15 September 2022
EMA/836730/2022
Committee for Medicinal Products for Human Use (CHMP)

# Extension of indication variation assessment report

Invented name: Vaxneuvance

Common name: pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure No. EMEA/H/C/005477/II/0001

Marketing authorisation holder (MAH) Merck Sharp & Dohme B.V.

## Note

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

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# Table of contents

# List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ADR | Adverse drug reaction |
| APaT | All participants as treated |
| ARDS | Adult respiratory distress syndrom |
| ART | Antiretroviral therapy |
| ATC | Anatomical therapeutic chemical |
| AUDIT-C | Alcohol use disorders identification test-concise |
| CAIH | Center for American Indian Health |
| CAP | Community acquired pneumonia |
| CDC | Centers for Disease Control and Prevention |
| CI | Confidence interval |
| cLDA | Constrained longitudinal data analysis |
| COPD | Chronic obstructive pulmonary disease |
| CSR | Clinical study report |
| ECDC | European Centre for Disease Prevention |
| EMA | European Medicines Agency |
| eVRC | Electronic vaccination report card |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GCP | Good clinical practice |
| GMC | Geometric mean concentration |
| GMFR | Geometric mean fold rise |
| GMT | Geometric mean titer |
| HAI | Hemagglutination inhibition |
| HIV | Human immunodeficiency virus |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IgG | Immunoglobulin G |
| IK | Intrinsic killing |
| IM | intramuscular |
| IPD | Invasive pneumococcal disease |
| IRT | Interactive response technology |
| LLOQ | Lower limits of quantitation |
| M&N | Miettinen & Nurminen |
| MedDRA | Medical dictionary for regulatory activities |
| MOPA | Multiplexed opsonophagocytic assay |
| OPA | Opsonophagocytic activity |
| PCV | Pneumococcal conjugate vaccine |
| PCV13 | Prevnar 13/Prevenar 13™ |
| PD | Pneumococcal disease |
| Pn ECL | Pneumococcal electrochemiluminescence |
| PP | Per protocol |
| PPV | Pneumococcal polysaccharide vaccine |
| PPV23 | Pneumovax 23 |
| PT | Preferred term |
| QIV | Quadrivalent influenza vaccine |
| RCDC | Reverse cumulative distribution curve |
| SAE | Serious adverse event |
| SOC | System organ class |
| US | United States |
| VRC | Vaccination report card |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 20 December 2021 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media for Vaxneuvance, based on final results from 1 Phase II study (V114-008) and 7 Phase III studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, V114-031); these are interventional studies to evaluate the safety, tolerability and immunogenicity of V114 in healthy and immunocompromised infants, children and adolescents. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to include editorial changes in the product information.
Version 1.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0343/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0343/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0343/2021, EMA/PDCO/546196/2021.

## *Information relating to orphan market exclusivity*

Not applicable.

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

## Derogation(s) of market exclusivity

Not applicable

### *Scientific advice*

The MAH requested Scientific advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

| Timetable | Actual dates |
|---|---|
| Submission date | 20 December 2021 |
| Start of procedure: | 23 January 2022 |
| CHMP Rapporteur Assessment Report | 17 March 2022 |
| PRAC Rapporteur Assessment Report | 25 March 2022 |
| PRAC members comments | 30 March 2022 |
| CHMP Co-Rapporteur Critique | 31 March 2022 |
| Updated PRAC Rapporteur Assessment Report | 1 April 2022 |
| PRAC Outcome | 7 April 2022 |
| CHMP members comments | 11 April 2022 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 13 April 2022 |
| Request for supplementary information (RSI) | 22 April 2022 |
| CHMP Rapporteur Assessment Report | 21 June 2022 |
| PRAC Rapporteur Assessment Report | 24 June 2022 |
| PRAC members comments | 29 June 2022 |
| Updated PRAC Rapporteur Assessment Report | 30 June 2022 |
| PRAC Outcome | 7 July 2022 |
| CHMP members comments | 11 July 2022 |
| Updated CHMP Rapporteur Assessment Report | 21 July 2022 |
| Request for supplementary information (RSI) | 21 July 2022 |
| PRAC Rapporteur Assessment Report | 22 August 2022 |
| PRAC members comments | 24 August 2022 |
| CHMP Rapporteur Assessment Report | 31 August 2022 |
| PRAC Outcome | 1 September 2022 |
| CHMP members comments | 5 September 2022 |
| Updated CHMP Rapporteur Assessment Report | 8 September 2022 |
| Opinion | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

*Streptococcus pneumoniae* causes pneumococcal disease (PD). Clinical manifestations of pneumococcal disease include invasive pneumococcal disease (IPD) and non-invasive disease. Invasive pneumococcal disease is defined as the isolation of *S. pneumoniae* from a normally sterile body site and can lead to meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis. The non-invasive disease can present as, e.g. acute otitis media, sinusitis and non-bacteraemic pneumonia.

