22 January 2015
EMA/CHMP/626561/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prevenar 13

Common name: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure No. EMEA/H/C/001104/II/0111

Note

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

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 16 July 2014 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Prevenar 13	pneumococcal polysaccharide conjugate	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication to add "pneumonia" to the authorised indication for adults (≥18 years of age), based on data from the recently completed Community–Acquired Pneumonia Immunization Trial in Adults (CAPiTA).

As a consequence the MAH proposed to update sections 4.1, 4.8 and 5.1 of the SmPC and to update the Package Leaflet accordingly.

The provision of the CAPiTA study addresses MEA 045.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0161/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0161/2012 was completed.

The PDCO issued an opinion on compliance for the PIP P/0161/2012.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Daniel Brasseur

Submission date:	16 July 2014
Start of procedure:	25 July 2014
CHMP and PRAC Rapporteurs' Joint preliminary assessment report circulated on:	12 September 2014
CHMP Co-Rapporteur's preliminary assessment report circulated on:	15 September 2014
CHMP and PRAC Rapporteurs' Joint updated assessment report circulated on:	1 October 2014, and 16 October 2014
PRAC RMP advice and assessment overview adopted by PRAC	9 October 2014
Request for Supplementary Information adopted on:	23 October 2014
CHMP Rapporteur's assessment report on responses circulated on:	19 December 2014
CHMP Rapporteur's updated assessment report on responses circulated on:	16 January 2015
CHMP opinion:	22 January 2015

2. Scientific discussion

2.1. Introduction

Prevenar 13 is a 13-valent pneumococcal conjugate vaccine (13vPnC), containing 13 pneumococcal capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated to cross-reactive material 197 (CRM197) carrier protein.

Prevenar 13 was first approved in the European Union (EU), on 09 December 2009 for active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age. Since that time the indication has been extended to include adults aged 50 years and older (24 October 2011), children and adolescents aged 6 to 17 years (20 December 2012), and adults aged 18 to 49 years (09 July 2013).

In this Type II variation, the Marketing Authorisation Holder (MAH) is submitting results from the recently completed Community–Acquired Pneumonia Immunization Trial in Adults (CAPiTA), which studied the efficacy of Prevenar 13 in preventing vaccine-serotype pneumococcal community-acquired pneumonia (CAP) and vaccine-serotype invasive pneumococcal disease (IPD) in adults aged 65 years and older.

Based on these data, the MAH is proposing to add "pneumonia" to the indication for adults (≥18 years of age).

The proposed indication is:

"Active immunisation for the prevention of invasive disease **and pneumonia** caused by *Streptococcus pneumoniae* in adults ≥18 years of age and the elderly.

The marketing authorisation for Prevenar 13 (13vPnC) was originally granted 09 December 2009 in the EU for use in children 6 weeks to 5 years of age for the prevention of invasive disease (IPD), pneumonia, and acute otitis media (AOM) caused by Streptococcus pneumoniae. Thereafter, subsequent variations were approved to expand the indication to include adults 50 years of age or older for the prevention of IPD (EMEA/H/C/1104/II/28), children and adolescents 6 to 17 years of age for the prevention of IPD, pneumonia, and AOM (EMEA/H/C/1104/II/55), and adults 18 to 49 years of age for the prevention of IPD (EMEA/H/C/1104/II/71). These approvals were based on the serotype-specific immunogenicity of 13vPnC as demonstrated in Phase 3 clinical trials.

At the time of approval of Prevenar 13 for adults 50 years of age and older for the prevention of IPD only, the MAH agreed to submit final results from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA, Study 6115A1-3006 [B1851025]), "A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease" as a postmarketing commitment (FUM 045).

The submission of the CAPiTA (6115A1-3006, B1851025) clinical study report (CSR) fulfils post-authorisation measure MEA 045 (formerly FUM 045). Three supplemental CSRs addressing the immunogenicity and remaining exploratory objectives are planned for submission in February 2015 to fulfil MEA 045.1.

2.2. Clinical efficacy

2.2.1. Main study

The current variation contains data from one clinical study the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), as described below.

A Phase 4, Randomized, Placebo-controlled Clinical Trial of 13-valent pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease

Methods

Study 6115A1-3006 is a parallel-group, randomized, placebo-controlled, double-blind, single-centre trial to evaluate the efficacy of 13vPnC in the prevention of first episodes of vaccine type (VT) pneumococcal community acquired pneumonia (CAP), first episodes of non-bacteremic/non-invasive (NB/NI) VT pneumococcal CAP, and first episodes of VT invasive pneumococcal disease (IPD) in approximately 85,000 subjects aged 65 years and older who had not previously received 23-valent pneumococcal polysaccharide vaccine (23vPS). In addition, a subset of approximately 2000 subjects (1000 in each study group) was to be evaluated for immunogenicity and nasopharyngeal carriage

Study participants

Inclusion/Exclusion Criteria: Subjects were eligible to participate in the study if they met all of the following inclusion criteria:

1. Male or female adults aged 65 years or older on the date of vaccination.
2. Registered with a general practitioner (GP) who was referring subjects to the trial.
3. Able to fulfil study requirements.

In addition to the above criteria, subjects in the immunogenicity subset also had to meet the following inclusion criterion:

1. Able to complete an electronic diary (e-diary) and fulfil other study procedures for the subset.

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

1. Previous vaccination with any licensed or experimental pneumococcal vaccine.
2. Residence in a nursing home, long-term care facility, or other institution, or requirement of semiskilled nursing care. (An ambulatory subject who is a resident of a retirement home or village was eligible for the trial.)
3. Contraindication for vaccination with 13vPnC.
4. Contraindication for vaccination with influenza vaccine, if influenza vaccine is to be administered.
5. Use of investigational vaccine or medication within 30 days before study vaccine administration.
6. History of severe adverse reaction associated with a vaccine or vaccine component.
7. Immune deficiency or suppression

In addition to the exclusion criteria above, subjects in the immunogenicity subset were ineligible if they met the following exclusion criterion:

1. Vaccination with influenza vaccine in the previous 7 days.

Treatments

Each subject received 1 dose (0.5 mL) of either 13vPnC or placebo at Visit 1 by intramuscular injection into the right deltoid.

Objectives

Only the objectives included in the current submission are listed below. Other exploratory objectives will be submitted in February 2015.

Primary Efficacy Objective:

- Demonstrate the efficacy of 13-valent pneumococcal conjugate vaccine (13vPnC) in the prevention of a first episode of confirmed vaccine-type (VT) pneumococcal community acquired pneumonia (CAP)

Secondary Efficacy Objectives:

- Demonstrate the efficacy of 13vPnC in the prevention of a first episode of confirmed nonbacteremic/noninvasive (NB/NI) VT pneumococcal CAP
- Demonstrate the efficacy of 13vPnC in the prevention of a first episode of VT invasive pneumococcal disease (IPD)

Exploratory Efficacy Objectives:

- Evaluate the efficacy of 13vPnC in the prevention of the following:
    - All episodes of confirmed VT pneumococcal CAP
    - A first episode of confirmed pneumococcal CAP
    - A first episode of confirmed NB/NI pneumococcal CAP
    - A first episode of CAP
    - A first episode of IPD
    - Death from confirmed VT pneumococcal CAP and VT-IPD
    - Death from confirmed pneumococcal CAP and IPD
    - Death from all causes
    - A first episode of confirmed VT pneumococcal CAP by individual 13vPnC serotypes
    - A first episode of confirmed NB/NI VT pneumococcal CAP by individual 13vPnC serotypes
- Investigate trends in efficacy by age

Safety Objectives:

- Evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of serious adverse events (SAEs) for 28 days after study vaccine administration for subjects not in the immunogenicity subset and for 6 months after study vaccine administration for subjects in the immunogenicity subset
- Evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs) for all subjects in the immunogenicity subset and within different age and sex groups
- Evaluate the rates of death from all causes for all subjects

Outcomes/endpoints

Surveillance for suspected pneumonia and IPD was conducted at 59 sentinel centres (58 hospitals and 1 outpatient diagnostic centres) located in the regions in the Netherlands in which subjects were enrolled. A standard diagnostic routine reflecting sentinel centre standard of care was used for all patients with lower respiratory tract infection symptoms seen in study sentinel centres whether they were admitted or treated as outpatients. This routine included medical history, physical examination, lateral and posterior-anterior chest radiographs, laboratory tests, urinary pneumococcal C-polysaccharide assay (BinaxNOW), sputum culture, and blood culture, as appropriate to the patient's presenting medical status. If a patient was suspected by the treating physician of having pneumonia on the basis of the results of this routine, sentinel centre staff determined if the patient was a CAPiTA

subject. If the patient was a study subject, an aliquot of urine was collected for the serotype-specific urinary antigen detection (SSUAD) and BinaxNOW assays performed by the sponsor; a pharyngeal swab for viral analysis conducted by the University Medical Centre Utrecht was also collected for the study. To achieve increased sensitivity and specificity of VT pneumococcal CAP identification compared to the conventional microbiological methods and the BinaxNOW assay, the sponsor developed the SSUAD assay. This validated assay was designed to detect the presence of VT S pneumonia polysaccharides in the urine of individuals presenting with suspected pneumonia. Digital chest radiographs were read centrally by a committee of radiologists.

CAP was defined as a positive chest radiograph and the presence of 2 or more of the following clinical criteria:

- Cough
- Production of purulent sputum or a change in the character of sputum
- Temperature >38.0°C or <36.1°C
- Auscultatory findings consistent with pneumonia, including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
- Leukocytosis (>10 × 109 white blood cells/liter or >15% bands)
- C-reactive protein value >3 times the upper limit of normal
- Hypoxemia with a partial oxygen pressure <60 mm Hg while the patient is breathing room air

Table 1 details the microbiological criteria used to differentiate different categories of pneumococcal CAP. An episode (or case) must have met the criteria in all 3 categories (clinical, radiological, and microbiological) to be considered an episode for the given category of pneumococcal CAP.

Table 1. Microbiological Definitions for Pneumococcal CAP Diagnosis Categories

CAP Diagnosis Category	Criteria: Episode of CAP Plus
Confirmed VT pneumococcal CAP[a]	Culture of VT *S pneumoniae* from blood, pleural fluid,[b] and /or other sterile site[c] OR positive VT SSUAD result[d,e]
Confirmed NVT pneumococcal CAP[a]	Culture of NVT *S pneumoniae* from blood, pleural fluid,[b] and/or other sterile site[c] OR positive BinaxNOW but negative VT SSUAD[d]
Confirmed pneumococcal CAP	Culture of *S pneumoniae* from blood, pleural fluid,[b] and /or other sterile site[c] OR positive BinaxNOW result[d] OR positive VT SSUAD result[d,e]
Culture-confirmed VT pneumococcal CAP[f]	Culture of VT *S pneumoniae* from blood, pleural fluid,[b] and/or other sterile site[c]
Culture-confirmed NVT pneumococcal CAP[f]	Culture of NVT *S pneumoniae* from blood, pleural fluid,[b] and/or other sterile site[c]
Culture-confirmed pneumococcal CAP	Culture of *S pneumoniae* from blood, pleural fluid,[b] and /or other sterile site[c]
Probable VT pneumococcal CAP	Culture of VT *S pneumoniae* from an evaluable sample of sputum[g]
Probable NVT pneumococcal CAP	Culture of NVT *S pneumoniae* from an evaluable sample of sputum[g]
Probable pneumococcal CAP	Culture of *S pneumoniae* from an evaluable sample of sputum[g]
Possible pneumococcal CAP	Predominant gram-positive cocci in pairs and chains in evaluable sputum on microscopy[g]

Abbreviations: CAP = community-acquired pneumonia; NVT = non–vaccine-type; *S pneumoniae* =*Streptococcus pneumoniae*; SSUAD = serotype-specific urinary antigen detection; VT = vaccine-type.

An episode of NB/NI VT pneumococcal CAP was an episode of VT pneumococcal CAP for which the blood culture result and any other available sterile site culture results are negative for *S pneumoniae*.

Surveillance for IPD was conducted by regular review of sentinel centre laboratory culture results. IPD was defined as the presence of *S pneumoniae* in a sterile site; a sterile site was defined as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid. Culture samples were analysed in local hospital laboratories, and *S pneumoniae* isolates were serotyped by the Netherlands Reference Laboratory for Bacterial Meningitis at Academic Medical Centre.

A committee of physicians experienced in clinical immunology reviewed all pneumococcal CAP or IPD episodes to determine the immune status of subjects at the time of presentation, except for episodes for which the subject had a condition resulting in immune deficiency or suppression (as defined in the eligibility criteria) at the time of presentation.

Surveillance for death, loss to follow-up, and receipt of any non-study pneumococcal vaccine was conducted during the case acquisition period by regular review of GP records and information reported

by subjects and GPs. A committee of physicians reviewed available documents from each death to determine the cause of death and whether or not the death was due to CAP or IPD.

