	89	14	15.7	(8.9, 25.0)	93	7	7.5	(3.1, 14.9)
Severe	50	15	30.0	(17.9, 44.6)	93	17	18.3	(11.0, 27.6)	94	5	5.3	(1.7, 12.0)
Any local reaction[g]	274	273	99.6	(98.0, 100.0)	269	262	97.4	(94.7, 98.9)	258	244	94.6	(91.1, 97.0)

a. N = number of subjects with known values. b. n = Number of subjects with the given characteristic. c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects. d. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm. e. 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. f. 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. g. Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement.

7.3.2. Treatment-related adverse events (adverse drug reactions)

7.3.2.1. Pivotal studies

7.3.2.1.1. Local reactions

At least 1 local reaction was reported within 14 days after vaccine administration for 82.2% of subjects in Cohort 1, 89.6% of subjects in Cohort 2, and 97.3% of subjects in Cohort 3 (Table 9).

Table 9. Subjects Reporting Local Reactions Within 14 Days After Vaccination With 13vPnC, Ages 60-64 Years (Cohort 1), 50-59 Years (Cohort 2), and 18-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Vaccine Group (as Administered) 13vPnC											
	60-64 Years Old (Cohort 1)				50-59 Years Old (Cohort 2)				18-49 Years Old (Cohort 3)			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Redness[d]												
Any	193	39	20.2	(14.8, 26.6)	152	24	15.8	(10.4, 22.6)	266	81	30.5	(25.0, 36.4)
Mild	189	30	15.9	(11.0, 21.9)	151	23	15.2	(9.9, 22.0)	258	68	26.4	(21.1, 32.2)
Moderate	185	16	8.6	(5.0, 13.7)	140	7	5.0	(2.0, 10.0)	227	27	11.9	(8.0, 16.8)
Severe	178	3	1.7	(0.3, 4.8)	137	1	0.7	(0.0, 4.0)	211	6	2.8	(1.1, 6.1)
Swelling[d]												
Any	197	38	19.3	(14.0, 25.5)	161	35	21.7	(15.6, 28.9)	302	119	39.4	(33.9, 45.2)
Mild	192	30	15.6	(10.8, 21.5)	160	33	20.6	(14.6, 27.7)	293	109	37.2	(31.7, 43.0)
Moderate	184	15	8.2	(4.6, 13.1)	138	6	4.3	(1.6, 9.2)	238	36	15.1	(10.8, 20.3)
Severe	178	1	0.6	(0.0, 3.1)	136	0	0.0	(0.0, 2.7)	209	3	1.4	(0.3, 4.1)
Pain[e]												
Any	331	265	80.1	(75.3, 84.2)	322	286	88.8	(84.9, 92.0)	787	761	96.7	(95.2, 97.8)
Mild	323	254	78.6	(73.8, 83.0)	306	263	85.9	(81.5, 89.6)	721	672	93.2	(91.1, 94.9)
Moderate	206	48	23.3	(17.7, 29.7)	190	75	39.5	(32.5, 46.8)	467	360	77.1	(73.0, 80.8)
Severe	178	3	1.7	(0.3, 4.8)	139	5	3.6	(1.2, 8.2)	238	38	16.0	(11.6, 21.3)
Limitation of arm movement[f]												
Any	214	61	28.5	(22.6, 35.1)	194	79	40.7	(33.7, 48.0)	499	375	75.2	(71.1, 78.9)
Mild	212	57	26.9	(21.0, 33.4)	189	73	38.6	(31.6, 46.0)	466	333	71.5	(67.1, 75.5)
Moderate	179	4	2.2	(0.6, 5.6)	140	4	2.9	(0.8, 7.2)	238	44	18.5	(13.8, 24.0)
Severe	180	3	1.7	(0.3, 4.8)	139	4	2.9	(0.8, 7.2)	237	37	15.6	(11.2, 20.9)
Any local reaction[g]	337	277	82.2	(77.7, 86.1)	327	293	89.6	(85.8, 92.7)	801	779	97.3	(95.9, 98.3)

a. N = number of subjects with known values. b. n = Number of subjects with the given characteristic. c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects. d. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm. e. 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. f. 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. g. Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement.