### *State the claimed the therapeutic indication*

V114 is proposed to be indicated for active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in infants, children, and adolescents from 6 weeks through 17 years of age (prior to 18th birthday).

### *Epidemiology*

*Streptococcus pneumoniae* (pneumococcus) continues to be a major cause of vaccine preventable PD worldwide with considerable morbidity and mortality, in infants, children, and adults, despite the significant reduction in burden of pneumococcal disease resulting from implementation and widespread use of currently available pneumococcal conjugate vaccines (PCVs).

IPD

IPD follows a seasonal pattern, with the number of cases peaking in the winter months. In the European Union (EU)/European Economic Area (EEA), in 2018, a total of 24,663 confirmed cases of IPD were reported. IPD incidence from 2012 through 2017 ranged from 4.6 to 5.8 and 11.4 to 13.7 in children 1-4 years and <1 year old, respectively. Annual incidence was 14.4 per 100 000 infants <1 year in 2018. In Europe in 2018, the case fatality rate of IPD was 15%. In children younger than 15 years, the case fatality rate of IPD is 4%. In the paediatric population, this morbidity and mortality disproportionately impacts children <5 years of age.

The overall incidence of IPD due to serotypes covered by vaccines currently licensed for routine use in children has decreased significantly in all age groups in regions where PCVs have been introduced into infant immunization schedules, with the exception of serotype 3. IPD cases caused by 2 serotypes not included in vaccines currently licensed for use in children, 22F and 33F, have increased in frequency in several regions and countries. Based on ECDC 2017 serotype distribution data, the serotypes contained in PCV13 still cause 25.3% and 22.4% of residual IPD in children <1 and children 1 to 4 years of age in the EU, respectively. The two serotypes 22F and 33F cause 8.5% and 6.8% of IPD in children <1 and children 1 to 4 years of age in the EU. Therefore, V114 which contains all serotypes in PCV13 plus 22F and 33F, has the potential to prevent 33.8% and 29.2% of IPD in children <1 and children 1 to 4 years of age in the EU.

Pneumonia

Pneumococcal pneumonia can be bacteremic or nonbacteremic. Bacteremic pneumococcal pneumonia is the most frequent presentation of IPD in adults, accounting for approximately 80-90% of IPD cases. Globally, pneumonia is the leading cause of death in children, killing approximately 800,000 under the age of 5 years in 2017, accounting for 15% of all deaths in that age group. *S. pneumoniae* is the most common cause of bacterial pneumonia in children. The WHO estimates that *S. pneumoniae* kills close to half a million children under 5 years of age worldwide every year. Most of these deaths occur in developing countries.

Acute otitis media

Acute otitis media (AOM), a middle ear infection commonly caused by *S. pneumoniae*, is a major cause of childhood morbidity. AOM is one of the most common childhood infections in children less than 5 years of age and the most frequent reason children are prescribed antibiotics. Approximately 68% of children will have had at least 1 episode of AOM by 6 years of age. Since the introduction of PCVs, there has been a decrease in AOM. Nevertheless, AOM remains common in paediatric populations.

## *Aetiology and pathogenesis*

*S. pneumoniae* is a gram-positive encapsulated diplococcus, which commonly asymptomatically colonizes the human nasopharynx. Carriage rates decline with age (approx. 1/3rd to 2/3rds of children and ≤10% of adults are colonized). Transmission occurs mainly via nasal shedding (mucus droplets). Usually, pneumococci are cleared, however sometimes they can cause mucosal disease by local spread to the middle ear, sinuses or lungs. Additionally, they can be the causative agents of systemic infections, causing IPD. The progression to disease depends on complex host-pathogen interactions, involving a multitude of bacterial virulence factors and inflammatory host cascades.

The capsular polysaccharide on the cell surface of the pneumococci is the most important virulence factor. The polysaccharide capsule exists in approx. 100 different chemical compositions called serotypes. The polysaccharide capsule interferes with phagocytosis by preventing complement C3b opsonisation of bacterial cells. The mechanism of action of all licensed pneumococcal vaccines is the induction of protective, serotype-specific, anti-capsular antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci. These functional antibodies against the capsular polysaccharides have been shown to be protective. Conferred protection is serotype-specific, no serotype-independent pneumococcal vaccines are available.

## *Clinical presentation, diagnosis*

IPD is associated with significant morbidity and mortality in both children and adults worldwide. Serious manifestations of IPD include meningitis, septicaemia and bacteraemic pneumonia.