Safety Evaluations: Figure 1 summarizes the safety evaluations and time periods for data collection for subjects in the immunogenicity subset. Figure 2 summarizes the safety evaluations and time periods for data collection for subjects not in the immunogenicity subset.

Figure 1. Safety Evaluations for Subjects in the Immunogenicity Subset

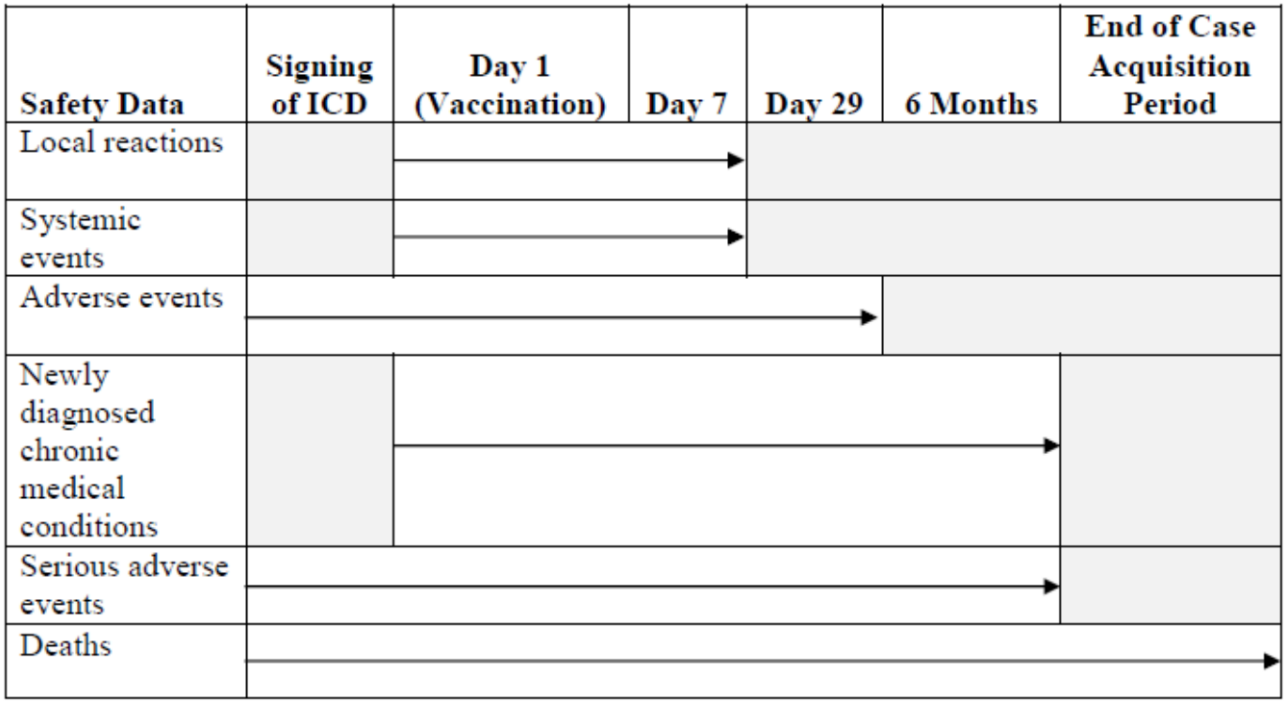
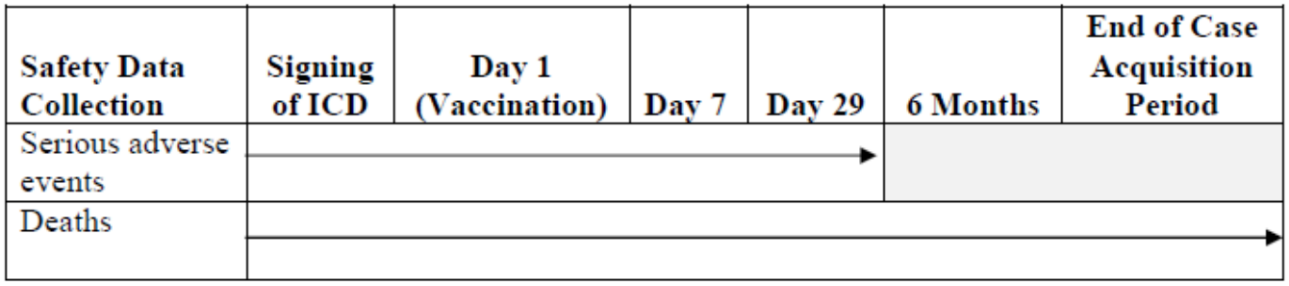


Figure 2. Safety Evaluations for Subjects Not in the Immunogenicity Subset



Efficacy Analysis

For the efficacy analyses other than the mortality and nasopharyngeal carriage analyses, 2 analysis populations were defined: per-protocol and modified intent-to-treat (mITT). The per-protocol population was the primary population for analysis of all primary and secondary efficacy objectives and all exploratory efficacy objectives except for those that assessed a combination of pneumococcal and non-pneumococcal CAP (ie, all episodes of CAP); for these objectives, only the mITT case-level population was used. All other efficacy objectives were also assessed using the mITT population.

For a subject to be included in the mITT population, the following criteria had to be satisfied:

- Subject must be identified with a CAP or IPD episode on the basis of clinical, radiological, and microbiological criteria.
- Onset of symptoms must be at least 14 days after study vaccine administration.

The mITT population was further categorized into 2 subgroups: immunodeficient/suppressed and immune-competent, according to the subject's immune status at the time of presentation at the hospital with CAP and/or IPD.

The per-protocol population was defined as subjects who satisfied the criteria specified for the mITT population, were eligible for the study, were vaccinated, and had no other major protocol violations. Episodes with onset of symptoms after the date of the following events were excluded from per-protocol analyses:

- Receipt of any pneumococcal vaccine subsequent to study vaccine
- Diagnosis with bronchial obstruction due to primary lung cancer, another malignancy metastatic to the lungs, or a history of post-obstructive pneumonia (not including chronic obstructive pulmonary disease)
- Diagnosis with acquired immunodeficiency syndrome (AIDS), known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis
- Diagnosis with immune deficiency or suppression (as defined in the exclusion criteria), or assessment by the immune status committee that the subject was immunosuppressed.

The efficacy of 13vPnC was based on the incidence rates in each vaccine group for first confirmed VT pneumococcal CAP. The 2-sided, O'Brien-Fleming–adjusted 95% confidence interval (CI) of efficacy (1 – relative risk) was presented, where relative risk was defined as the incidence rate of first-confirmed VT pneumococcal CAP in subjects who received 13vPnC relative to subjects who received placebo, computed using the exact method based upon the total number of subjects diagnosed with first confirmed VT pneumococcal CAP.

The independent data monitoring committee conducted a planned interim analysis and reviewed 74 episodes of per-protocol confirmed VT pneumococcal CAP cases in September 2011. Predefined stopping criteria were not met, so the study continued until the accrual of at least 130 confirmed VT pneumococcal CAP episodes. Adjustment for 1 interim analysis was based upon an O'Brien-Fleming procedure, and the type 1 error rate at final analysis was adjusted to 0.0480 to ensure an experiment wise error rate of no more than 5%. After testing of the primary endpoint of first confirmed VT pneumococcal CAP at the final analysis, the overall hierarchical testing procedure of Glimm et al was applied to the testing of first confirmed NB/NI VT pneumococcal CAP using the O'Brien-Fleming procedure. First confirmed NB/NI VT pneumococcal CAP was tested at final analysis only if significant efficacy was demonstrated for first confirmed VT pneumococcal CAP. The vaccine was considered efficacious against each of these 2 endpoints if the 2-sided 95.2% CI of vaccine efficacy (VE) exceeded 0. VE against first episode of VT-IPD was assessed in a manner similar to that for the primary endpoint only once (at final analysis). The vaccine was considered efficacious against VT-IPD if the 2-sided 95% CI of VE exceeded 0. Sensitivity analyses of the primary and secondary endpoints were performed to evaluate the effect of missed SSUAD sample collection.

Multiplicity adjustment was performed using the Benjamini and Hochberg false discovery rate procedure with a type 1 error rate of 5%.

The safety population (all subjects who received study vaccine and had any safety data) was used for mortality analyses. The numbers of death from all causes, death from confirmed pneumococcal CAP or IPD, and death from confirmed VT pneumococcal CAP or VT-IPD were summarized by vaccine group, and the time to death for each vaccine group was displayed using Kaplan-Meier methodology and statistically analysed.

Subgroup analyses were performed for CAP and IPD efficacy endpoints that demonstrated a treatment difference. These subgroup efficacy analyses were based on immune status (immune-deficient/suppressed, immune competent), age at vaccination (<75 years, ≥75 years, ≥75 to <85 years, and ≥85 years), sex, race, and smoking status. Additionally, the proportion of subject deaths was summarized by the causes myocardial infarction, stroke, and influenza, and by age, sex, race, and smoking status.

Frequencies and percentages were calculated for categorical health outcomes data, and means and standard deviations were calculated for continuous data. Data for each health outcomes variable were descriptively summarized for each of the following categories:

- CAP episodes
- Confirmed pneumococcal CAP episodes
- Confirmed VT pneumococcal CAP episodes
- Confirmed NB/NI VT pneumococcal CAP episodes
- VT-IPD episodes
- Confirmed VT pneumococcal CAP and VT-IPD episodes

Results of the health outcomes analysis will be reported in a supplemental CSR.

Safety Analysis

All subjects who received study vaccine were included in the safety population. Subjects who lacked any safety data were excluded from the analysis.

The proportions of subjects in the immunogenicity subset reporting local reactions and systemic events on any day within the 7-day period after vaccination were summarized for each vaccine group. Local

reactions and systemic events were also summarized by age (subjects <75 years of age and ≥75 years of age), sex, and race groups. AEs were categorized according to MedDRA and summarized by vaccine group for subjects in the immunogenicity subset. All summaries show, by vaccine group, the number and percentage of subjects reporting at least 1 event and the number of events. Additional summaries by AE severity or by vaccine relationship were produced. AEs were also summarized by age (subjects <75 years of age and ≥75 years of age), sex, and race groups. SAEs were categorized according to MedDRA and summarized by vaccine group for all subjects. All summaries showed, by vaccine group, the number and percentage of subjects reporting at least 1 event and the number of events. Separate summaries were produced for different time frames. Subjects in the immunogenicity subset had their SAEs summarized for the 28-day reporting period and for the 6-month reporting period.

Causes of death were coded and categorized according to MedDRA and summarized by vaccine group for all subjects.

Statistics

As planned in the protocol, the per-protocol population was used for determination of VE. At the interim analysis, the Data Monitoring Committee evaluated VE against the primary endpoint (first episode of VT pneumococcal CAP). If clinically significant VE had been observed for the primary endpoint, the DMC was to evaluate the VE against the first secondary endpoint (first episode of NB/NI VT pneumococcal CAP). To account for the multiple assessments of these 2 endpoints, a statistical adjustment was made. The type 1 error rate was set at approximately 0.0052 at the interim analysis and approximately 0.0480 at the final analysis to ensure an experiment-wise error rate of no more than 5%. Thus, for these 2 endpoints, a 95.2% CI was used rather than a 95% CI at final analysis, and final statistical inference for these 2 endpoints was based on $p<0.048$, rather than on $p<0.05$.

Results

Recruitment and Participant flow

The number of subjects invited to participate in CAPiTA and the number who responded positively, negatively, or did not respond are provided in Table 2. No comparison of demographics can be made between respondents and invitees because only study participants consented to provide demographic information. Consent to provide personal data was not requested or received for the other invitees who did not participate in the trial.

Table 2

Table 7. Number of Subjects Invited to Participate in CAPiTA and Responses Received

	Totals
Invitations sent	561,989
Responders	481,898
"Yes" responses	135,742
"No" responses	346,156
Non responders	71,843
Showed	88,425
Vaccinated	84,496
Screen failures	3,090
Did not undergo screening	839

Table 8. Rate of Medical Conditions in Subjects Aged 65 Years and Older in the Netherlands[17] and Baseline Medical History in CAPiTA Participants

	Netherlands		Study 6115A1-3006 (CAPiTA)	
Periods[a]	2008	2009	Baseline[b]	
Total population	16,405,399	16,485,787	Total study population[d] (≥65 years)	84,492
Subjects ≥65 years	2,414,826	2,471,815		
	%	%		
Medical Conditions[c]			Baseline Medical History[e]	%
			Any medical history	42.3
Asthma, chronic bronchitis, COPD	11.3	11.8	Asthma	4.9
Diabetes type 1	2.2	1.8	Diabetes mellitus: Insulin use	3.2
Diabetes type 2	10.7	11.8	Diabetes mellitus: No insulin use	9.3
Heart condition	7.0	7.3	Heart disease	25.4
Myocardial infarction	8.2	10.5		
Hypertension	37.2	40.5		
			Liver disease	0.5
			Lung disease	10.2
			Splenectomy	<0.1
Smoking	16.2	15.0	Smoking	12.3

Note: the categories for CAPiTA are taken from Table 20 (Solicited Medical History by Category and Diagnosis Status - Safety Population) and Table 21 (Baseline Smoking Status - Safety Population) of the CSR.

a. 2008 and 2009 data reported here as these were the main recruiting years for CAPiTA

b. Baseline medical history was collected from CAPiTA subjects at study enrollment, from 15 September 2008 to 30 January 2010.

c. Not mutually exclusive. However reporting of heart condition, myocardial infarction and diabetes did not overlap

d. N = number of subjects vaccinated.

e. Abnormality, disease, or disorder. These diagnoses are as specified in the database. Not mutually exclusive.