The most frequent local reaction was pain, which occurred in 80.1% of subjects in Cohort 1, 88.8% of subjects in Cohort 2, and 96.7% of subjects in Cohort 3. The percentage of subjects reporting severe pain was higher in Cohort 3 (16.0%) than in Cohort 1 (1.7%) and Cohort 2 (3.6%). Most reports of redness, swelling, or limitation of arm movement were of mild or moderate severity. Severe redness and severe swelling were each reported in ≤ 2.8% of subjects in Cohorts 1, 2, and 3. The percentage of subjects reporting severe limitation of arm movement was much higher in Cohort 3 (15.6%) than in Cohort 1 (1.7%) and Cohort 2 (2.9%). For Cohort 3, at least 1 local reaction was reported within 14 days after vaccine administration for 99.6% of 18 to 29 year old subjects, 97.4% of 30 to 39 year old subjects, and 94.6% of 40 to 49 year old subjects (Table 8). The percentages of subjects with any redness, any swelling, and any limitation of arm movement were highest in 18 to 29 year old subjects and lowest in 40 to 49 year old subjects. High, and similar, percentages of subjects reported any pain in the 3 age subgroups. However, the percentage of subjects with severe pain was highest in 18 to 29 year old subjects and lowest in 40 to 49 year old subjects. Although the frequency of severe pain and limitation of arm movement was significantly higher in younger adults in Cohort 3 than in older adults in the other 2 cohorts, only 4 younger adults had unscheduled doctor visits due to pain at the injection site and/or limitation of arm movement. In all 4 cases the symptoms were mild or moderate. There was no unscheduled doctor visit for severe pain or limitation of arm movement. The mean durations of local reactions were similar for the age subgroups in Cohort 3, and did not exceed 2.8 days. Most local reactions occurred during the first 4 days after vaccination and then tapered off in Cohorts 1, 2, and 3. In Cohort 3, the highest values for any local reaction, any pain, any limitation of arm movement, and any swelling occurred on Day 2. The percentages of subjects with any local reaction, any pain, any limitation of arm movement, any redness and any swelling were higher in Cohort 3 than in Cohort 1 or Cohort 2 during the first 4 days after vaccination.

7.3.2.1.2. Systemic reactions

At least one systemic event occurring within 14 days after vaccine administration was reported by the majority of subjects who received 13vPnC in Cohort 3 (approximately 96%), Cohort 2 (approximately 84%), and Cohort 1 (approximately 83%; Table 10). The 3 most frequently reported systemic events in Cohort 3 (new generalised muscle pain, headache, and fatigue) were reported by higher percentages of subjects in Cohort 3 (82.0%, 81.4%, and 80.5%) than in Cohort 1 (56.2%, 54.0%, and 63.2%) or Cohort 2 (61.8%, 65.9%, and 63.3%). In general, the percentages of subjects with individual systemic events were reported by higher percentages of subjects in Cohort 3 than in Cohort 1 or Cohort 2. At least one systemic event occurring within 14 days after vaccine administration was reported by the majority of subjects in the 18- to 29 year old (approximately 99%), 30- to 39- year-old (approximately 94%), and 40- to 49 year old (approximately 93%) age subgroups in Cohort 3 (Table 11). In general, the percentages of subjects with individual systemic events were highest in the 18 to 29 year old age subgroup.

Table 10. Subjects Reporting Systemic Events Within 14 Days After Vaccination, Ages 60-64 Years (Cohort 1), 50-59 Years (Cohort 2) and 18-49 Years (Cohort 3) Study 6115A1-004 Safety Population

	Vaccine Group (as Administered) 13vPnC											
	60-64 Years Old (Cohort 1)				50-59 Years Old (Cohort 2)				18-49 Years Old (Cohort 3)			
Systemic Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever												
Any (≥38°C)	181	14	7.7	(4.3, 12.6)	137	2	1.5	(0.2, 5.2)	221	16	7.2	(4.2, 11.5)
Mild (≥38°C but <38.5°C)	179	7	3.9	(1.6, 7.9)	137	2	1.5	(0.2, 5.2)	214	9	4.2	(1.9, 7.8)
Moderate (≥38.5°C but <39°C)	178	1	0.6	(0.0, 3.1)	136	0	0.0	(0.0, 2.7)	211	4	1.9	(0.5, 4.8)
Severe (≥39°C but ≤40°C)	177	0	0.0	(0.0, 2.1)	136	0	0.0	(0.0, 2.7)	210	3	1.4	(0.3, 4.1)
Potentially life threatening (>40°C)	180	8	4.4	(1.9, 8.6)	136	0	0.0	(0.0, 2.7)	208	1	0.5	(0.0, 2.6)
Fatigue	277	175	63.2	(57.2, 68.9)	248	157	63.3	(57.0, 69.3)	554	446	80.5	(77.0, 83.7)
Headache	252	136	54.0	(47.6, 60.2)	246	162	65.9	(59.6, 71.8)	527	429	81.4	(77.8, 84.6)
Chills	204	48	23.5	(17.9, 30.0)	158	31	19.6	(13.7, 26.7)	286	109	38.1	(32.5, 44.0)
Rash	194	32	16.5	(11.6, 22.5)	148	21	14.2	(9.0, 20.9)	249	53	21.3	(16.4, 26.9)
Vomiting	180	7	3.9	(1.6, 7.8)	144	10	6.9	(3.4, 12.4)	240	36	15.0	(10.7, 20.2)
Decreased appetite	202	43	21.3	(15.9, 27.6)	166	42	25.3	(18.9, 32.6)	363	202	55.6	(50.4, 60.8)
New generalized muscle pain	249	140	56.2	(49.8, 62.5)	238	147	61.8	(55.3, 68.0)	561	460	82.0	(78.6, 85.1)
Aggravated generalized muscle pain	215	70	32.6	(26.3, 39.3)	188	75	39.9	(32.8, 47.3)	370	207	55.9	(50.7, 61.1)
New generalized joint pain	197	48	24.4	(18.5, 31.0)	165	52	31.5	(24.5, 39.2)	307	128	41.7	(36.1, 47.4)
Aggravated generalized joint pain	205	51	24.9	(19.1, 31.4)	168	43	25.6	(19.2, 32.9)	269	77	28.6	(23.3, 34.4)
Any systemic event[d]	327	270	82.6	(78.0, 86.5)	314	265	84.4	(79.9, 88.2)	752	718	95.5	(93.7, 96.8)