The most frequent complication of AOM is hearing impairment, which may occur despite antibiotic therapy, leading to profound language and cognitive sequelae in the intellectually developing child. Left untreated, AOM can lead to perforated eardrum, hearing loss and mastoiditis.

## *Management*

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data. Most cases with clinical symptoms consistent with IPD require initiation of empiric treatment before bacterial culture results are known. Initial treatment generally includes broad-

spectrum antibiotics that have efficacy against *S. pneumoniae* as well as other likely pathogens. The increase in pneumococcal resistance to penicillin and other commonly used antimicrobial agents complicates treatment decisions and may lead to treatment failures with subsequent increased morbidity and healthcare costs.

Prevention of PD in children includes universal routine childhood vaccination with PCVs as well as prophylactic use of antibiotics and pneumococcal polysaccharide vaccine (PPV) in special populations (e.g., children with functional or anatomic asplenia). Pneumococcal vaccines have shown efficacy and effectiveness against invasive and noninvasive pneumococcal disease caused by the serotypes contained in those vaccines in both children and adults. Currently two vaccines are licensed for this indication in children in the EU: Prevenar13 (PCV13) and Synflorix (only for children up to 5 years of age). Another pneumococcal vaccine is licensed but not for the intended infant population (PNEUMOVAX23).

### 2.1.2. About the product

V114 is a pneumococcal conjugate vaccine (PCV) that contains 15 distinct pneumococcal capsular polysaccharides, each individually conjugated to the CRM197 carrier protein originating from *Corynebacterium diphtheriae* C7: serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F.

V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in the licensed vaccine Prevenar 13™ (PCV13), plus 2 additional serotypes (22F and 33F) that are not included in any currently licensed PCV.

Conjugation of polysaccharides changes the nature of the immune response to polysaccharide antigens from T-cell independent to T-cell dependent, as it stimulates a T-helper response. Due to the conjugation, V114 elicits a T-cell dependent immune response that induces antibodies which enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. Carrier protein-specific helper T-cells support specificity, functionality, and maturation of serotype-specific B cells. V114 may not prevent disease caused by *Streptococcus pneumoniae* serotypes that are not contained in the vaccine.

The proposed indication is:

*Vaxneuvance is indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to less than 18 years of age.*

The recommended posology in infants and children <2 years for V114 consists of 2- or 3-doses, each of 0.5 mL, with the first dose given as early as 6 to 12 weeks of age, followed by a toddler dose of 0.5 mL given between 11 to 15 months of age. For children 7 months to less than 18 years of age who are pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower valency pneumococcal conjugate vaccines, a catch-up schedule should be considered. The catch-up schedule consists of 3-doses in infants 7 to <12 months of age, 2 doses in children aged 12 months to <2 years and 1 dose in children and adolescents of 2 to <18 years of age.

## 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

**Development programme**

The clinical development program for V114 to support licensure in children 6 weeks through 17 years of age includes immunogenicity and safety data from 8 clinical studies: 1 Phase 2 (V114-008) and 7 Phase 3 (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, V114-031).

**Compliance with CHMP guidance**

The most relevant CHMP guidelines applied:

"Guideline on clinical evaluation of vaccines" (CPMP/VWP/164653/05, Rev.1)

**Scientific Advice**

During the course of development, the sponsor sought regulatory and scientific advice from EMA's Committee for Medicinal Products for Human Use (CHMP). These are detailed below:

**EMEA/H/SA/1492/1/2010/PED/III.** CHMP stated that the Pn ECL assay must be adequately bridged to the WHO reference ELISA protocol in order to maintain the serological link to the protective efficacy that has been demonstrated for the 7-valent PnC vaccine. The choice of Prevenar 13 as the licensed comparator vaccine is agreed as it has the highest number of serotypes in common with V114. The proposed Phase III studies and immunological endpoints (in particular the WHO ELISA threshold of 0.35 µg/mL and the OPA≥1:8) will support the IPD indication, however, the Company should conduct post-marketing studies to evaluate vaccine effectiveness against AOM and pneumonia. The post-marketing program should also include population-based surveillance of the incidence rates of IPD in several different countries for an appreciable number of years using national surveillance systems in particular for the new serotypes for which efficacy against IPD is not known. The proposed noninferiority criteria would require careful justification. It was recommended to use Prevenar 7 to bridge to the data on efficacy for the seven serotypes in the Prevenar 7 vaccine