Mortality rates in CAPiTA were similar in the placebo and the 13vPnC groups and were lower than national rates observed in the Netherlands in individuals 65 years and older. This result is not unanticipated because the study selected for immunocompetent subjects who did not reside in a nursing home, whereas the national population includes all elderly adults (i.e. does not exclude nursing home residents and individuals with immunocompromised conditions).

Subjects in the immunogenicity subset were enrolled from 15 September 2008 to 20 March 2009. Subjects not in the immunogenicity subset were enrolled in 2 phases: from 13 October to 28 November 2008 (26,490 subjects) and from 11 March 2009 to 30 January 2010 (55,995 subjects). Surveillance for CAP, IPD, death, loss to follow-up, and use of non-study pneumococcal vaccine continued until 28 August 2013. Data collection continued until 01 October 2013, the last day a study subject admitted to a sentinel centre during the surveillance period was discharged.

Table 14 summarizes the disposition of all subjects. Subjects who completed the study were those who were participating in the study (had not died, had not been lost to follow-up or had not withdrawn) at the end of the case acquisition period. The percentages of subjects who discontinued from the study and the reasons for discontinuation were well balanced between the 2 vaccine groups. The percentage of subjects who discontinued over the course of the study (12.5% over 4 years) was less than the 5% annual rate assumed in the sample size calculation.

The disposition of subjects per age group was similar in each age group, except that death rates were higher in the older age groups.

Table 3. Disposition of All Subjects

	Vaccine Group							
	Screened Only N[a]=3094		13vPnC N[a]=42240		Placebo N[a]=42256		Total N[a]=87590	
	n[b]	%	n[b]	%	n[b]	%	n[b]	%
Consented[c]	3094	100.0	42240	100.0	42256	100.0	87590	100.0
Randomized[d]	0	0.0	42240	100.0	42256	100.0	84496	96.5
Not randomized	3094	100.0	0	0.0	0	0.0	3094	3.5
Vaccinated	N/A		42240	100.0	42256	100.0	84496	100.0
Completed	N/A		37004	87.6	36936	87.4	73940	87.5
Discontinued	N/A		5236	12.4	5320	12.6	10556	12.5
Reasons for discontinuation								
Death	N/A		3006	7.1	3005	7.1	6011	7.1
Loss to follow-up	N/A		2038	4.8	2135	5.1	4173	4.9
Subject request	N/A		166	0.4	150	0.4	316	0.4
Investigator request	N/A		20	<0.1	23	<0.1	43	<0.1
Protocol violation	N/A		3	<0.1	5	<0.1	8	<0.1
Other	N/A		2	<0.1	2	<0.1	4	<0.1
Adverse event	N/A		1	<0.1	0	0.0	1	<0.1

Conduct of the study

Influenza vaccination

To facilitate study recruitment, it was originally planned that all subjects except those in the immunogenicity subset would receive commercially available TIV at the same visit as study vaccine. Subjects could, however, receive study vaccine even if TIV was not administered for nonmedical reasons at this visit. This plan was followed during the first phase of enrolment (October to November 2008: 26,490 subjects), but for logistical reasons TIV was not administered concomitantly with 13vPnC in the second phase of enrolment (March 2009 to January 2010: 55,995 subjects). Most of the subjects enrolled in the first phase of enrolment received TIV at Visit 1, accounting for 30.4% of the subjects in the trial. These rates were well balanced between the 2 vaccine groups. Investigators reported that for the years 2009 and 2010, a total of 3 subjects received TIV at Visit 1 although TIV was not provided to the enrolment sites during that time period. In the autumn and winter of 2009-2010 in response to the global H1N1 influenza epidemic, a vaccination campaign against H1N1 influenza was conducted using Focetria or Pandemrix with a 2-dose schedule in addition to routine vaccination with TIV.49. These new pandemic vaccines had not been evaluated for coadministration with 13vPnC. Thus, the sponsor advised the investigators that any study subjects who received one of these vaccines should not have it administered within 7 days before or after 13vPnC.

Baseline characteristics

The proportion of males in the study population (>55%) is higher than expected in a European population aged 65 and older, in which women are expected to be more numerous than men.

No definitive reason can be identified for the higher proportion of males than females enrolled in CAPiTA. The percentages of males and females who were invited to participate in CAPiTA, who responded "Yes" or "No," and who were randomised are provided in Table 4.

Table 4

Table 11. Percentages of Males and Females Invited to Participate in CAPiTA, Who Responded and Were Randomised[18]

Sex	Invited	Said "Yes"	Said "No"	Randomised
Male	44.6%	52.8%	40.7%	56.0%
Female	55.4%	47.2%	59.3%	44.0%

NOTE: percentages for pre-randomisation are from 2009-2010 (2008 figures not available).

Outcomes and estimation

Inclusion of Episodes

Table 5 shows the inclusion of episodes in the per-protocol case-level population for the primary efficacy endpoint (first confirmed VT pneumococcal CAP).

Table 5. Breakdown of First Confirmed VT Pneumococcal CAP Episodes –Per-Protocol Case-Level Population

Visit Classification	Vaccine Group 13vPnC N[a]=42240 n[b]	Placebo N[a]=42256 n[b]	Total N[a]=84496 n[b]
All visits for suspected pneumonia[c]	1541	1668	3209
Visits with onset at least 14 days after vaccination[c]	1528	1651	3179
Visits meeting clinical criteria[c]	1486	1623	3109
Visits meeting radiological criteria[c]	955	1021	1976
Visits meeting additional criteria[c,d]	1495	1620	3115
First visits of all CAP episodes (first visits that meet all above criteria)[c,e]	876	938	1814
All episodes of CAP[f]	876	938	1814
All episodes of confirmed pneumococcal CAP[g]	144	185	329
All episodes of VT confirmed pneumococcal CAP[h]	70	112	182
All episodes of VT confirmed pneumococcal CAP belonging to the per-protocol case-level population[i]	53	92	145
First episodes of VT confirmed pneumococcal CAP - per-protocol case-level population[j]	49	90	139

No explanation has been found in the documentation regarding the lower incidence rate of CAP as initially anticipated (the incidence was less than half of the anticipated).

Primary Endpoint: Prevention of a First Episode of Confirmed VT Pneumococcal CAP

Table 6 presents the analysis of efficacy of 13vPnC in prevention of a first episode of confirmed VT pneumococcal CAP in the per-protocol population. Statistically significant VE (45.56%) was demonstrated (p=0.0006), and the 95.2% LCI was 21.82%. These results met the protocol-defined criterion for demonstration of VE.

Table 6. Vaccine Efficacy for the Primary Efficacy Endpoint of First Episode of Confirmed VT Pneumococcal CAP – Per-Protocol Case-Level Population

		Vaccine Group				
		13vPnC N[a]=42240	Placebo N[a]=42256			
Efficacy Endpoint	Total Number of Episodes	n[b]	n[b]	VE (%)	(95.2% CI[c])	p-Value[d]
First case of confirmed VT pneumococcal CAP	139	49	90	45.56	(21.82, 62.49)	0.0006

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; SSUAD = serotype-specific urinary antigen detection; VE = vaccine efficacy; VT = vaccine-type.
Note: The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.
a. N = number of subjects who received the vaccine in the vaccine group.
b. n = Number of subjects who experienced a first episode of the specific event during the study.
c. Confidence intervals were derived using the Clopper-Pearson method. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis.
d. p-Value for the null hypothesis that VE=0.

The VE against confirmed VT pneumococcal CAP was statistically significant, and reduced the incidence by almost half. However, this is only a smaller proportion of all CAP cases.

Table 7 shows the results of subgroup analyses of the same endpoint by age at vaccination, sex, race, and smoking status. With the exception of the subgroup of subjects aged 85 years and older, fewer episodes occurred in the 13vPnC group than in the placebo group for every subgroup. The number of episodes (9) in this oldest age group is, however, too small to draw any conclusion from these data. This small number of episodes also introduced the potential for differences between the episodes in the 2 vaccine groups. For example, in this subgroup, ranges of age at vaccination differed (85.3 to 96.7 years in the 13vPnC group, 85.2 to 85.8 years in the placebo group. This study was neither controlled nor powered for subgroup comparisons, and only 3.5% of subjects enrolled were aged 85 years and older.

Table 7. Vaccine Efficacy for the Primary Efficacy Endpoint of First Case of Confirmed VT Pneumococcal CAP – Per-Protocol Case-Level Population

Efficacy Endpoint Subgroup	Total Number of Cases	Vaccine Group 13vPnC N[a]=42240 n[b]	Vaccine Group Placebo N[a]=42256 n[b]	VE (%)	(95.2% CI[c])	p-Value[d]
First case of confirmed VT pneumococcal CAP	139	49	90	45.56	(21.82, 62.49)	0.0006
Age <75	87	28	59			
Age ≥75	52	21	31			
Age ≥75 and <85	43	15	28			
Age ≥85	9	6	3			
Male	95	34	61			
Female	44	15	29			
Race: White	134	48	86			
Race: Nonwhite	5	1	4			
Smoking	32	12	20			
Nonsmoking	107	37	70			

Table 8 summarizes these results by serotype. This study was not powered to detect serotype-specific VE. All 13 VT serotypes, including the 7vPnC serotypes, were observed throughout the course of the study. A subject could contribute only 1 episode to the first table row (VT), corresponding to episodes in the primary endpoint. However, a subject could be reported in more than 1 category, by individual serotype. Two (2) serotypes were identified in 1 subject in the placebo group (serotypes 5 and 19A in Subject 204-603604). The most frequently identified serotypes were 1, 3, 7F, and 19A, and these serotypes accounted for the majority of events that contributed to the overall analysis. Post hoc analysis of these serotypes (not adjusted for multiplicity) showed that the VE for serotype 7F was statistically significant (77%; p=0.0015). The VEs for serotype 3 (VE=56%; p=0.0931) and serotype 19A (VE=56%; p=0.0755) approached statistical significance but did not achieve it. The VE for serotype 1 was not statistically significant (VE=18%; p=0.8238). Too few events were observed for the other serotypes to draw a statistical inference.

The study was not powered for demonstration of VE for individual serotypes, but the exploratory analysis shown below is of interest. It is reassuring that protection against e.g. serotype 3, which has shown poor immunogenicity in some studies, did not tend to be different than the overall VE. VE against serotype 1 is the most concerning, as there were almost as many cases in the vaccine group as in the placebo group, and the total number of cases was 20, which makes it one of the more common serotypes.

Table 8. Counts of First Episode of Confirmed VT Pneumococcal CAP by Individual Serotypes – Per-Protocol Case-Level Population

		Vaccine Group	
		13vPnC N[a]=42240	Placebo N[a]=42256
Serotype	Total Number of Episodes	n[b]	n[b]
VT	139	49	90
1	20	9	11
3	23	7	16
4	5	2	3
5	3	1	2
6A	9	5	4
6B	7	4	3
7F	27	5	22
9V	2	1	1
14	4	2	2
18C	9	4	5
19A	26	8	18
19F	2	0	2
23F	3	1	2

Abbreviations: CAP = community-acquired pneumonia; SSUAD = serotype-specific urinary antigen detection; VT = vaccine-type.
Note: Subjects can be reported in more than one serotype category. All serotypes identified by culture or SSUAD are included in the counts. The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.
a. N = number of subjects who received the vaccine in the vaccine group.
b. n = Number of cases associated with the given serotype.

Table 9 presents the analysis of efficacy of 13vPnC in prevention of a first episode of confirmed VT pneumococcal CAP in the mITT population and subgroup analysis by immune status. Statistically significant VE (37.74%) was demonstrated (p=0.0028), and the 95.2% LCI was 14.31%. Although there were a number of subject and episode characteristics that contributed to inclusion of an episode in the mITT population (such as an eligibility violation or residence in a long-term care facility for more than 48 hours immediately before symptom onset), the lower apparent VE in this population is likely caused by the distribution of episodes within the immune-deficient/suppressed subgroup, ie, more episodes in the 13vPnC group than in the placebo group. The immunedeficient/suppressed subgroup comprises subjects who at the time of symptom onset were immune-deficient/suppressed or were determined by the immune status committee to be immunosuppressed to the degree represented by this list of conditions. Of the 25 subjects in this subgroup, most had developed hematologic or generalized malignancies during the course of the study. The discrepancy between the total number of episodes (172) and the number of episodes in the 2 subgroups (169) is a result of immune status not being assessed for 3 subjects at the time of onset of symptoms for the episode.