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

Table 11. Subjects Reporting Systemic Events Within 14 Days After Vaccination by Age Groups, Ages 18-29 Years, 30-39 Years, and 40-49 Years (Cohort 3) Study 6115A1-004 Safety Population

	Age Group (Years)											
	18-29 Years Old				30-39 Years Old				40-49 Years Old			
Systemic Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever												
Any (≥38°C)	43	6	14.0	(5.3, 27.9)	87	8	9.2	(4.1, 17.3)	91	2	2.2	(0.3, 7.7)
Mild (≥38°C but <38.5°C)	41	4	9.8	(2.7, 23.1)	82	3	3.7	(0.8, 10.3)	91	2	2.2	(0.3, 7.7)
Moderate (≥38.5°C but <39°C)	38	1	2.6	(0.1, 13.8)	83	3	3.6	(0.8, 10.2)	90	0	0.0	(0.0, 4.0)
Severe (≥39°C but ≤40°C)	38	1	2.6	(0.1, 13.8)	82	2	2.4	(0.3, 8.5)	90	0	0.0	(0.0, 4.0)
Potentially life threatening (>40°C)	37	0	0.0	(0.0, 9.5)	81	1	1.2	(0.0, 6.7)	90	0	0.0	(0.0, 4.0)
Fatigue	177	161	91.0	(85.7, 94.7)	186	150	80.6	(74.2, 86.1)	191	135	70.7	(63.7, 77.0)
Headache	162	146	90.1	(84.5, 94.2)	174	139	79.9	(73.2, 85.6)	191	144	75.4	(68.7, 81.3)
Chills	73	40	54.8	(42.7, 66.5)	104	43	41.3	(31.8, 51.4)	109	26	23.9	(16.2, 33.0)
Rash	47	10	21.3	(10.7, 35.7)	98	25	25.5	(17.2, 35.3)	104	18	17.3	(10.6, 26.0)
Vomiting	54	17	31.5	(19.5, 45.6)	88	8	9.1	(4.0, 17.1)	98	11	11.2	(5.7, 19.2)
Decreased appetite	104	78	75.0	(65.6, 83.0)	124	64	51.6	(42.5, 60.7)	135	60	44.4	(35.9, 53.2)
New generalized muscle pain	190	179	94.2	(89.9, 97.1)	181	142	78.5	(71.7, 84.2)	190	139	73.2	(66.3, 79.3)
Aggravated generalized muscle pain	107	84	78.5	(69.5, 85.9)	131	68	51.9	(43.0, 60.7)	132	55	41.7	(33.2, 50.6)
New generalized joint pain	72	39	54.2	(42.0, 66.0)	114	45	39.5	(30.4, 49.1)	121	44	36.4	(27.8, 45.6)
Aggravated generalized joint pain	57	23	40.4	(27.6, 54.2)	103	28	27.2	(18.9, 36.8)	109	26	23.9	(16.2, 33.0)
Any systemic event[d]	258	255	98.8	(96.6, 99.8)	246	232	94.3	(90.6, 96.9)	248	231	93.1	(89.3, 96.0)

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

The mean durations of systemic events were generally similar and did not exceed 5.9 days for Cohorts 1, 2, and 3, and 5.8 days for the age subgroups. The mean durations of systemic events were similar for the age subgroups in Cohort 3, and did not exceed 5.9 days. Systemic events that extended beyond 14 days after vaccination were reported by 108 subjects in Cohort 3. In Cohort 3, the percentages of subjects with fatigue and decreased appetite were highest on Day 2 but were fairly similar across the other days of the 14 day observation interval. On Day 2, the percentages of subjects with fatigue and decreased appetite were higher in Cohort 3 (27.4% and 10.5%) than in Cohort 1 (17.2% and 3.0%) or Cohort 2 (17.3% and 4.2%). In all 3 cohorts, new generalised muscle pain was reported primarily in the first 2 days and aggravated generalised muscle pain had the highest incidence on Day 2. The percentages of subjects with new generalised muscle pain on Days 1 and 2 were higher in Cohort 3 (27.8% and 26.9%) than in Cohort 1 (14.1% and 13.7%). The percentage of subjects with new generalised muscle pain in Cohort 3 was also higher than in Cohort 2 (13.9%) on Day 2. The percentage of subjects with aggravated generalised muscle pain in Cohort 3 (16.6%) on Day 2 was higher than in Cohort 1 (6.0%) or Cohort 2 (8.9%).

The incidences of the other systemic events were fairly similar across days, and were also similar among the 3 cohorts.