**EMEA/H/SA/1492/1/FU/1/2017/III.** CHMP was consulted and agreed on the scope of the proposed paediatric development plan before the Applicant submitted the paediatric investigational plan (PIP). It was concluded that the use of V114 from the age of 6 weeks can be supported as well as the rationale for a waiver below 6 weeks. The study planned with the 3, 5, 12-15 months of age dosing schedule was not necessary. The data obtained from the study with the more stringent 2, 4, 12-15 months dosing schedule should suffice to support a posology that covers the more relaxed 3, 5, 12-15 months schedule. The suggestion to administer V114 concomitantly with vaccines administered in the frame of routine child vaccination programs as offered in several European countries is supported. The criteria proposed to conclude non-inferiority for immune responses to the 13 shared serotypes and superiority for the two non-shared serotypes are agreed. In addition, it is recommended that a secondary analysis compares the percentages of children who achieve immune responses to the two additional serotypes at or above the threshold value of the lowest percentage of children who achieve immune responses documented for any shared serotype.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 1 Tabulated overview of clinical studies supporting extension of indication**

| Study ID<br><br># study centres/ location | Design | No. of subjects by group | Study population | Primary efficacy endpoint(s) |
|---|---|---|---|---|
| **Pivotal** | | | | |
| V114-025<br>58 sites<br>Australia, Belgium, Czech Republic, Estonia, Germany, Greece, Poland, Russia, Spain | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of a 3-dose regimen of V114 in healthy infants | Randomization ratio: 1:1<br>V114:<br>Randomized: 591<br>Received ≥1 dose: 588[a]<br>Completed: 569<br>Prevenar 13™:<br>Randomized: 593<br>Received ≥1 dose: 591<br>Completed: 570 | Pneumococcal vaccine-naïve healthy infants approximately 2 months of<br>Sex: 611 M/ 568 F<br>Median Age: 8.0 wks | Serotype-specific IgG response rates and IgG GMCs for all 15 serotypes included in V114 at 30 days PTD |
| V114-029<br>75 sites<br>Thailand, Turkey, US | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114 in healthy infants | Randomization ratio: 1:1<br>V114:<br>Randomized: 860<br>Received ≥1 dose: 858<br>Completed: 758<br>Prevenar 13™:<br>Randomized: 860<br>Received ≥1 dose: 856[a]<br>Completed: 734 | Pneumococcal vaccine-naïve healthy infants approximately 2 months of<br>Sex: 890 M/ 824 F<br>Median Age: 8.0 wks | Serotype-specific IgG response rates and IgG GMCs for all 15 serotypes included in V114 at 30 days PPS<br>Serotype-specific IgG GMCs for all 15 serotypes included in V114 at 30 days PTD |
| **Supportive studies** | | | | |

| Study ID<br><br># study centres/ location | Design | No. of subjects by group | Study population | Primary efficacy endpoint(s) |
|---|---|---|---|---|
| V114-008<br><br>47 sites<br><br>Canada, Denmark, Finland, Israel, Spain, US | Phase 2, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of 2 different lots of V114 | Randomization ratio: 1:1:1<br><br>V114 Lot 1:<br>Randomized: 351<br>Received ≥1 dose: 350<br>Completed: 308<br><br>V114 Lot 2:<br>Randomized: 350<br>Received ≥1 dose: 347<br>Completed: 305<br><br>PCV13:<br>Randomized: 350<br>Received ≥1 dose: 347<br>Completed: 308 | Pneumococcal vaccine-naïve healthy infants approximately 2 months of<br><br>Sex: 528 M/ 523 F<br><br>Median Age: 9.0 wks | Serotype-specific IgG responses for the 13 shared serotypes at 30 days PPS<br><br>Serotype-specific IgG response rates and IgG GMCs for all 15 serotypes included in V114 at 30 days PPS |
| V114-023<br><br>19 sites<br><br>Brazil, Colombia, Dominican Republic, Greece, Italy, Panama, US | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of V114 in children with sickle cell disease | Randomization ratio: 2:1<br><br>V114:<br>Randomized: 70<br>Received ≥1 dose: 69<br>Completed: 65<br><br>Prevenar 13™:<br>Randomized: 34<br>Received ≥1 dose: 34<br>Completed: 34 | Children 5 through 17 years of age (inclusive) with sickle cell disease without prior administration of any pneumococcal vaccine within 3 years of study entry<br><br>Sex: 56 M/ 47 F<br><br>Median Age: 11.0 yrs | Serotype-specific IgG GMCs for all 15 serotypes included in V114 at Day 30 |
| V114-024<br><br>25 sites<br><br>Finland, Malaysia, Poland, Russia, Thailand | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114 in infants, children, and adolescents | Randomization ratio: 1:1<br><br>V114:<br>Randomized: 303<br>Received ≥1 dose: 303<br>Completed: 302<br><br>Prevenar 13™:<br>Randomized: 303<br>Received ≥1 dose: 303<br>Completed: 303 | Healthy children who are either pneumococcal vaccine-naïve or who previously received a partial or full regimen of PCV<br><br>Participants 7 to 11 months:<br>Sex: 66 M/ 62 F<br>Median Age: 8.0 mo<br><br>Participants 12 to 23 months:<br>Sex: 58 M/ 68 F<br>Median Age: 18.0 mo<br><br>Participants 2 through 17 years:<br>Sex: 184 M/ 168 F<br>Median Age: 4.0 yrs | Serotype-specific IgG GMCs for all 15 serotypes included in V114 at 30 days after the last dose of study intervention |