Table 9. Vaccine Efficacy for the Primary Efficacy Endpoint of First Episode of Confirmed VT Pneumococcal CAP – Modified Intent-to-Treat Case-Level Population

		Vaccine Group				
		13vPnC N[a]=42240	Placebo N[a]=42256			
Efficacy Endpoint Subgroup	Total Number of Episodes	n[b]	n[b]	VE (%)	(95.2% CI[c])	p-Value[d]
First episode of confirmed VT pneumococcal CAP	172	66	106	37.74	(14.31, 55.05)	0.0028
Modified intent-to-treat immune-competent[e]	144	51	93			
Modified intent-to-treat immune-deficient/suppressed[e]	25	14	11			

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; SSUAD = serotype-specific urinary antigen detection; VE = vaccine efficacy; VT = vaccine-type.

Note: The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

a. N = number of subjects who received the vaccine in the vaccine group.

b. n = Number of subjects who experienced a first episode of the specific event during the study.

c. Confidence intervals were derived using the Clopper-Pearson method. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis.

d. p-Value for the null hypothesis that VE=0.

e. The discrepancy between the total number of episodes (172) and the number of episodes in the 2 subgroups (169) is a result of immune status not being assessed for 3 subjects at the time of onset of symptoms for the episode.

Secondary Endpoints

Prevention of a First Episode of Confirmed NB/NI VT Pneumococcal CAP

Table 10 presents the analysis of efficacy of 13vPnC in prevention of a first episode of confirmed NB/NI VT pneumococcal CAP in the per-protocol population. Statistically significant VE (45.00%) was demonstrated (p=0.0067), and the 95.2% LCI was 14.21%. These results met the protocol-defined criterion for demonstration of VE.

Table 10. Vaccine Efficacy for the Secondary Efficacy Endpoint of First Episode of Confirmed NB/NI VT Pneumococcal CAP – Per-Protocol Case-Level Population

		Vaccine Group				
		13vPnC N[a]=42240	Placebo N[a]=42256			
Efficacy Endpoint	Total Number of Episodes	n[b]	n[b]	VE (%)	(95.2% CI[c])	p-Value[d]
First episode of confirmed NB/NI VT pneumococcal CAP	93	33	60	45.00	(14.21, 65.31)	0.0067

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; NB/NI = nonbacteremic/ noninvasive; SSUAD = serotype-specific urinary antigen detection; VE = vaccine efficacy; VT = vaccine-type.

Note: The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

a. N = number of subjects who received the vaccine in the vaccine group.

b. n = Number of subjects who experienced a first episode of the specific event during the study.

c. Confidence intervals were derived using the Clopper-Pearson method. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis.

d. p-Value for the null hypothesis that VE=0.

The same subgroups analyses as for the primary endpoint were performed for this secondary endpoint, and the results were in agreement with those for the primary endpoint. Likewise the results by serotype were in agreement with those for the primary endpoint.

Prevention of a First Episode of VT-IPD

Table 11 presents the analysis of efficacy of 13vPnC in prevention of a first episode of VT-IPD in the per-protocol population. Statistically significant VE was demonstrated (p=0.0005), and the 95% LCI was 41.43%. These results met the protocol-defined criterion for demonstration of VE. The VE for VT-IPD (75.00%) was higher than the VEs for VT pneumococcal CAP (45.56%) and NB/NI VT pneumococcal CAP (45.00%).

Table 11. Vaccine Efficacy for the Secondary Efficacy Endpoint of First Episode of VT-IPD – Per-Protocol Case-Level Population

		Vaccine Group				
		13vPnC N[a]=42240	Placebo N[a]=42256			
Efficacy Endpoint	Total Number of Episodes	n[b]	n[b]	VE (%)	(95% CI[c])	p-Value[d]
First episode of VT-IPD	35	7	28	75.00	(41.43, 90.78)	0.0005

Abbreviations: CI = confidence interval; IPD = invasive pneumococcal disease; SSUAD = serotype-specific urinary antigen detection; VE = vaccine efficacy; VT = vaccine-type.

Note: The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

a. N = number of subjects who received the vaccine in the vaccine group.

b. n = Number of subjects who experienced a first episode of the specific event during the study.

c. Confidence intervals were derived using the Clopper-Pearson method. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis.

d. p-Value for the null hypothesis that VE=0.

Table 12 summarizes these results by serotype. For 1 subject in the placebo group (Subject 081-489511), S pneumoniae was detected by culture, but the serotype for the episode was derived from the SSUAD assay because no viable isolate was available for serotyping (Listing 16.4.3). All VT serotypes except 23F were observed, and for all serotypes except serotype 14, there were more episodes in the placebo group than in the 13vPnC group. This study was not powered to detect serotype-specific VE. Too few events were observed to draw any statistical inference for serotype-specific comparisons of VE for this secondary endpoint.

Table 12. Counts of First Episode of VT-IPD by Individual Serotypes – Per-Protocol Case-Level Population

		Vaccine Group	
		13vPnC N[a]=42240	Placebo N[a]=42256
Serotype	Total Number of Cases	n[b]	n[b]
VT	35	7	28
1	6	1	5
3	5	1	4
4	3	1	2
5	1	0	1
6A	2	0	2
6B	2	0	2
7F	8	1	7
9V	1	0	1
14	2	2	0
18C	1	0	1
19A	3	1	2
19F	1	0	1

Abbreviations: IPD = invasive pneumococcal disease; SSUAD = serotype-specific urinary antigen detection; VT = vaccine-type.

Note: Subjects can be reported in more than one serotype category. All serotypes identified by culture or SSUAD are included in the counts. The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

a. N = number of subjects who received the vaccine in the vaccine group.

b. n = Number of cases associated with the given serotype.

The results by serotype were generally in agreement with the primary endpoint. Although the study was not powered for analysis of individual serotypes, there is nothing that causes concern in the above results.

Cumulative Number of Episodes by Vaccine Group

Figure 3, Figure 4, and Figure 5 show the cumulative number of episodes plotted against the time from vaccination by vaccine group for the primary and secondary endpoints in the per-protocol population. These post hoc analyses were conducted after unblinding of the study and review of interim and final analysis efficacy tables. In Figure 7 (confirmed VT pneumococcal CAP), the latest episode in the 13vPnC group occurred 1679 days (4.6 years) after vaccination; 2 episodes in the 13vPnC group occurred 4 or more years after vaccination.

The latest episode in the placebo group occurred 1690 days (4.6 years) after vaccination; 6 episodes in the placebo group occurred 4 or more years after vaccination. In Figure 8 (confirmed NB/NI VT pneumococcal CAP), the latest episode in the 13vPnC group occurred 1250 days (3.4 years) after vaccination; no episodes in the 13vPnC group occurred 4 or more years after vaccination. The latest episode in the placebo group occurred 1690 days (4.6 years) after vaccination; 5 episodes in the

placebo group occurred 4 or more years after vaccination. In Figure 9 (VT-IPD), the latest episode in the 13vPnC group occurred 1202 days (3.3 years) after vaccination; no episodes in the 13vPnC group occurred 4 or more years after vaccination. The latest episode in the placebo group occurred 1504 days (4.1 years) after vaccination; a total of 2 episodes in the placebo group occurred 4 or more years after vaccination. Differences were clearly evident between the 13vPnC group and the placebo group in accumulation of episodes for the primary and secondary endpoints and provide evidence of efficacy beginning shortly after vaccination and persistence of efficacy throughout the duration of the trial (mean follow-up time per subject was 3.97 years).

Figure 3- Cumulative Distribution of First Episodes of Confirmed VT Pneumococcal CAP Versus Time Since Vaccination – Per Protocol Case-Level Population (Post Hoc Analysis)

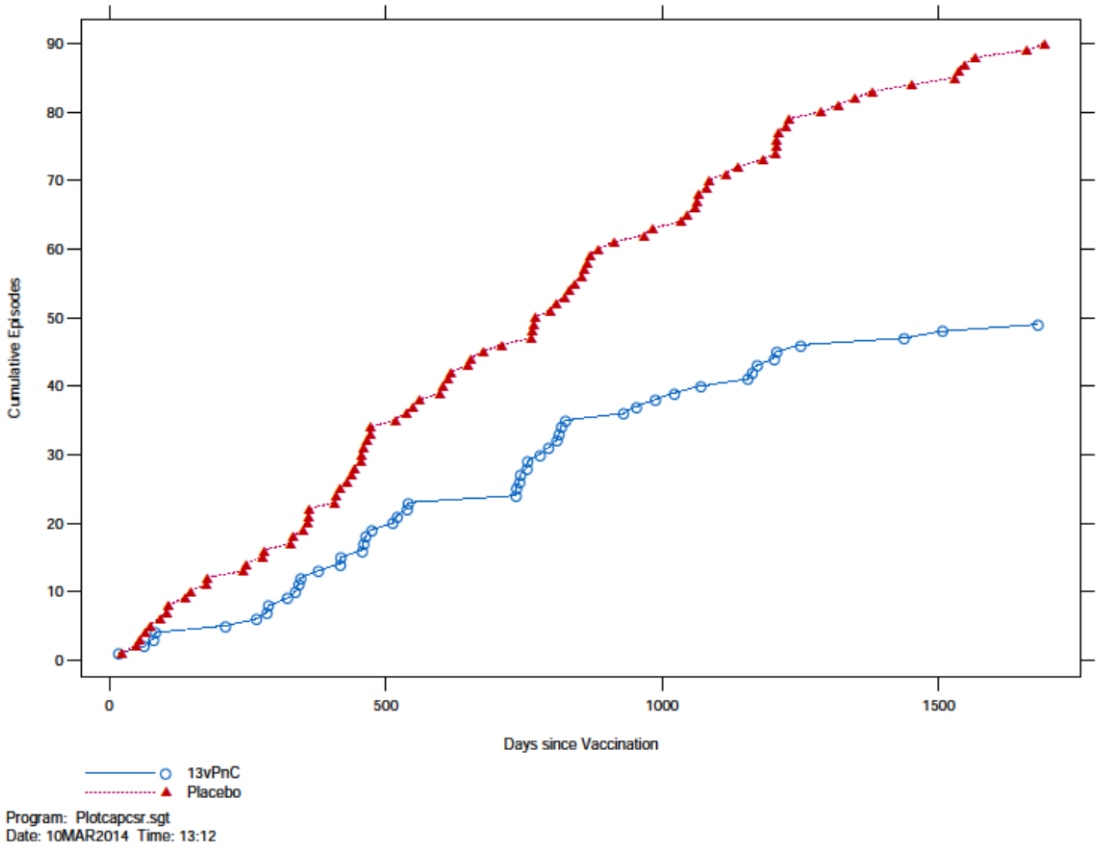


Figure 4. Cumulative Distribution of First Episodes of Confirmed NB/NI VT Pneumococcal CAP Versus Time Since Vaccination – Per-Protocol Case-Level Population (Post Hoc Analysis)