In each of the age subgroups in Cohort 3, the incidences of fatigue and decreased appetite were highest on Day 2 but were fairly similar across the other days, new generalised muscle pain was reported primarily in the first 2 days, aggravated generalised muscle pain had the highest incidence on Day 2, and the other systemic events were fairly similar across days. For the subjects in the 18 to 29 year old age subgroup, the incidences of fatigue and new generalised muscle pain were higher than in the 2 older age subgroups on Days 1 and 2, and the incidences of headache and aggravated muscle pain were higher than in the 2 older age subgroups on Day 2.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Pivotal studies

No deaths were reported for subjects in Cohort 3, or in Cohort 2. One (1) subject in Cohort 1 died due to pancreatic cancer and liver cancer, which was considered unrelated to study vaccine.

SAEs occurring within approximately 1 month after vaccination were reported for 2 subjects (migraine, basal cell carcinoma) in Cohort 3, for 2 subjects (cellulitis, ovarian cancer) in Cohort 2 and for 1 subject (haemangioma) in Cohort 1. In Cohort 3, the migraine was reported by a subject in the 30 to 39 year old age group and the basal cell carcinoma was reported by a subject in the 40 to 49 year old age group. Except for the SAE of migraine reported by the subject in Cohort 3, none of the serious AEs reported within 1 month after vaccination in Cohorts 1, 2, and 3 were considered by the investigator to be related to study vaccine, and all of the SAEs were thought to have resolved.

SAEs were reported at the 6 month follow-up contact for 2 subjects (0.2%) in Cohort 3, for 5 subjects (1.2%) in Cohort 2, and for 12 subjects (2.9%) in Cohort 1. In Cohort 3, the types of SAEs reported at the 6 month follow-up contact included reproductive system and breast disorders and injury, poisoning and procedural complications. A SAE in the category of injury, poisoning and procedural complications was also reported in Cohort 2. In Cohort 3, the SAE of hip fracture was reported by 1 subject and the SAE of ovarian cyst ruptured was reported by 1 subject in the 18 to 29 year old subgroup. Both SAEs were severe, neither was considered to be related to study vaccine, and both of the SAEs resolved.

No AEs that led to withdrawal were reported for Cohort 3, Cohort 2, or for subjects who received 13vPnC in Cohort 1.

7.3.4. Discontinuation due to adverse events

Not applicable.

7.4. Laboratory tests

Not applicable.

7.5. Postmarketing experience

There is no marketing experience for 13vPnCin the age extension age group.

7.6. Other safety issues

7.6.1. Study 6096A1-4001 in preterm infants

7.6.1.1. Adverse events

7.6.1.1.1. Infant series

AEs were reported in slightly over half of subjects in each group. Infections and infestations was the most common category of AEs (Group 1, 45.0%; Group 2, 41.0%). The most frequent individual AEs in this system organ class were bronchiolitis and upper respiratory tract infections. Gastrointestinal disorders, the next most frequently occurring category of AE, was reported statistically significantly more often in Group 1 than in Group 2 (13 [13%] versus 4 [4%] subjects, p=0.040); no other statistical differences in AEs were noted.

The frequency of AEs reported after each individual dose in the infant series was similar in the 2 groups (23% to 34% across doses and groups.

During the infant series, severe AEs were reported in 7 (7.0%) subjects in Group 1 and 2 (2.0%) subjects in Group 2; severe AEs reported most often were classified as Infections and infestations (pneumonia most frequent). There were no significant differences between groups in incidence of severe AEs during the infant series.

7.6.1.1.2. Local reactions

Dose 1: The percentage of subjects experiencing any local reaction within 7 days after Dose 1 was somewhat higher in preterm infants of Group 1 (66.3%) than in infants born at term in Group 2 (57.6%). The percentage of each individual local reaction was also somewhat higher in Group 1 than in Group 2. Tenderness was the most common local reaction in both groups, occurring in 48.9% subjects in Group 1 and 42.0% subjects in Group 2. Most local reactions after Dose 1 were mild; no severe local reaction was reported in either group.

Dose 2: Local reactions within 7 days after Dose 2 of the infant series were reported by similar percentages of subjects in Group 1 (62.9%) and Group 2 (60.7%). Tenderness was the most common local reaction in Group 1 (48.2%) and Group 2 (38.6%). The majority of local reactions were reported as mild. Only 1 (1.3%) severe local reaction was reported after Dose 2 (severe tenderness in Group 2).

Related AEs occurred during the infant series in 8 (8.0%) subjects in Group 1 and in 5 (5.0%) subjects in Group 2. Irritability was the most common related AE in both groups. No significant differences between the groups were noted for any related AE during the infant series overall or after Dose 1, Dose 2, or Dose 3.

7.6.1.1.3. Toddler Dose:

During the toddler dose (the period from the toddler dose to the blood draw 1month after vaccination), 31.3% of subjects in Group 1 and 26.8% in Group 2 experienced AEs. Infections and infestations were the most common category of AEs, experienced by 27.3% and 21.6%

subjects in Group 1 and Group 2, respectively. There were no significant differences between groups in reported AEs during this time period. Only 1 subject experienced a severe AE during the toddler dose (RSV pneumonia, Group 1). Only 1 subject experienced an event reported to be related to the study vaccine (that is, rash in Group 1).