| Study ID<br><br># study centres/ location | Design | No. of subjects by group | Study population | Primary efficacy endpoint(s) |
|---|---|---|---|---|
| V114-027<br><br>31 sites<br><br>Thailand, Turkey, US | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the interchangeability of V114 and Prevenar 13™ with respect to safety, tolerability, and immunogenicity in healthy infants | Randomization ratio 1:1:1:1:1<br><br>Group 1: P/P/P/P<br>Randomized: 179<br>Received ≥1 dose: 179<br>Completed: 164<br><br>Group 2: P/P/P/V<br>Randomized: 181<br>Received ≥1 dose: 181<br>Completed: 167<br><br>Group 3: P/P/V/V<br>Randomized: 180<br>Received ≥1 dose: 178<br>Completed: 147<br><br>Group 4: P/V/V/V<br>Randomized: 180<br>Received ≥1 dose: 179<br>Completed: 160<br><br>Group 5: V/V/V/V<br>Randomized: 180<br>Received ≥1 dose: 179<br>Completed: 167 | Pneumococcal vaccine-naïve healthy infants approximately 2 months of age<br><br>Sex: 473 M/ 423 F<br>Median Age: 9.0 wks | Serotype-specific IgG GMCs for 13 shared serotypes at 30 days PTD |
| V114-030<br><br>12 sites<br><br>South Africa, Thailand, Ukraine | Phase 3, randomized, double-blind, active comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114 followed by PPV23 8 weeks later in children infected with HIV | Randomization ratio: 1:1<br><br>V114:<br>Randomized: 203<br>Received ≥1 dose PCV: 203<br>Vaccinated with PPV23: 203<br>Completed: 203<br><br>PCV13:<br>Randomized: 204<br>Received ≥1 dose PCV: 204<br>Vaccinated with PPV23: 202<br>Completed: 201 | Children 6 through 17 years of age infected with HIV<br><br>Gender:<br>212 M/ 195 F<br><br>Median Age: 13.0 yrs | Serotype-specific IgG GMCs for all 15 serotypes included in V114 at Day 30 |
| V114-031<br><br>72 sites<br><br>Australia, Canada, Finland, Germany, Israel | Phase 3, randomized, double blind, active comparator controlled, multicenter study to evaluate the safety and tolerability of V114 in healthy infants | Randomization ratio<br>5:1 (term infants)<br>1:1 (preterm infants)<br><br>V114:<br>Randomized: 1972<br>Received ≥1 dose: 1967 [a]<br>Completed: 1847<br><br>PCV13:<br>Randomized: 437<br>Received ≥1 dose: 436 [a]<br>Completed: 400 | Pneumococcal vaccine-naïve healthy infants approximately 2 months of<br><br>Sex: 1232 M/ 1171 F<br>Median Age: 9.0 wks | Secondary Immunogenicity Endpoints:<br><br>Serotype-specific IgG GMCs for all 15 serotypes included in V114 at 30 days PPS, pretoddler dose, and 30 days PTD<br><br>Serotype-specific IgG response rate for all 15 serotypes included in V114 at 30 days PPS |

| Study ID<br><br># study centres/ location | Design | No. of subjects by group | Study population | Primary efficacy endpoint(s) |
|---|---|---|---|---|
| CD4=cluster of differentiation 4; CTD=Common Technical Document; F=female; GMC=geometric mean concentration; HIV=human immunodeficiency virus; IgG=immunoglobulin G; M=male; mo=months; PCV=Pneumococcal Conjugate Vaccine; PCV13= Prevenar 13™; PPS=post primary series; PPV23=PNEUMOVAX™23; PTD=post toddler dose; US=United States; V=V114; wks=weeks; yrs=years.<br><br>Note: Per protocol, for studies V114-027, V114-029, V114-008, primary series included 3 doses of PCV administered at ~2, 4, 6 months of age and toddler dose of PCV was administered at ~12 to 15 months of age. For study V114-025, primary series included 2 doses of PCV administered at ~2 and 4 months of age (term infants) or 3 doses of PCV administered at ~2, 3, 4 months of age (preterm infants) and toddler dose of PCV was administered at ~11 to 15 months of age.<br><br>[a] One participant in V114-025, 1 participant in V114-029, and 5 participants in V114-031 inadvertently received both V114 and Prevenar 13™. | | | | |

An overview of the clinical studies included in the present submission is provided in Table 1. As discussed in the scientific advice, there are no efficacy studies with V114, as efficacy will be inferred based on immunogenicity.