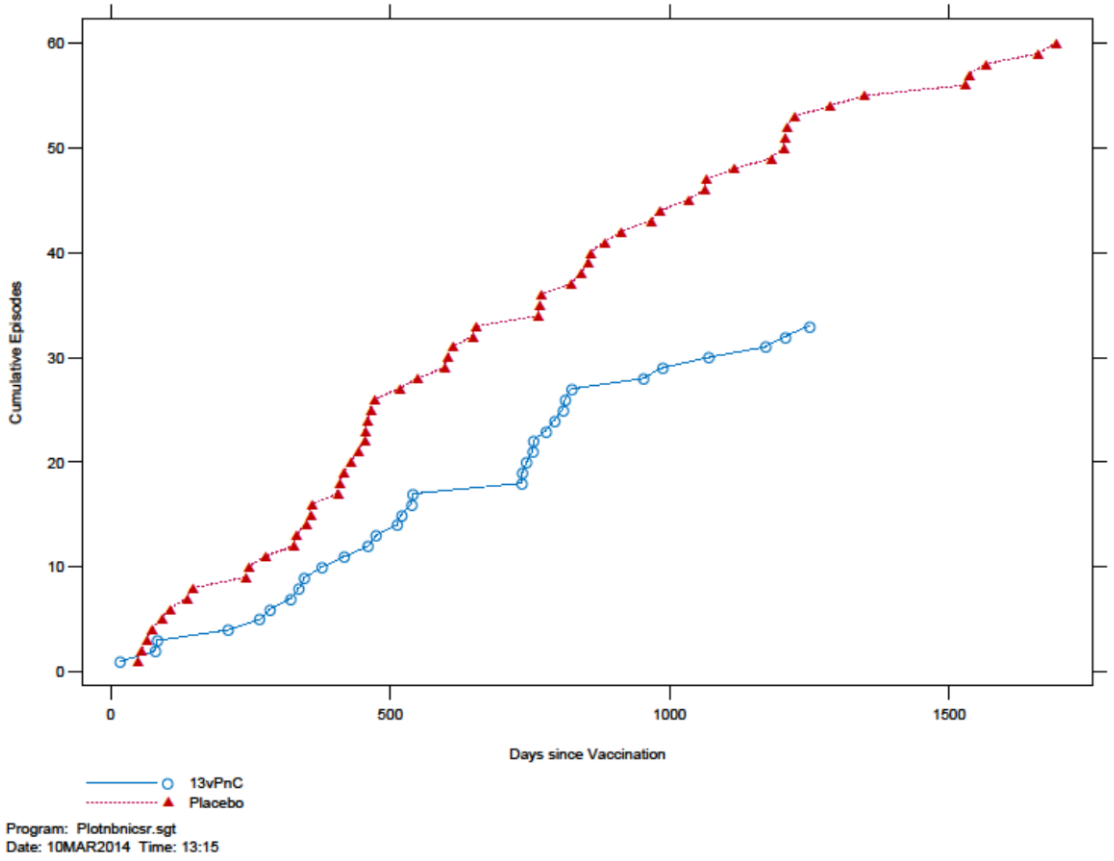
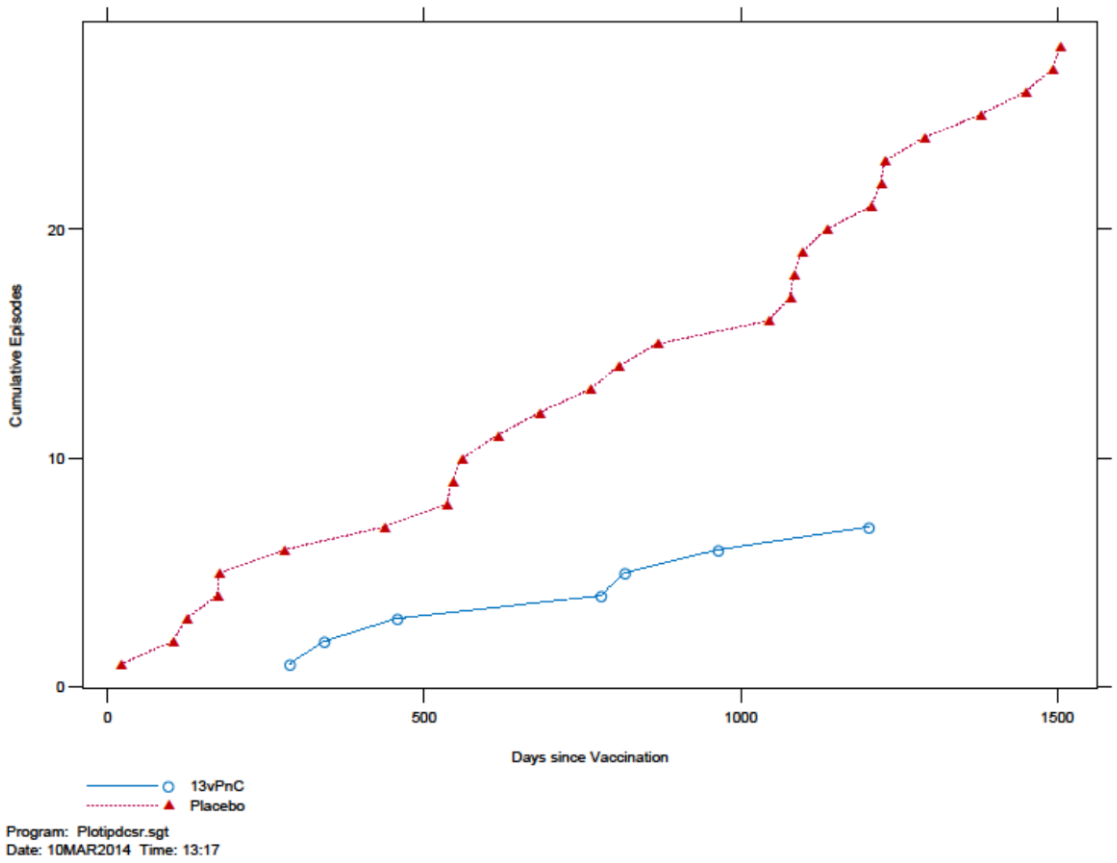


Figure 5. Cumulative Distribution of First Episodes of VT-IPD Versus Time Since Vaccination – Per-Protocol Case-Level Population (Post Hoc Analysis)



The cumulative distribution curves do not indicate any waning efficacy during the follow-up period.

Ancillary analyses

Exploratory Endpoints – Per Protocol and mITT Populations

The exploratory endpoints addressed in this submission are provided in Table 13. In the per protocol population, VE was statistically significant for the prevention of all episodes of confirmed VT pneumococcal CAP (42.39%, adjusted p = 0.0039) when adjusted for multiple comparisons. VE for the prevention of a first episode of confirmed pneumococcal CAP and first episode of IPD (including episodes caused by VT and NVT serotypes) was also statistically significant (30.56%, adjusted p = 0.0077, and 51.79%, adjusted p = 0.0039, respectively). For a first episode of NB/NI pneumococcal CAP, VE (24.14%, adjusted p=0.1056) approached statistical significance.

Results for these same endpoints in the mITT population, which included subjects who became immune-deficient/suppressed after vaccination over the course of the study, were not notably different than those in the per protocol population. No statistically significant VE was observed in the mITT population for the first episode of CAP, an endpoint that is predominantly composed of non-pneumococcal CAP. The 5.08% VE against first episodes of all-cause CAP observed in this study was consistent with a 46% reduction in VT pneumococcal CAP, as approximately 13% of the first CAP episodes observed in subjects in the placebo group (787 episodes) were episodes of confirmed VT pneumococcal CAP (106 episodes).

No difference was observed between the 2 vaccine groups for VE in the prevention of death from all causes or from pneumococcal-related causes. The number of deaths associated with pneumococcal disease during this study was small (4 deaths from VT pneumococcal disease and 13 deaths from all pneumococcal disease among 6011 deaths that occurred during the study). The study was not powered to detect a difference between the 2 vaccine groups for these endpoints, and the number of deaths that occurred was too small to draw a statistical inference.

Table 13. Vaccine Efficacy for Selected Exploratory Efficacy Endpoints

	Total Number of Episodes or Deaths	13vPnC N[a]=42240	Placebo N[a]=42256				
Exploratory Endpoint		**n[b]**	**n[b]**	**VE (%)**	**(95% CI[c])**	**p-Value[d]**	**p-Value[e]**
Per-protocol case-level population							
All episodes of confirmed VT pneumococcal CAP[f]	145	53	92	42.39	(18.36, 59.71)	0.0015	0.0039
First episode of confirmed pneumococcal CAP[f]	244	100	144	30.56	(9.75, 46.74)	0.0058	0.0077
First episode of confirmed NB/NI pneumococcal CAP[f]	153	66	87	24.14	(-5.68, 45.76)	0.1056	0.1056
First episode of IPD	83	27	56	51.79	(22.38, 70.72)	0.0019	0.0039
Modified intent-to-treat case-level population							
All episodes of confirmed VT pneumococcal CAP[f]	182	70	112	37.50	(15.00, 54.31)	0.0023	0.0057
First episode of confirmed pneumococcal CAP[f]	309	135	174	22.41	(2.29, 38.50)	0.0305	0.0508
First episode of confirmed NB/NI pneumococcal CAP[f]	199	90	109	17.43	(-10.17, 38.25)	0.2018	0.2523
First episode of CAP	1534	747	787	5.08	(-5.05, 14.24)	0.3194	0.3194
First episode of IPD	100	34	66	48.48	(20.94, 66.98)	0.0018	0.0057
Safety population							
Death from confirmed VT pneumococcal CAP or VT-IPD[f,g]	4	2	2	0.00	(-1279.60, 92.75)	>.999	>.999
Death from confirmed pneumococcal CAP or IPD[f,g]	13	6	7	14.29	(-197.86, 76.20)	>.999	>.999
Death from all causes	6011	3006	3005	-0.03	(-5.26, 4.93)	>.999	>.999

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; IPD = invasive pneumococcal disease; NB/NI = nonbacteremic/noninvasive; SSUAD = serotype-specific urinary antigen detection; VE = vaccine efficacy; VT = vaccine-type.

a. N = number of subjects who received the vaccine in the vaccine group.

b. n = Number of episodes or deaths. Some subjects may have experienced more than one episode.

c. Confidence intervals were derived using the Clopper-Pearson method.

d. p-Value for the null hypothesis that VE=0.

e. p-Value for the null hypothesis that VE=0, adjusted for multiplicity using the Benjamini and Hochberg false discovery rate procedure within each population group.

f. The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

g. Number of deaths for which the Mortality Assessment Committee assessed that the death was due to CAP or IPD and for which there was an episode detected by the sentinel system with resolution date within 7 days before death. These deaths are related to CAP and IPD episodes that are members of the per-protocol case-level population.

Summary of main study

Table 14 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14. Summary of Efficacy for CAPiTA trial

Title: A Phase 4, Randomized, Placebo-controlled Clinical Trial of 13-valent pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease		
Study identifier	6115A1-3006 (B1851025)	
Design	Phase 4, parallel-group, randomized, placebo-controlled, double-blind, event-driven, single-centre trial.	
	Duration of main phase:	Recruitment was 17 months (September 2008 to end January 2010)
	Duration of run-in phase:	Surveillance for community acquired pneumonia (CAP) and invasive pneumococcal disease (IPD) was from the beginning of recruitment (September 2008) to end of collection of primary endpoint episodes (August 2013)
	Duration of extension phase:	not applicable
Hypothesis	Efficacy superiority vs placebo	
Treatment groups	Prevenar 13	Single vaccination of 13vPnC 42,240 randomised
	Placebo	Single vaccination of Placebo (5mM succinate buffer, 0.15M sodium chloride, 0.02% polysorbate 80 and 0.125 mg aluminium as aluminium phosphate per 0.5mL dose) 42,256 randomised

Endpoints and definitions	Primary Endpoint	Efficacy of 13vPnC in preventing a 1st episode of confirmed vaccine-type pneumococcal CAP.(VT-CAP)	Events for a first episode of VT-CAP was defined as immunocompetent subjects presenting with signs and symptoms of pneumonia at identified sentinel hospitals; having 2 or more of the protocol defined clinical criteria; were chest X-ray confirmed for CAP; and had microbiological confirmation of vaccine type *Streptococcus pneumonia* identified by sterile culture, or by serotype specific urinary antigen detection test. All chest X-rays were reviewed by an Adjudication committee of four experienced radiologists who determined if the chest X-rays were consistent with CAP. All episodes meeting the criteria of sufficient clinical criteria, chest x-rays consistent with CAP and having microbiological *S.pneumonia* identified, were reviewed by a committee of four experienced clinical immunologists (Immune Status Committee) to determine if subjects were immunocompetent at the time of the CAP episode. Vaccine type was determined by serotyping sterile cultures, and from serotype specific urinary antigen detection assays. At least 130 per-protocol events were required for final analysis.
	Secondary Endpoints	Efficacy of 13vPnC in preventing a 1st episode of confirmed non-bacteremic/ noninvasive vaccine type pneumococcal CAP. (NB/NI VT-CAP)	Same criteria and committee's as for the primary endpoint, except the microbiological confirmation was: blood culture was taken and was negative for *S.pneumoniae*; all other sterile culture results, if taken were also negative for *S.pneumoniae*. Vaccine type was determined by serotype specific urinary detection test.