Local reactions occurring within 7 days after the toddler dose were reported somewhat more frequently than after any dose of the infant series. After the toddler dose local reactions were reported in 75.3% of subjects in Group 1 and 68.2% in Group. The most frequently reported local reaction was tenderness, occurring in 69.8% of subjects in Group 1 and 55.3% of subjects in Group 2. Most local reactions were mild in severity, although severe local reactions were reported in 3 subjects, all in Group 1 (that is, 2 [2.7%] subjects with severe tenderness and 1 [1.4%] with severe swelling). The mean durations of local reactions were generally similar in the 2 groups and did not exceed 3.8 days.

7.6.1.2. Serious adverse events, AE withdrawals, deaths

7.6.1.2.1. Infant series:

Serious adverse events (SAEs) were reported during the infant series in 14.0% of subjects in Group 1 and in 5.0% of subjects in Group 2 (p=0.051). There were no statistically significant differences between groups for individual SAEs or categories of SAEs during the infant series. SAEs were categorised most often as Infections and infestations in Group 1 (12%) and Group 2 (5%). SAEs occurring in Group 1 were most often respiratory infections (including RSV), to which preterm infants are particularly susceptible. Respiratory infections were also predominant in Group 2. As expected, among the preterm subgroups, Group 1C had a higher percentage of SAEs (28%) than did subjects with a later GA in Group 1B (14%) or Group 1A (no SAEs) during the infant series.

After the infant series and before the toddler dose, SAEs were reported in 8.0% of subjects in Group 1 and in 9.0% of subjects in Group 2.

7.6.1.2.2. Toddler dose:

During the toddler dose, SAEs were reported in 2.0% of subjects in Group 1 and 1.0% in Group 2; no statistically significant differences between groups were observed (5.3.5.2, 6096A1-4001, Table 58). Two SAEs were reported, that is, bronchiolitis in Group 1A and RSV in Group 1C.

Related SAEs, AE withdrawals, deaths: No SAE was thought to be related to vaccination during the study period. There were no safety-related withdrawals and no deaths were reported during the study period.

Other significant adverse events

Two (2) subjects experienced febrile convulsion during the reporting period. One (1) subject was in Group 1 and 1 was in Group 2. At the onset of the febrile convulsions, the subjects were 12 and 14 months of age, respectively. Each subject had a simultaneous AE or SAE on the day of the febrile convulsion, including respiratory tract infection and bronchopneumonia, respectively. Febrile convulsion onset was 17 days after dose 4 for the subject in Group 1 and 139 days after Dose 3 for the subject in Group 2.

7.6.2. Study 6096A1-3014: Children and adolescents with sickle cell disease

The safety objective was to evaluate the acceptability of the safety profile of 13vPnC, as measured by the incidence rates of local reactions, systemic events, and AEs. All participants who received at least 1 dose of the study vaccine were included in the safety population for each study.

7.6.2.1. Local reactions

The frequency of local reactions was similar after Dose 1 and after Dose 2 (91.7% and 88.5%, respectively). Pain was the most frequently reported local reaction after Dose 1 and Dose 2 (in

89.6% and 85.6%, respectively). Redness was reported in less than a third of subjects and swelling in approximately half of subjects after each dose. Most local reactions were mild in severity after each dose.

Twelve (12) cases of severe reactions were reported after Dose 1 and 11 cases after Dose 2; most severe reactions after each dose were due to severe pain (10 subjects [11.1%] Dose 1; 11 subjects [15.9%] Dose 2). The other 2 severe reactions both occurred after Dose 1 (severe redness and severe swelling). Mean duration of each local reaction did not exceed 3.2 days after Dose 1 or Dose 2 and durations were generally similar for each.

7.6.2.2. Systemic reactions

The percentage of subjects reporting a systemic event within 7 days after vaccination was similar for Dose 1 (87.5%) and Dose 2 (89.3%). The most common systemic events, occurring in similar percentages of subjects after Dose 1 and Dose 2, were muscle pain (74.8% versus 75.5%, respectively) and fatigue (66.1% versus 62.5%, respectively). The frequency of other systemic events was not notably different after Dose 1 and Dose 2, except for diarrhoea (13.3% versus 25%, respectively). The most commonly reported severe systemic events after Dose 1 and Dose 2, respectively, were severe muscle pain (10.1% versus 16.4%), severe fatigue (14.4% versus 13.4%), and severe headache (12.0% versus 10.6%). Most fevers were between ≥38^{0}C but ≤38.4^{0}C after each dose and were reported in 13.6% of subjects after Dose 1 and 9.5% after Dose 2. Fever >40^{0}C was reported in 1 subject each after Dose 1 (1.3%) and Dose 2 (1.7%). Antipyretic medication use was somewhat more frequent after Dose 1 (58.2% of subjects) than after Dose 2 (43.6% of subjects).

The mean durations of systemic events were similar after each dose, except for headache (4.5 days for Dose 1 versus 2.8 days for Dose 2). Mean durations did not exceed 4.5 days after either dose.