This application for licensure is based on the inference of V114 efficacy for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of noninferior immune responses to the 13 shared serotypes in PCV13. A surrogate of protection for IPD has been defined in children of an IgG titer of 0.35 µg/mL. All studies were controlled randomised double-blind trials. The applicant has declared that studies were conducted in accordance with GCP principles; there is no sign from studies that this would not be the case.

A total of 7 phase 3 studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, and V114-031) and 1 phase 2 study (V114-008) were conducted with V114. PCV13 was included as a comparator in all studies. In total 8,381 infants and children were enrolled in the studies across 26 countries, which randomized in different ratios to various regimens. Of these 8,381 participants, in total of 5,336 infants and children (including 221 preterm infants [<37 weeks gestational age at birth]) received at least 1 dose of V114. The clinical program targeted both healthy and immunocompromised infants and children 6 weeks through 17 years of age for whom pneumococcal vaccination is indicated:

- 4 studies in healthy infants 6 to 12 weeks of age (including preterm infants): V114-008, V114-025, V114-029 and V114-031)
- 1 study in healthy children 7 months through 17 years of age (V114-024)
- 1 study in children 5 through 17 years of age with SCD (V114-023)
- 1 study in children 6 through 17 years with HIV (V114-030)

Studies in healthy infants evaluated a 3-dose PCV regimen (2-dose primary series followed by a toddler dose) (V114-025) and 4-dose PCV regimen (3-dose primary series followed by a toddler dose) (V114-008, V114-027, V114-029, V114-031). Additional studies evaluated the interchangeability of PCV13 (the current standard of care) and V114 at any time during a 4-dose PCV regimen (V114-027), catch-up vaccination in children who were pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower valency PCVs (V114-024), and use of V114 in paediatric populations at increased risk for pneumococcal disease, including preterm infants (V114-025, V114-027, V114-029, V114-031), children with SCD (V114-023), and children with HIV (V114-030).

The clinical evaluation of safety and immunogenicity of V114 aligns with WHO recommendations and feedback from regulatory agencies, as follows:

- The active comparator in all Phase 2 and Phase 3 paediatric studies was PCV13, the licensed PCV with the most serotypes in common with V114.
- Safety was evaluated across all paediatric age groups (from infants 6 weeks of age to children through 17 years of age).
- Immunogenicity was evaluated through (1) demonstration of serotype-specific immune responses that are noninferior to PCV13 for the 13 shared serotypes and for 2 serotypes unique to V114 (22F, 33F) after the primary series and/or after the toddler dose, (2) generation of antibodies to opsonize and kill *S. pneumoniae*, and (3) induction of immune memory after the primary series.

***CHMP's comment***

The clinical development programme has been agreed by the CHMP and PDCO. No efficacy trials are planned as these are not considered feasible. It is acknowledged that a majority of participants included in the studies are healthy infants 6 to 12 weeks of age, which is the main population in which V114 will be used.

The serological threshold 0.35 µg/mL has been defined to be used for non-inferiority comparison to support protection against invasive pneumococcal disease in children only. No correlate of protection exists for AOM and pneumonia. In addition, no correlate of protection for IPD has been established for the new serotypes included in the current vaccine. The MAH stated that the final clinical study results from an ongoing AOM vaccine-efficacy trial (V114-032) are anticipated for submission to the Agency by end of 2Q2027. In addition, PSURs will contain 1) information on spontaneous reports of breakthrough disease/vaccine failure for IPD, AOM and pneumonia, 2) V114 efficacy/effectiveness/impact studies and publications in children for all 3 indications, and 3) new data on serotype distribution and incidence from IPD surveillance from countries where V114 is broadly used. Together these data will provide information on vaccine effectiveness.

A matched case-control study indicated that PCV13 was effective in the prevention of IPD in children (Moore et al. Lancet Respir Med 2016). In addition, since IPD cases caused by serotypes included in the PCV13 have decreased over time, give further indication on efficacy (PCV13 SmPC). The fact that PCV13 is considered efficacious reduces the need to bridge back to the data on efficacy for the seven serotypes in the Prevenar 7 vaccine as suggested in the scientific advice in 2010.