		Efficacy of 13vPnC in preventing a 1st episode of vaccine type -IPD. (VT-IPD)	The definition of IPD is *S.pneumoniae* identified from a sterile site which includes blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone or joint fluid. To meet this endpoint, episodes must have a vaccine type serotype present, and subjects must be immunocompetent as determined by the Immune Status Committee. Vaccine type was determined by serotyping sterile cultures.
	Safety endpoint	Incidence rates of serious adverse events. Rates of death from all causes for all subjects.	Serious adverse events were collected for 28 days post vaccination in all subjects post vaccination; and for 6 months post vaccination in a sub-set of subjects (2,011 subjects). Death data was collected from time of vaccination until all endpoint data had been collected (end August 2013). Cause of death was determined by a committee of physicians (Mortality Assessment Committee).
Database lock	17 January 2014		

Results and analysis

Analysis description	**Primary analysis: Per protocol population analysis**		
Analysis population and time point description	Modified intent to treat (mITT) analysis included all subjects who had an episode of CAP. This was further categorised into immune competent and immune suppressed pneumococcal CAP or IPD. Per protocol analysis are those episodes that satisfied the mITT analysis population criteria as well as being immunocompetent. In addition subjects should have met the following criteria: was eligible for the study; received the study vaccine; was 65 years or older on the date of vaccination no major protocol violations; did not receive any other pneumococcal vaccine during the course of the study; was not hospitalized or in a nursing home for more than 48 hours prior to symptom onset; and did not have any of the protocol defined excluding diagnoses. The safety population included all subjects who received study vaccine and did not lack safety data.		
Descriptive statistics and estimate variability	Treatment group	13vPnC	Placebo
	Number of subjects	44,240	42,256

	Primary endpoint: First Episode confirmed VT pneumococcal CAP	49	90
	Secondary endpoint: First episode confirmed pneumococcal NB/NI VT-CAP	33	60
	Secondary endpoint: First episode VT-IPD	7	28

Effect estimate per comparison	Primary endpoint: First Episode confirmed VT pneumococcal CAP	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	45.56%
		95.2% Confidence Interval (CI) [1]	21.82% – 62.49%
		P-value[2]	0.0006
	Secondary endpoint: First episode confirmed pneumococcal NB/NI VT-CAP	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	45%
		95.2% Confidence Interval (CI) [1]	14.21% – 65.31%
		P-value[2]	0.0067
	Secondary endpoint: First episode VT-IPD	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	75%
		95% Confidence Interval (CI) [1]	41.43% – 90.78%
		P-value[2]	0.0005
Notes	1. Confidence intervals were derived using the Clopper-Pearson method with adjustment for one interim analysis. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis 2. p-Value for the null hypothesis that VE=0.		
Analysis description	**Secondary analysis: modified intent to treat population analysis (mITT)**		

Analysis population and time point description	Modified intent to treat (mITT) analysis included all subjects who had an episode of CAP. This was further categorised into immune competent and immune suppressed pneumococcal CAP or IPD.		
Descriptive statistics and estimate variability	Treatment group	13vPnC	Placebo
	Number of subjects	44,240	42,256
	Primary endpoint: First Episode confirmed VT pneumococcal CAP mITT	66	106
	Secondary endpoint: First episode confirmed pneumococcal NB/NI VT-CAP mITT	43	73
	Secondary endpoint: First episode VT-IPD	8	33
Effect estimate per comparison	Primary endpoint: First Episode confirmed VT pneumococcal CAP mITT	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	37.74%
		95.2% Confidence Interval (CI) [3]	14.31% – 55.05%
		P-value[4]	0.0028
	Secondary endpoint: First episode confirmed pneumococcal NB/NI VT-CAP mITT	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	41.1%
		95.2% Confidence Interval (CI) [3]	12.7% – 60.7%
		P-value[4]	0.0068
	Secondary endpoint: First episode VT-IPD mITT	Comparison groups	Efficacy of 13vPnC compared to placebo
		Vaccine Efficacy (VE)	75.76%
		95% Confidence Interval (CI) [3]	46.47% – 90.33%
		P-value[4]	0.0001

Notes	3. Confidence intervals were derived using the Clopper-Pearson method with adjustment for one interim analysis. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this final analysis 4. p-Value for the null hypothesis that VE=0.

2.2.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The CAPiTA study is a parallel-group, randomized, placebo-controlled, double-blind, single-centre trial to evaluate the efficacy of 13vPnC in the prevention of first episodes of vaccine type pneumococcal community acquired pneumonia (CAP), first episodes of non-bacteremic/non-invasive VT pneumococcal CAP, and first episodes of VT invasive pneumococcal disease in approximately 85,000 subjects aged 65 years and older who had not previously received 23-valent pneumococcal polysaccharide vaccine (23vPS).

The study was appropriately designed, although some questions remained on the recruitment of participants. According to data provided, 25% (135,742/561,989) of invitees accepted to participate into the study and 16% (88,425/561,989) participated into the study. Although those proportions are not unexpected in large studies in population such as the CAPiTA study, variations from the source population should be carefully analysed before drawing conclusions on the study results. For example, a lower proportion of persons reported smoking habits in the CAPiTA population but the proportion of asthma and lung disease (grouped) is slightly superior. The lower mortality rate is indicative of a population in better health condition. Also, more men than women aged 65 and older participated, which confirms a likely biased selection of study subjects. As such, SmPC section 5.1 clarifies that the CAPITA study enrolled volunteers > 65 years of age whose demographic and health characteristics may differ from the population of the same age visiting general practitioners.

No explanation has been found in the documentation regarding the lower incidence rate of CAP as initially anticipated. The question of an effect of the herd immunity remains uncertain. Although the MAH demonstrated that vaccine-type pneumococcal pneumonia was still observed in the placebo group, those data are not conclusive in the absence of comparison to data from a similar population non-exposed to the herd effect. However, the proportion of VT-CAP compared to all-CAP is the same for estimated rates and observed rates, which could be an argument against a herd effect (assuming that this proportion would decrease in case of a herd effect).

Efficacy data and additional analyses

The primary endpoint was first episode of VT pneumococcal CAP, and a statistically significant protection was demonstrated (46%, 95% CI: 22; 62%). Further subgroup analyses support this result, e.g. by age group. Because of the low number of subjects aged > 85 years in the CAPiTA study, no conclusion can be drawn regarding efficacy in very old subjects. An appropriate warning is advised in SmPC section 5.1 on insufficient data for Prevenar 13 in adults > 85 years based on the very low number of VT pneumococcal CAP cases in this age group (6 in the Prevenar 16 group, 3 in the placebo group). In addition the results per serotype were also reassuring, and no specific serotype seems to be concerning although there were few cases of some serotypes. The study was not powered to

demonstrate efficacy against each individual serotype. It was also reassuring that there was no evident waning of protection throughout the course of the study.

The efficacy against any pneumococcal CAP was as expectedly lower than protection against VT pneumococcal CAP, 31% in the PP population, and 22% in the mITT population, but statistically significant.

Efficacy against IPD was higher compared to protection against CAP, which is expected in analogy with what has been demonstrated in children.

However, the first episode of VT pneumococcal CAP constitutes only a minor proportion of all CAP episodes. In an exploratory analysis of efficacy against any first episode of CAP there is very low efficacy (5%, non-significant). In addition, there is no effect on overall mortality, or even on death related to VT pneumococcal CAP or IPD. In contrast, the effect on any episode on IPD is reassuring (52% and 48% in PP and mITT populations respectively).

2.2.3. Conclusions on the clinical efficacy

The sought indication includes all adults, although the study only included subjects 65 years and older. The extrapolation to all adults is acceptable, considering that younger adults are more likely to respond with sufficient antibody levels compared to elderly, and it is therefore highly likely that the protection would be of a similar or of higher magnitude. The incidence of pneumonia is lower in younger healthy adults, and as a consequence the absolute benefit of vaccinating younger adults is smaller, but may still be meaningful.

Appropriate text has been added to the SmPC section 5.1, stating limitations of the study.

2.3. Clinical safety

2.3.1. Introduction

For all subjects, information regarding deaths was to be collected throughout the case acquisition period. In addition, serious adverse events (SAEs) that occurred within 28 days after study vaccine administration were to be reported.

Additional safety information was collected for subjects in the immunogenicity subset, including:

- Local reactions and systemic events occurring within 7 days after vaccination (monitored and recorded by subjects in electronic diaries);
- All adverse events (AEs) occurring within 28 days after vaccination;
- SAEs occurring within 6 months after vaccination.

Patient exposure

Data were summarised for all subjects who received study vaccine and had any safety data (ie, safety population: 42,237 subjects in the 13vPnC group; 42,255 subjects in the placebo group). The immunogenicity subset comprised 1006 subjects who received 13vPnC and 1005 subjects who received placebo.

Adverse events

Local Reactions Within 7 Days (Immunogenicity Subset Only)

Local reactions occurring within 7 days after vaccination were reported more frequently in the 13vPnC group than in the placebo group, respectively: redness (4.9%, 1.2%); swelling (6.8%, 1.2%); pain (36.1%, 6.1%); limitation of arm movement (14.1%, 3.2%). For all 4 types of local reactions, the difference in incidence between the vaccine groups was statistically significant ($p<0.001$). In addition, for each type of local reaction, mild and moderate local reactions were statistically significantly more frequent in the 13vPnC group than in the placebo group ($p<0.05$), whereas there were no statistically significant differences between the groups in the frequency of severe reactions.

The proportion of subjects reporting local reactions was summarised by age (≥75 years of age and <75 years of age), sex, and race subgroups. The pattern of local reactions in these subgroups was consistent with that of the overall analysis.

Systemic Events Within 7 Days (Immunogenicity Subset Only)

Pre-specified systemic events included fever (temperature ≥38.0°C), diarrhea, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalised muscle pain, aggravated generalised muscle pain, new generalised joint pain, and aggravated generalised joint pain. The use of medications to treat fever and the use of medications to treat pain were also recorded in response to e-diary prompts.

Among subjects who received 13vPnC, the most frequently reported systemic events were fatigue (18.8%), new generalised muscle pain (18.4%), and headache (15.9%); all other types of systemic events were reported by <10% of subjects in the 13vPnC group. The frequencies of fever, fatigue, rash, new generalised muscle pain, aggravated generalised muscle pain, and use of medication to treat fever were statistically significantly higher in the 13vPnC group than in the placebo group, while the frequency of diarrhoea was statistically significantly higher in the placebo group than in the 13vPnC group. The differences between the 13vPnC and placebo groups in the frequency of severe events were not statistically significant for any of the systemic events.

The frequency of fever (any temperature ≥38.0°C) was low: 2.9% in the 13vPnC group and 1.3% in the placebo group. Most reports of fever were mild or moderate (ie, <39°C), and there were no confirmed reports of fever >40°C.

When the proportion of subjects reporting systemic events was summarised by age (≥75 years and <75 years), sex, and race subgroups, the pattern of systemic events in the subgroups was consistent with that of the overall analysis.

Overall, the pattern of results for systemic events was consistent with the acceptable safety profile observed in previous studies of 13vPnC in adults.

Adverse Events Within 28 Days (Immunogenicity Subset Only)

Among subjects in the immunogenicity subset, adverse events occurring within 28 days (1 month) after vaccination were reported for 18.7% of subjects who received 13vPnC and for 14.3% of subjects receiving placebo ($p=0.010$). The difference in the incidence of AEs between the vaccine groups appears to be accounted for by a higher incidence of injection site reactions and muscular pain in the 13vPnC group than in the placebo group.

Statistically significant differences in incidence between the 2 vaccine groups were observed for the general disorders and administration site conditions SOC (5.9% of subjects vaccinated with 13vPnC and 1.4% of subjects receiving placebo, $p<0.001$) as well as for 4 PTs within this SOC, which represented injection site reactions (erythema, pain, pruritus, and swelling). The frequency of AEs in

the musculoskeletal and connective tissue disorders SOC was also statistically significantly higher in the 13vPnC group (2.7%) than in the placebo group (1.3%) (p=0.037), although the difference in incidence between the groups did not reach significance for any of the PTs within this SOC, most of which represented types of muscular pain.

AEs reported within 1 month after vaccination were summarised by age (≥75 years and <75 years), sex, and race subgroups. The pattern of AEs in these subgroups was consistent with the overall analysis.

Newly Diagnosed Medical Conditions Within 6 Months (Immunogenicity Subset Only)

Newly diagnosed chronic medical conditions (including autoimmune or neuroinflammatory disease) were to be reported from 1 month after vaccination to 6 months after vaccination for subjects in the immunogenicity subset only. No statistically significant differences were observed between the 2 vaccine groups.

Serious adverse event / deaths / other significant events

Deaths (All Subjects – Safety Population)

A total of 6011 subjects died during the case acquisition period: 3006 (7.1%) in the 13vPnC group and 3005 (7.1%) in the placebo group. There were no statistically significant differences between the 2 groups in the incidence of primary cause of death by SOC, and no single MedDRA PT for cause of death was reported in ≥1% of subjects in either vaccine group. The most frequent causes of death (by SOC) in the 13vPnC and placebo groups, respectively, were neoplasms (2.9% and 2.8%) and cardiac disorders (1.4% and 1.3%).

All deaths recorded throughout the study were also summarised by age (≥75 years and <75 years), sex, and race subgroups for all subjects. The pattern of all deaths in the subgroups was consistent with the overall analysis.

In addition, deaths occurring within 28 days after vaccination were summarised for all subjects. Deaths occurring within 28 days after vaccination were reported for 10 subjects (<0.1%) in each vaccine group. No statistically significant (p<0.05) differences were observed between the 2 vaccine groups.