7.6.2.3. Adverse events

AEs were reported for 62 (39.2%) subjects after Dose 1 and for 23 (16.4%) subjects after Dose 2. AEs after each dose were most often classified as congenital, familial and genetic disorders (15.8% for Dose 1 and 3.6% for Dose 2, that is, [specific AE was sickle cell anaemia with crisis]). AEs were also frequently categorised as Infections and infestations (11.4% of subjects) after Dose 1 and as Musculoskeletal and connective tissue disorders (3.6% of subjects) after Dose 2. The most frequent individual AEs reported in more than 2% of subjects were: sickle cell anaemia with crisis (15.8%), pyrexia (6.3%), headache (3.2%), and vascular occlusion (3.2%) after Dose 1; and sickle cell anaemia with crisis (3.6%) and pain in extremity (2.9%) after Dose 2. Severe AEs were reported in 13 (8.2 %) subjects after Dose 1 and 5 (3.6%) subjects after Dose 2; severe AEs after each dose were most often classified as congenital, familial, and genetic disorders. All severe AEs in this category were sickle cell anaemia with crisis, reported in 7 (4.4%) subjects after Dose 1 and 2 (1.4%) subjects after Dose 2. No life-threatening AEs were reported in this study.

Related AEs were reported in 6 (3.8%) subjects after Dose 1 and in 2 (1.4%) subjects after Dose 2. All individual related AEs were reported in single subjects after each dose. The majority of related AEs were categorised as General disorders and Administration site conditions after Dose 1. Of the 2 related events after Dose 2, one was categorised as an Eye disorder (periorbital oedema) in 1 subject and the other as an Administration site condition (injection site swelling) in the second subject. All related AEs resolved.

7.6.2.4. Serious adverse events, AE withdrawals, deaths

Serious AEs were reported in 25.3% of subjects after Dose 1 and in 7.9% of subjects after Dose 2. The majority of SAEs reported after each dose were classified as congenital, familial and genetic disorders; all subjects in this category had sickle cell anaemia with crisis, which was reported more frequently after Dose 1 (22 subjects, 13.9%, 30 SAEs) than after Dose 2 (5

subjects, 3.6%, 6 SAEs). Other SAEs after Dose 1 were most frequently categorised as Infections and infestations (7.6%). All SAEs resolved. Two SAEs (osteomyelitis [underlying pathogen unknown] and back pain of severe intensity) were reported by the investigator as related to the study vaccine within 14 days after Dose 1. Both SAEs were in a single subject. Both SAEs resolved. One subject was withdrawn from the study because of severe injection site pain and severe systemic events (severe muscle pain, headache, joint pain), as well as fatigue, fever and vomiting reported within 7 days following Dose 1 (at the request of the parents prior to the second dose).

7.6.2.5. Other significant adverse events

Two pregnancies occurred after Dose 2. Neither subject withdrew from the study, as dosing had been completed.

7.6.3. Study 6115A1-3017 in HIV-infected adults

The percentage of subjects reporting AEs after any vaccine dose was 63.5% for all subjects in the safety population. AEs were most frequently classified as Infections and infestations (27.7% of subjects), and Gastrointestinal disorders (14.3%). The most frequently reported individual AEs were upper respiratory tract infection (7.0%), fatigue (4.0%), diarrhoea (3.3%), bronchitis (3.3%), and rash (3.3%). The AEs were consistent with events expected in an adult HIV population.

The incidence of AEs after any vaccine dose was similar for subjects with 1 previous dose of 23vPS (58.1%) and for subjects with ≥2 previous doses of 23vPS (68.6%). In each subgroup, AEs were most frequently categorised as Infections and infestations, and upper respiratory tract infection was the individual AE reported most often (6.3% and 7.7%, respectively).

7.6.3.1. Local reactions

In general, the percentages of subjects with local reactions (≥1 previous dose) within 14 days after vaccination was similar for each of the 3 vaccine doses; local reactions were reported by 79.7% of subjects after Dose 1, by 81.5% after Dose 2, and by 82.4% after Dose 3. Local pain was the most common injection site reaction and the frequency was similar after each dose (78.8% Dose 1, 81.4% Dose 2, and 81.9% Dose 3). The percentages of subjects with any redness and any swelling remained relatively low after Dose 1 (5.6% and 6.8%, respectively), Dose 2 (8.2% and 12.7%, respectively), and Dose 3 (9.5% and 11.2%, respectively).

The majority of local reactions after each dose were mild. Twenty-five (25) subjects experienced severe local reactions in the study; 18 subjects reported severe pain, 4 reported severe swelling, and 3 reported severe redness. The percentage of subjects with severe pain was higher after Dose 2 (8.1%, 10 subjects) and Dose 3 (5.7%, 6 subjects) than after Dose 1 (1.3%, 2 subjects). The percentage with severe swelling and severe redness was comparable after each dose (1.7%). Similar results were observed for subjects with 1 previous dose of 23vPS and subjects with ≥2 previous doses of 23vPS. Mean duration of redness, swelling, and pain were similar after each of the 3 vaccine doses and did not exceed 3.3 days. The mean durations of local reactions were similar in subjects with 1 previous dose of 23vPS and subjects with ≥2 previous doses of 23vPS after each vaccine dose and did not exceed 4.5 days in each subgroup.