## 2.3.2. Pharmacokinetics

No biopharmaceutic studies were conducted in support of this application. This is acceptable, as pharmacokinetic studies are not routinely conducted as part of the evaluation of vaccines, as described in the CHMP "Guidance on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

## 2.3.3. Pharmacodynamics

The pharmacodynamic profile of V114 is defined by the immunogenicity profile. The overall strategy of the development of V114 was agreed by the CHMP via scientific advice. Immunogenicity results are described in the Clinical Efficacy sections.

## *Mechanism of action*

V114 elicits a T-cell dependent immune response to induce antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

## *Primary and secondary pharmacology*

In the V114 paediatric clinical program, vaccine-induced, serotype-specific immune responses in the form of immunoglobulin G (IgG) and opsonophagocytic antibody activity (OPA) for all 15 serotypes included in V114 were measured using validated pneumococcal electrochemiluminescence (Pn ECL) assays and multiplex opsonophagocytic assay (MOPA), respectively. During MAA these assays were considered fit for purpose. However, the bridge to WHO ELISA was not considered for adults, as no surrogate of protection exists for adults, and therefore not described during the MAA procedure.

A surrogate of protection against IPD for children of 0.35 µg/mL has been derived from a meta-analysis of 3 efficacy trials.

The benefits of the ECL multiplex technology over the enzyme-linked immunosorbent assay (ELISA) methodology include speed, smaller sample volumes (particularly desirable for infants), increased dynamic range, and the ability to multiplex. The WHO Expert Committee on Biological Standardization has recommended that in-house assays used in immunogenicity studies designed to evaluate protection against IPD be bridged to the WHO reference assay in order to maintain the link between immune responses to vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevnar.

A study was performed to bridge the validated Pn ECL assay to the WHO reference assay. This bridging study included 116 paediatric serum samples immunized with three doses of V114 (adjuvanted or non-adjuvanted), collected from the United States as part of the Merck Phase 1/2 clinical studies. The paediatric samples were selected with antibody concentrations that spanned the entire range of response, with a concerted effort to secure samples with serotype-specific IgG concentrations near the WHO ELISA threshold value of 0.35 µg/mL in order to better assess the concordance between the two assays in the region of the threshold value. The study also included 12 adult serum samples vaccinated with a 23-valent pneumococcal polysaccharide vaccine provided by Professor David Goldblatt.

Each of the 128 serum samples (116 paediatric samples and 12 Goldblatt samples) was tested across three independent runs in the Pn ECL assay and across three independent runs in the WHO ELISA. Within each of the ECL runs, samples were tested in duplicate at the 1:1000 dilution (or further dilution if necessary). Within each of the WHO ELISA runs, samples were tested in a series of 8, 2.5-fold dilutions starting at the 1:50 dilution. The sample quantifiable median concentrations (log transformed) were used to estimate the concordance slope, the average fold difference, and the accuracy, correlation, and concordance coefficients.

Generally, Pn ECL v2.0 and WHO ELISA assays resulted in fairly similar concentrations throughout the range of response. However, serotype 5 antibody concentration was 52% higher on average in the Pn ECL as compared to the WHO ELISA. For the other 14 serotypes, the average difference in antibody concentration between the Pn ECL and the WHO ELISA was between -22% and 29%.

As indicated in Table 2, the concordance slope estimates ranged from 0.97 to 1.33 for the set of paediatric samples. Across the 15 evaluated serotypes, the concentration in the Pn ECL ranged from 0.63-fold to 1.49-fold that of the ELISA at 0.35 µg/mL for the paediatric sample set.