Table 15

7.21 Deaths Within 28 Days After Vaccination by System Organ Class – Safety Population (Post-Hoc Analysis)

	Vaccine Group				
	13vPnC N[a]=42237		Placebo N[a]=42255		
System Organ Class \ Preferred Term	No. of Subjects	%	No. of Subjects	%	p-Value[b]
All deaths	10	<0.1	10	<0.1	>.99
Cardiac disorders	4	<0.1	3	<0.1	0.726
Acute myocardial infarction	2	<0.1	1	<0.1	0.625
Cardiac arrest	1	<0.1	2	<0.1	>.99
Cardiac failure	1	<0.1	0	0.0	0.500
General disorders and administration site conditions	2	<0.1	1	<0.1	0.625
Death	0	0.0	1	<0.1	>.99
Sudden cardiac death	2	<0.1	0	0.0	0.250
Infections and infestations	1	<0.1	0	0.0	0.500
Pneumonia bacterial	1	<0.1	0	0.0	0.500
Injury, poisoning and procedural complications	1	<0.1	2	<0.1	>.99
Foreign body aspiration	1	<0.1	0	0.0	0.500
Road traffic accident	0	0.0	1	<0.1	>.99
Subdural haematoma	0	0.0	1	<0.1	>.99
Nervous system disorders	1	<0.1	3	<0.1	0.625
Cerebral haemorrhage	0	0.0	1	<0.1	>.99
Cerebral infarction	1	<0.1	0	0.0	0.500
Subarachnoid haemorrhage	0	0.0	1	<0.1	>.99
Thrombotic cerebral infarction	0	0.0	1	<0.1	>.99
Vascular disorders	1	<0.1	1	<0.1	>.99
Aortic aneurysm	0	0.0	1	<0.1	>.99
Aortic aneurysm rupture	1	<0.1	0	0.0	0.500

Note: The Mortality Assessment Committee reviewed available documents from each death that occurred in the case acquisition period to determine a primary cause of death. Primary cause of death was categorized according to MedDRA. The timeframe within 28 days after vaccination includes the day of vaccination as Day 1, through and including Day 28.

a. N = number of subjects who received the vaccine.

b. Fisher exact test, 2-sided, used to calculate the p-value for the difference between vaccine groups in percentages of subjects reporting an event.

Program ID: Study 6115A1-3006-WW-NL/CP SAF_DEATH_SOC_POSTHOC.SAS. Runtime ID: 16MAY2014 17:14

Other Serious Adverse Events

Serious adverse events (SAEs) were to be reported through Day 29 for all subjects, and through 6 months after vaccination for subjects in the immunogenicity subset.

SAEs Within 6 Months (Immunogenicity Subset Only – Safety Population)

In the immunogenicity subset, within 6 months after vaccination, a total of 90 SAEs were reported for 70 subjects (7.0%) in the 13vPnC group, and 69 SAEs were reported for 60 subjects (6.0%) in the placebo group. None of these SAEs were considered related to study vaccine.

The most frequently reported types of SAEs (by SOC) in the 13vPnC group were cardiac disorders (1.8%) and infections and infestations (1.1%), while the most frequently reported types of SAEs in the placebo group were musculoskeletal and connective tissue disorders (1.5%) and neoplasms (1.3%). No SAE (by MedDRA PT) occurred in ≥1% of subjects in either vaccine group.

The only statistically significant differences between the 2 vaccine groups in the incidence of SAEs by SOC or by PT were observed for osteoarthritis and prostate cancer, which were reported more frequently in the placebo group than in the 13vPnC group. Statistical significance was approached for the difference between the 2 vaccine groups in the cardiac disorders SOC (18 subjects in the 13vPnC group and 8 subjects in the placebo group; p=0.074). The most common events in this SOC were angina pectoris (5 subjects in the 13vPnC group and 2 subjects in the placebo group), atrial fibrillation (4 subjects in the 13vPnC group and 1 subject in the placebo group), and cardiac failure (4 subjects in the 13vPnC group). The excess of reports among subjects in the 13vPnC group occurred more than 2 months after vaccination and did not exhibit temporal clustering after vaccination. No cardiac event occurred within 2 days after vaccination in either vaccine group. The events that occurred closest to vaccination were cardiac asthma on Day 4 in a subject in the placebo group, and cardiac failure on Day 5 in a subject in the 13vPnC group. Within the first 4 weeks after vaccination, there were 2 additional events in the 13vPnC group: atrial fibrillation and angina pectoris. All of these subjects had significant pre-existing cardiovascular conditions, and none of these events resulted in death. During Weeks 5 through 8, there were 6 additional events reported in the placebo group, and 1 in the 13vPnC group. The remaining events after Week 8 occurred predominantly in the 13vPnC group between Day 86 and Day 182, but there was no temporal clustering.

SAEs Within 28 Days (All Subjects – Safety Population)

Among all subjects in the safety population, within 28 days (1 month) after vaccination, a total of 352 SAEs were reported for 327 subjects (0.8%) in the 13vPnC group, and 337 SAEs were reported for 314 subjects (0.7%) in the placebo group. None of these SAEs were considered related to study vaccine.

The most frequently reported types of SAEs in the 13vPnC and the placebo groups, respectively, were cardiac disorders (0.2% and 0.2%) and neoplasms (0.2% and 0.1%). No SAE (by MedDRA PT) occurred in ≥1% of subjects in either vaccine group. The only statistically significant differences in incidence of SAEs between the 2 vaccine groups by SOC or by PT were in the general disorders and administration site conditions SOC and for the non-cardiac chest pain PT within that SOC. Of the 30 subjects who had SAEs categorised in this SOC, 14 had events of noncardiac chest pain (12 in the 13vPnC group and 2 in the placebo group), and 6 had events of chest pain (5 in the 13vPnC group and 1 in the placebo group). The PTs of non-cardiac chest pain and chest pain largely represented events for which a subject with known cardiovascular disease was admitted to the hospital to rule out myocardial infarction and evaluation did not result in a new cardiac diagnosis. All of the subjects with these PTs had a history of cardiovascular disease or risk factors, except for 1 subject in the 13vPnC group with noncardiac chest pain. None of these events occurred within 2 days after vaccination; events occurred between Day 3 and Day 29 (the last day of the reporting period). The incidence of SAEs in the cardiac disorders SOC was similar between the 2 vaccine groups (75 events in 72 subjects in the 13vPnC group, 78 events in 74 subjects in the placebo group).

Discontinuation due to adverse events

One subject in the 13vPnC group (002-002026) withdrew from the study on Day 15 because of a cerebral infarction. No other subjects were withdrawn from the study for a safety-related reason.

Summary Tables- Safety Population

Table 16. Consolidated Adverse Events for Subjects of All Ages – Safety Population

	Vaccine Group									
	13vPnC N= 42237			Placebo N= 42255				Total N= 84492		
	No. of Subjects [a]	%	No. of Events [b]	No. of Subjects [a]	%	No. of Events [b]	p-Value [c]	No. of Subjects [a]	%	No. of Events [b]
Total AEs [d]	556	1.32	673	484	1.15	566	0.025	1040	1.23	1239
Serious AEs – Total [e]	381	0.90	423	359	0.85	389	0.417	740	0.88	812
Fatal	21	0.05	21	23	0.05	25	0.880	44	0.05	46
Hospitalization/prolong existing hospitalization	327	0.77	365	311	0.74	337	0.525	638	0.76	702
Life-threatening	12	0.03	12	11	0.03	11	0.839	23	0.03	23
Disability/incapacity	5	0.01	5	5	0.01	5	>.99	10	0.01	10
Other (medically significant)	84	0.20	86	70	0.17	70	0.260	154	0.18	156
AE leading to drop-out	1	0.00	1	0	0.00	0	0.500	1	0.00	1
Psychiatric disorders	2	0.00	2	2	0.00	2	>.99	4	0.00	4
Nervous system disorders	58	0.14	60	49	0.12	50	0.386	107	0.13	110
Cerebrovascular disorders	24	0.06	24	21	0.05	22	0.659	45	0.05	46
Accidents and injuries	5	0.01	5	8	0.02	8	0.581	13	0.02	13
Cardiac disorders	93	0.22	99	84	0.20	89	0.500	177	0.21	188
Vascular disorders	26	0.06	27	13	0.03	13	0.038	39	0.05	40
Infections and infestations	85	0.20	93	108	0.26	114	0.113	193	0.23	207
Anticholinergic syndrome	0	0.00	0	0	0.00	0	NE	0	0.00	0
Quality of life decreased	0	0.00	0	0	0.00	0	NE	0	0.00	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	32	0.08	32	36	0.09	37	0.716	68	0.08	69
Other AE appearing more frequently in older patients [f]	188	0.45	248	144	0.34	180	0.016	332	0.39	428

Abbreviations: AE = adverse event; NE = not estimable; SAE = serious adverse event.

a) Number (No.) of subjects reporting at least 1 event of type specified. This represents the number of subjects reporting at least 1 event.

b) The total number of events of the type specified. Subjects can be represented more than once. This represents the total number of events.

c) Fisher exact test, 2-sided, used to calculate the p-value for the difference between vaccine groups in percentages of subjects reporting an event.

d) Comprised of:
All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All AEs reported in the immunogenicity subset (N=2,011; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination)
Note: Non-serious AEs were only recorded in the immunogenicity subset.

e) Comprised of:
All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination).

f) Comprised of:
AEs and SAEs occurring in the immunogenicity subset (N=2,011) from Day 1 to Day 29 post vaccination.
Note: Non-serious AEs were only recorded in the immunogenicity subset.

Table 1. Consolidated Adverse Events for Subjects ≥65 and <75 Years of Age – Safety Population

	Vaccine Group									
	13vPnC N= 29003			Placebo N= 29061				Total N= 58064		
	No. of Subjects [a]	%	No. of Events [b]	No. of Subjects [a]	%	No. of Events [b]	p-Value [c]	No. of Subjects [a]	%	No. of Events [b]
Total AEs [d]	334	1.15	402	310	1.07	359	0.342	644	1.11	761
Serious AEs – Total [e]	221	0.76	240	221	0.76	238	>.99	442	0.76	478
Fatal	6	0.02	6	13	0.04	13	0.167	19	0.03	19
Hospitalization/prolong existing hospitalization	190	0.66	208	186	0.64	200	0.836	376	0.65	408
Life-threatening	3	0.01	3	6	0.02	6	0.508	9	0.02	9
Disability/incapacity	3	0.01	3	4	0.01	4	>.99	7	0.01	7
Other (medically significant)	48	0.17	50	46	0.16	46	0.837	94	0.16	96
AE leading to drop-out	0	0.00	0	0	0.00	0	NE	0	0.00	0

Table 16. Consolidated Adverse Events for Subjects of All Ages – Safety Population

	Vaccine Group									
	13vPnC N= 42237			Placebo N= 42255			Total N= 84492			
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]	No. of Subjects[a]	%	No. of Events[b]
Psychiatric disorders	2	0.01	2	1	0.00	1	0.625	3	0.01	3
Nervous system disorders	32	0.11	33	32	0.11	33	>.99	64	0.11	66
Cerebrovascular disorders	10	0.03	10	11	0.04	12	>.99	21	0.04	22
Accidents and injuries	3	0.01	3	5	0.02	5	0.727	8	0.01	8
Cardiac disorders	53	0.18	55	49	0.17	50	0.693	102	0.18	105
Vascular disorders	15	0.05	16	10	0.03	10	0.326	25	0.04	26
Infections and infestations	48	0.17	53	73	0.25	78	0.029	121	0.21	131
Anticholinergic syndrome	0	0.00	0	0	0.00	0	NE	0	0.00	0
Quality of life decreased	0	0.00	0	0	0.00	0	NE	0	0.00	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	22	0.08	22	20	0.07	20	0.760	42	0.07	42
Other AE appearing more frequently in older patients[f]	121	0.42	158	102	0.35	124	0.203	223	0.38	282

Table 2. Consolidated Adverse Events for Subjects ≥75 and <85 Years of Age – Safety Population

	Vaccine Group									
	13vPnC N= 11727			Placebo N= 11753			Total N= 23480			
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]	No. of Subjects[a]	%	No. of Events[b]
Total AEs[d]	189	1.61	230	145	1.23	175	0.015	334	1.42	405
Serious AEs – Total[e]	133	1.13	150	110	0.94	120	0.138	243	1.03	270
Fatal	14	0.12	14	9	0.08	10	0.307	23	0.10	24
Hospitalization/prolong existing hospitalization	114	0.97	129	99	0.84	109	0.303	213	0.91	238
Life-threatening	8	0.07	8	5	0.04	5	0.423	13	0.06	13
Disability/incapacity	2	0.02	2	0	0.00	0	0.249	2	0.01	2
Other (medically significant)	30	0.26	30	18	0.15	18	0.085	48	0.20	48

Table 2. Consolidated Adverse Events for Subjects ≥75 and <85 Years of Age – Safety Population

	Vaccine Group									
	13vPnC N= 11727			Placebo N= 11753				Total N= 23480		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]	No. of Subjects[a]	%	No. of Events[b]
AE leading to drop-out	1	0.01	1	0	0.00	0	0.499	1	0.00	1
Psychiatric disorders	0	0.00	0	0	0.00	0	NE	0	0.00	0
Nervous system disorders	22	0.19	23	14	0.12	14	0.187	36	0.15	37
Cerebrovascular disorders	13	0.11	13	9	0.08	9	0.404	22	0.09	22
Accidents and injuries	1	0.01	1	3	0.03	3	0.625	4	0.02	4
Cardiac disorders	33	0.28	34	30	0.26	34	0.707	63	0.27	68
Vascular disorders	10	0.09	10	3	0.03	3	0.057	13	0.06	13
Infections and infestations	31	0.26	34	30	0.26	31	0.899	61	0.26	65
Anticholinergic syndrome	0	0.00	0	0	0.00	0	NE	0	0.00	0
Quality of life decreased	0	0.00	0	0	0.00	0	NE	0	0.00	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	8	0.07	8	11	0.09	12	0.647	19	0.08	20
Other AE appearing more frequently in older patients[f]	61	0.52	82	41	0.35	55	0.048	102	0.43	137

Abbreviations: AE = adverse event; NE = not estimable; SAE = serious adverse event.

a. Number (No.) of subjects reporting at least 1 event of type specified. This represents the number of subjects reporting at least 1 event.

b. The total number of events of the type specified. Subjects can be represented more than once. This represents the total number of events.

c. Fisher exact test, 2-sided, used to calculate the p-value for the difference between vaccine groups in percentages of subjects reporting an event.

d. Comprised of:

All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All AEs reported in the immunogenicity subset (N=2,011; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination).