7.6.3.2. Systemic events

In general, the percentages of subjects with systemic events did not increase over the 3 vaccine doses (88.4% Dose 1, 85.6% Dose 2, and 83.3% Dose 3). The most frequently occurring systemic events at vaccine doses 1, 2, and 3 were fatigue (60.0%, 63.3%, and 56.3%, respectively), headache (61.6%, 56.1%, and 46.7%, respectively) and new generalised muscle pain (65.0%, 71.9%, and 65.9%, respectively). The percentage of subjects with fever ≥38.0°C was low at vaccine doses 1, 2 and 3 (6.2%, 5.1%, and 7.7%, respectively). Most fevers were <38.5°C after each dose. The frequency of systemic events was generally similar in subjects with 1 previous dose of 23vPS and subjects with ≥2 previous doses of 23vPS after each vaccine. After

Dose 3, fatigue, headache, new generalised joint pain, and vomiting were observed for slightly higher percentages of subjects with ≥2 previous doses of 23vPS (62.0%, 51.9%, 36.1%, and 14.8%, respectively) than in subjects with 1 previous dose of 23vPS (48.5%, 40.0%, 26.3%, and 6.3%, respectively). The mean durations of systemic events were similar after each of the 3 vaccine doses and did not exceed 6.3 days. The mean durations of systemic events after each dose were similar in subjects who had received 1 or had received ≥2 previous doses of 23vPS and did not exceed 6.7 days in each subgroup.

Severe AEs were reported after any dose for 44 subjects (13.4). The severe adverse events reported in more than 1 subject included: diarrhoea (4 subjects, 1.2%), coronary artery disease (2 subjects, 0.6%), non-cardiac chest pain (2 subjects, 0.6%), headache (2 subjects, 0.6%), depression (2 subjects, 0.6%), and substance abuse (2 subjects, 0.6%). The incidences of severe AEs reported after any dose was similar for subjects with 1 previous dose of 23vPS and for subjects with ≥2 previous doses of 23vPS. Life-threatening AEs were reported in 3 subjects (0.9%), each after Dose 1 (myocardial infarction, respiratory failure, and deep vein thrombosis).

AEs judged by the investigator to be related to the study vaccine were reported in 8.8% of subjects. The incidence of related AEs after any dose was similar in those with 1 previous 23vPS dose or with ≥2 previous 23vPS doses. Related adverse events reported in more than 1 subject after any dose included fatigue (4 subjects, 1.2%), nausea (3 subjects, 0.9%), influenza like illness (2 subjects, 0.6%), myalgia (2 subjects, 0.6%), and rash (2 subjects, 0.6%).

No deaths were reported in Study 6115A1-3017.

Serious adverse events (SAEs) were reported in 43 subjects (13.1%) in this study. The incidences of SAEs reported after any dose were similar for subjects with 1 previous dose of 23vPS (10.6%) and for subjects with ≥2 previous doses of 23vPS (15.4%). For subjects with ≥1 previous dose of 23vPS, the most frequently occurring types of SAEs after any vaccine dose were Infections and infestations (2.7%), neoplasms benign, malignant and unspecified (2.7%), and cardiac disorders (2.1%).

Related SAEs, AE withdrawals: None of the SAEs reported after any dose was considered related to the study vaccine. AEs that led to withdrawal were reported by 6 subjects. None of the AEs that led to withdrawal was considered related to study vaccine by the investigator.

7.7. Evaluator's overall conclusions on clinical safety

The safety of 13vPnC administered to the 18 to 49 year old subjects in Cohort 3 was compared with the safety of the 13vPnC vaccine administered to the older subjects (60 to 64 years old and 50 to 59 years old) in Cohorts 1 and 2, respectively. The safety of 13vPnC administered to subjects in each of the age subgroups in Cohort 3 was also assessed. Local reactions and systemic events occurring within 14 days after vaccine administration were reported by higher percentages of subjects in Cohort 3 compared with the older subjects in Cohorts 1 and 2. In the age subgroups in Cohort 3, in general, the percentages of subjects with local reactions and systemic events were generally highest in the youngest (18 to 29 year old) age subgroup.

In relation to the percentages of subjects who reported AEs within approximately 1 month after vaccination, there were no differences between Cohort 3 and the older cohorts or within the age subgroups in Cohort 3. The percentage of subjects reporting any AEs at the 6 month follow-up contact was slightly lower in Cohort 3 (0.3%) than in Cohort 2 (1.5%) and Cohort 1 (2.9%).

These findings were consistent with those expectable post vaccination and no new safety issues were identified. An acceptable safety profile was demonstrated for the administration of 13vPnC to subjects 18 to 49 years of age.

In the studies in special populations (premature infants, children and adolescents with SCD and adults with HIV infection), there were also no unexpected safety issues identified.

In Study 6096A1-4001 there was a high incidence of local reactions, more so in the toddler dose than in the infant series, consistent with immunological priming. These were generally mild and resolved quickly (as did the related systemic events). There were however, two documented febrile convulsions. In both these infants, there were thought to be concomitant infections. This study did not suggest any new or unexpected safety signal among preterm infants compared with their term counterparts.

In Study 6096A1-3014 in children and adolescents with SCD, the reported local and systemic reactions were also consistent with the known and expected ones post vaccination and there were no unanticipated reactions or AEs. The AE and SAE data in the study reflected the underlying condition of SCD.

In Study 6115A1-3017 in HIV infected adults, an acceptable safety profile was demonstrated for the administration of 13vPnC in subjects aged 18 years and older previously immunized with 23vPS. No new safety issues were identified in this population after administration of 3 doses of 13vPnC.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

- Study 6115A1-004 Cohort 3 evaluated the immunogenicity and safety of 13vPnC to support extension of the indication for 13vPnC to subjects 18 years to 49 years of age who had not received prior 23vPS vaccination. The primary immunological comparisons were the serotype-specific OPA GMTs for the 13 pneumococcal serotypes contained in 13vPnC, when measured 1 month after study vaccine administration in subjects 18 to 49 years of age in Cohort 3 relative to those in subjects 60 to 64 years of age in Cohort 1. The results demonstrated that all 13 serotypes elicited immunologic responses in Cohort 3 that were noninferior to those in Cohort 1 and were statistically significantly higher in Cohort 3 for all serotypes except serotype 3.
- In addition the immune response in each of the 3 age subgroups of Cohort 3 was statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3, which elicited a non-inferior response.
- Among the age subgroups, OPA GMTs were generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.
- A high antibody response in Cohort 3 was still present 1 year after vaccination. Except for serotype 3, the OPA GMTs were higher for Cohort 3 than for Cohort 1 one year after vaccination and were still well above baseline (pre vaccination) levels.
- Even though the proportion of subjects with risk conditions for pneumococcal disease was generally low in Cohort 3 with percentages as follows: asthma, 5.2%; cardiac disorders 3.3%; and diabetes mellitus, 2.9%, according to previously submitted data, these types of risk conditions are not expected to negatively impact the immune response to vaccination with 13vPnC. The marketing authorisation holder (MAH) had previously compared (descriptive comparison) the responses of subjects with risk conditions (cardiovascular, pulmonary, renal diseases, diabetes mellitus) to those of non-risk subjects in the 2 older cohorts (aged 60 to 64 years and 50 to 59 years, 23vPS-naïve) in Study 6115A1-004; in 60 to 64 year old, 23vPS-naïve subjects in Study 6115A1-3010; and in 23vPS-preimmunised subjects ≥70 years of age in Study 6115A1-3005. The results for subjects at risk and for those not at risk were similar and confirmed that immunocompetent subjects with these

underlying diseases elicit antibody responses to 13vPnC that are similar to those of healthy subjects.

- In the efficacy data submitted for inclusion in the PI, comparable immunogenicity and safety is also shown in all at risk groups studied (preterm infants, children and adults with SCD and HIV infected adults).

8.2. First round assessment of risks

The risks of 13vPnC in the proposed usage are:

- An acceptable safety profile was demonstrated for the administration of 13vPnC to subjects 18 to 49 years of age.
- Safety and tolerability of 13vPnC administered to subjects aged 18 to 49 years in Cohort 3 was compared with the safety and tolerability of 13vPnC administered to older subjects aged 60 to 64 years and 50 to 59 years in Cohorts 1 and 2, respectively. Local reactions and systemic events occurring within 14 days after vaccine administration were, in general, reported by higher percentages of subjects in Cohort 3 compared with the older subjects in Cohorts 1 and 2.
- In the age subgroups of Cohort 3, the percentages of subjects with local reactions were generally highest in the youngest (aged 18 to 29 years) subgroup. Medical care was only required for a few subjects and these subjects had mild or moderate symptoms; that is, none had severe pain or limitation of arm movement.
- Local reactions generally did not last more than 2.8 days for Cohort 3. Fever was reported in 7.2 % of subjects of Cohort 3 and was generally mild or moderate except for 1 case of fever >40° in the subgroup aged 30 to 39 years. The mean durations of systemic events also were generally similar for the 3 cohorts and did not exceed 5.5 days in Cohort 3 overall.
- The percentages of subjects reporting AEs were not different among the 3 cohorts of Study 6115A1-004, or among the age subgroups within Cohort 3. At the 6 month follow-up contact slightly fewer subjects reported AEs in Cohort 3 (0.3%) than in Cohort 2 (1.5%) and Cohort 1 (2.9%). Most AEs were the types of diseases and conditions commonly observed among adults in these age groups. There were few reports of related AEs, severe or life threatening AEs, or SAEs and incidences were similar in Cohort 3 as in Cohort 1 and Cohort 2.
- There were no deaths or AEs that led to withdrawal from the study in Cohort 3.
- In the safety data submitted with the three other studies in at-risk groups, no new safety alerts were identified and most of the adverse events reflected the background conditions/risks associated with the primary diseases in these groups.

9. First round assessment of benefit-risk balance

The benefit-risk balance of 13vPnC, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

The clinical evaluator would recommend licensing of 13vPnC for use in adults 18 to 49 years of age for the prevention of pneumococcal disease.

11. Clinical questions

Nil.

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

13. Second round benefit-risk assessment

Not applicable.

14. Second round recommendation regarding authorisation

Not applicable.

15. References

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