Note: Non-serious AEs were only recorded in the immunogenicity subset.

e. Comprised of:

All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination).

f. Comprised of:

AEs and SAEs occurring in the immunogenicity subset (N=2,011) from Day 1 to Day 29 post vaccination.

Note: Non-serious AEs were only recorded in the immunogenicity subset.

Table 3. Consolidated Adverse Events for Subjects ≥85 Years of Age – Safety Population

	Vaccine Group									
	13vPnC N= 1504			Placebo N= 1438				Total N= 2942		
	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]	No. of Subjects[a]	%	No. of Events[b]
Total AEs[d]	33	2.19	41	29	2.02	32	0.798	62	2.11	73
Serious AEs – Total[e]	27	1.80	33	28	1.95	31	0.787	55	1.87	64
Fatal	1	0.07	1	1	0.07	2	>.99	2	0.07	3
Hospitalization/prolong existing hospitalization	23	1.53	28	26	1.81	28	0.568	49	1.67	56
Life-threatening	1	0.07	1	0	0.00	0	>.99	1	0.03	1
Disability/incapacity	0	0.00	0	1	0.07	1	0.489	1	0.03	1
Other (medically significant)	6	0.40	6	6	0.42	6	>.99	12	0.41	12
AE leading to drop-out	0	0.00	0	0	0.00	0	NE	0	0.00	0
Psychiatric disorders	0	0.00	0	1	0.07	1	0.489	1	0.03	1
Nervous system disorders	4	0.27	4	3	0.21	3	>.99	7	0.24	7
Cerebrovascular disorders	1	0.07	1	1	0.07	1	>.99	2	0.07	2
Accidents and injuries	1	0.07	1	0	0.00	0	>.99	1	0.03	1
Cardiac disorders	7	0.47	10	5	0.35	5	0.775	12	0.41	15
Vascular disorders	1	0.07	1	0	0.00	0	>.99	1	0.03	1
Infections and infestations	6	0.40	6	5	0.35	5	>.99	11	0.37	11
Anticholinergic syndrome	0	0.00	0	0	0.00	0	NE	0	0.00	0
Quality of life decreased	0	0.00	0	0	0.00	0	NE	0	0.00	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2	0.13	2	5	0.35	5	0.278	7	0.24	7
Other AE appearing more frequently in older patients[f]	6	0.40	8	1	0.07	1	0.125	7	0.24	9

Abbreviations: AE = adverse event; NE = not estimable; SAE = serious adverse event.

a. Number (No.) of subjects reporting at least 1 event of type specified. This represents the number of subjects reporting at least 1 event.

b. The total number of events of the type specified. Subjects can be represented more than once. This represents the total number of events.

c. Fisher exact test, 2-sided, used to calculate the p-value for the difference between vaccine groups in percentages of subjects reporting an event.

d. Comprised of:
All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All AEs reported in the immunogenicity subset (N=2,011; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination).
Note: Non-serious AEs were only recorded in the immunogenicity subset.

e. Comprised of:
All SAEs reported in the CAPiTA safety population (N= 84,492; Day 1 to Day 29 post vaccination);
All SAEs reported in the immunogenicity subset (N=2,011; month 1 to month 6 post vaccination).

f. Comprised of:
AEs and SAEs occurring in the immunogenicity subset (N=2,011) from Day 1 to Day 29 post vaccination.
Note: Non-serious AEs were only recorded in the immunogenicity subset.

2.3.2. Discussion on clinical safety

In the analysis of SAEs within 6 months after vaccination for subjects in the immunogenicity subset, a difference between the 2 vaccine groups approaching statistical significance was observed for the cardiac conditions System Organ Class (SOC). The excess of reports among subjects in the 13vPnC group occurred more than 2 months after vaccination and did not exhibit temporal clustering after vaccination. No event occurred within 2 days of vaccination in either vaccine group. This difference was not observed in the analysis of SAEs within 1 month after vaccination for all subjects.

In the analysis of SAEs within 1 month after vaccination for all subjects, the only statistically significant differences in incidence of SAEs between the 2 vaccine groups by SOC or by preferred term (PT) were in the general disorders and administration site conditions SOC and in the non-cardiac chest pain PT within that SOC. There were also more subjects with the PT of chest pain observed in the 13vPnC group than in the placebo group in this SOC. The PTs of non-cardiac chest pain and chest pain largely represented events for which a subject with known cardiovascular disease was admitted to the hospital to rule out myocardial infarction and evaluation did not result in a new cardiac diagnosis. All of the subjects with these PTs had a history of cardiovascular disease or risk factors, except for 1 subject in the 13vPnC group with non-cardiac chest pain. None of these events occurred within 2 days after vaccination. The incidence of SAEs in the cardiac disorders SOC was similar between the 2 vaccine groups.

A comprehensive review of cardiac events in all of the categories of safety data in this study revealed no evidence of a cardiac effect.

No new safety signal was identified in this large study, and the safety profile of 13vPnC remains unchanged from the profile observed in previous studies with 13vPnC in adults.

2.3.3. Conclusions on clinical safety

Overall, there is no new safety concern identified in the CAPiTA study. Subjects receiving 13vPnC had a greater frequency of local reactions within the first 7 days of vaccination compared to subjects receiving placebo, which is entirely expected. A greater frequency of most systemic reactions was also noted in subjects receiving 13vPnC compared to placebo. The most frequently occurring systemic events were fatigue (18.8%), new generalised muscle pain (18.4%), and headache (15.9%).

Adverse events occurring within 28 days (1 month) after vaccination were reported for 18.7% of subjects who received 13vPnC and for 14.3% of subjects receiving placebo (p=0.010). The difference in the incidence of AEs between the vaccine groups appears to be accounted for by a higher incidence of injection site reactions and muscular pain in the 13vPnC group than in the placebo group.

There was no difference in the frequency of new medical conditions or death between vaccination groups.

Regarding SAEs, there was an imbalance (although not statistically significant) in the number of subjects who experienced PTs in the cardiac disorders SOCs within 6 months of vaccination and a statistically significant difference in the number of subjects who experienced non-cardiac chest pain with 28 days of vaccination. However, none of these events occurred within 2 days and none were assessed as vaccine-related.

It is agreed that there is no clear evidence of a cardiac effect from the data provided.

2.3.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.4. Risk management plan

2.4.1. PRAC advice

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.0 is acceptable. The PRAC endorsed RMP assessment report is attached.

The CHMP endorsed this advice without changes.

2.5. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6. Significance of paediatric studies

The CHMP is of the opinion that studies 6096A1-006, 6096A1-500, 6096A1-501, 6096A1-008, 6096A1-007, and 6096A1-009 started before and completed after 26 January 2007, which are contained in the agreed Paediatric Investigation Plan, which is completed, and have been completed after 26 January 2007, are considered as significant.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Statistically significant efficacy has been demonstrated for the prevention of first episodes of confirmed VT pneumococcal CAP (primary objective), confirmed NB\NI VT pneumococcal CAP and VT-IPD (secondary objectives) in subjects aged 65 years and older in both, per protocol and modified intent-to-treat populations. The duration of protective efficacy against a first episode of VT pneumococcal CAP, NB/NI VT pneumococcal CAP, and VT-IPD extended throughout the 4-year study

Uncertainty in the knowledge about the beneficial effects

Because of the low number of subjects aged > 85 years in the CAPiTA study no conclusion can be drawn regarding efficacy in very old subjects.

Also, numbers of episodes by serotype were too small to draw definitive conclusions regarding serotype-specific efficacy.

No data were presented in adults < 65 years of age. The extrapolation to all adults is deemed acceptable though, considering that younger adults are more likely respond with sufficient antibody levels compared to elderly, and it is therefore highly likely that the protection would be of a similar or of higher magnitude.

Risks

No new safety signal has been detected. Results of safety evaluations performed during the study confirmed an acceptable safety profile for 13vPnC administered to adults ≥65 years of age.

Benefit-risk balance

The results of the CAPiTA study demonstrated that 13vPnC prevents VT pneumococcal including nonbacteremic/noninvasive vaccine-type Community Acquired Pneumonia and vaccine-type invasive pulmonary disease in adults aged 65 years and older with an acceptable safety profile consistent with findings from other Prevenar 13 clinical studies in adults. The safety and efficacy data from the CAPiTA study thus demonstrate a positive benefit-risk profile for vaccination of adults aged 65 years and older consistent with the overall benefit risk profile of 13vPnC in adults 18 years or older.

These results, together with the safety and immunogenicity data from Phase 3 studies with Prevenar-13 in adults, support the vaccination of adults 50 years and older who are at increased risk of pneumococcal pneumonia as well as those 18-49 with one or more underlying conditions putting them at an increased risk of pneumococcal pneumonia.

Discussion on the Benefit-Risk Balance

The reported incidence of community-acquired pneumonia (CAP) and IPD in Europe varies by country, increases with age from 50 years and is highest in individuals aged ≥ 65 years. *S. pneumoniae* is the most frequent cause of CAP, and is estimated to be responsible for approximately 30% of all CAP cases requiring hospitalisation in adults in developed countries.

Pneumonia is the most common clinical presentation of pneumococcal disease in adults. Bacteraemic pneumonia (approximately 80% of IPD in adults), bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults.

The CAPiTA study is a parallel-group, randomized, placebo-controlled, double-blind, single-centre trial to evaluate the efficacy of 13vPnC in the prevention of first episodes of vaccine type pneumococcal community acquired pneumonia (CAP), first episodes of non-bacteremic/non-invasive VT pneumococcal CAP, and first episodes of VT invasive pneumococcal disease in approximately 85,000 subjects aged 65 years and older who had not previously received 23-valent pneumococcal polysaccharide vaccine (23vPS). The efficacy analyses for CAPiTA show that vaccination with 13vPnC provides clear benefit to elderly adults aged 65 years and older; statistically significant VE was demonstrated for the prevention of first episodes of confirmed VT pneumococcal CAP, confirmed NB/NI VT pneumococcal CAP, and VT-IPD; these results were observed in both the per protocol and mITT populations. Efficacy was apparent throughout the course of the study (approximately 4-year mean follow up) without evidence of waning of VE. VE was also statistically significant for the prevention of all episodes of confirmed VT pneumococcal CAP. For episodes caused by VT and NVT serotypes, statistically significant efficacy of 13vPnC was observed for a first episode of confirmed pneumococcal CAP and first episode of IPD. In general, numbers of episodes by serotype were too small to draw definitive conclusions regarding serotype-specific efficacy, but post hoc analysis showed statistically significant VE for serotype 7F for episodes of confirmed VT pneumococcal CAP and confirmed NB/NI VT pneumococcal CAP.

Although efficacy of 13vPnC has not been studied in younger adults, immune responses to 13vPnC observed in adults 18 to 64 years of age are similar to or higher than those among adults > 65 years of age. The absolute benefit of vaccinating younger adults is smaller, but may still be meaningful, especially in those with highest risk i.e. with chronic underlying medical conditions, specifically

anatomical or functional asplenia, diabetes mellitus, asthma, chronic cardiovascular, pulmonary, kidney or liver conditions, and immunodeficiency.

No new safety signal was identified in this large study, and the safety profile of 13vPnC remains unchanged from the profile observed in previous studies with 13vPnC in adults.