**Table 2 Concordance slope, average % difference and fold difference at 0.35 µg/mL - paediatric samples**

| | | | Concordance Slope | | Average %Difference | | Fold Differerence | Agreement Coefficient | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Serotype | N1* | Slope | 95% CI | %Difference | 95% CI | at 0.35 mcg/mL** | Correlation | Accuracy | Concordance |
| ECL vs. ELISA | 1 | 91 | 1.05 | (1.00, 1.11) | 10.27 | (4.84, 15.99) | 1.09 | 0.97 | 0.99 | 0.96 |
| | 3 | 73 | 1.17 | (0.95, 1.43) | 3.46 | (-11.54, 21.00) | 1.00 | 0.75 | 0.99 | 0.75 |
| | 4 | 75 | 1.11 | (1.04, 1.18) | 15.40 | (9.38, 21.76) | 1.11 | 0.97 | 0.98 | 0.95 |
| | 5 | 102 | 1.07 | (0.93, 1.22) | 52.14 | (40.62, 64.60) | 1.49 | 0.83 | 0.84 | 0.70 |
| | 6A | 89 | 1.29 | (1.13, 1.46) | -10.32 | (-20.22, 0.80) | 0.74 | 0.86 | 0.97 | 0.83 |
| | 6B | 93 | 1.05 | (1.00, 1.10) | -4.32 | (-8.63, 0.18) | 0.91 | 0.97 | 1.00 | 0.97 |
| | 7F | 107 | 0.99 | (0.95, 1.03) | 22.43 | (18.39, 26.60) | 1.23 | 0.98 | 0.98 | 0.96 |
| | 9V | 88 | 1.33 | (1.22, 1.46) | 27.77 | (16.81, 39.74) | 1.20 | 0.92 | 0.93 | 0.86 |
| | 14 | 109 | 0.97 | (0.94, 1.01) | 20.90 | (15.98, 26.04) | 1.26 | 0.98 | 0.99 | 0.97 |
| | 18C | 77 | 1.11 | (1.04, 1.18) | 28.61 | (22.51, 35.02) | 1.26 | 0.96 | 0.94 | 0.90 |
| | 19A | 94 | 1.28 | (1.14, 1.43) | -12.67 | (-21.76, -2.52) | 0.77 | 0.87 | 0.97 | 0.85 |
| | 19F | 109 | 1.22 | (1.15, 1.28) | -21.38 | (-27.24, -15.05) | 0.63 | 0.96 | 0.96 | 0.93 |
| | 22F | 116 | 1.05 | (0.98, 1.13) | 1.50 | (-5.21, 8.69) | 0.94 | 0.94 | 1.00 | 0.93 |
| | 23F | 72 | 1.08 | (1.00, 1.17) | -7.79 | (-13.93, -1.22) | 0.89 | 0.95 | 0.99 | 0.95 |
| | 33F | 116 | 1.01 | (0.97, 1.06) | -7.99 | (-11.41, -4.43) | 0.91 | 0.97 | 1.00 | 0.97 |
| | Overall | 1411 | 1.08 | (1.05, 1.10) | 5.96 | (3.73, 8.24) | 1.01 | 0.93 | 1.00 | 0.93 |

Note: 1) N1 is the number of test samples with quantifiable concentrations in both assays, used to estimate the concordance slope and the average % difference. 2) To calculate the fold difference at the serostatus cutoff point of 0.35 µg/mL, 0.35 µg/mL was used as the concentration of the WHO ELISA.

Both the concordance method and the reverse cumulative distribution function method were used to determine serotype specific Pn ECL threshold values.

For the paediatric sample set, using the 0.35 µg/mL cut off for the Pn ECL v2.0 and WHO ELISA assays, the agreement rates in serostatus assignment were greater than 80% for all serotypes, see Table 3. Using either the concordance threshold value or the RCDF threshold value for individual serotypes resulted in only a slight improvement in serostatus agreement rates as compared to the 0.35 µg/mL cutoff.

**Table 3 Summary of Serostatus Agreement for the Paediatric Sample Set**

| Serotype | **Pediatric Samples** | | | | | |
|---|---|---|---|---|---|---|
| | N | ECL Threshold Value Concordance Method | RCDF Method | 0.35 ug/mL | Agreement Rate Concordance Method | RCDF Method |
| 1 | 116 | 0.38 | 0.40 | 89.7% | 90.5% | 92.2% |
| 3 | 113 | 0.35 | 0.56 | 83.2% | 83.2% | 88.5% |
| 4 | 116 | 0.39 | 0.36 | 93.1% | 94.8% | 94.0% |
| 5 | 116 | 0.52 | 0.56 | **80.2%** | 86.2% | 87.9% |
| 6A | 116 | 0.26 | 0.30 | 86.2% | 87.1% | 87.1% |
| 6B | 116 | 0.32 | 0.33 | 95.7% | 96.6% | 95.7% |
| 7F | 116 | 0.43 | 0.42 | **89.7%** | 94.0% | 94.0% |
| 9V | 115 | 0.42 | 0.46 | 87.8% | 91.3% | 92.2% |
| 14 | 116 | 0.44 | 0.43 | **93.1%** | 95.7% | 95.7% |
| 18C | 116 | 0.44 | 0.44 | 94.0% | 94.8% | 94.8% |
| 19A | 116 | 0.27 | 0.24 | **80.2%** | 81.0% | 78.4% |
| 19F | 116 | 0.22 | 0.24 | **81.0%** | 86.2% | 87.9% |
| 22F | 116 | 0.33 | 0.40 | 94.8% | 94.8% | 94.8% |
| 23F | 116 | 0.31 | 0.31 | 95.7% | 95.7% | 95.7% |
| 33F | 116 | 0.32 | 0.34 | 96.6% | 96.6% | 95.7% |

| Serotype | Pediatric Samples | | | | | |
|---|---|---|---|---|---|---|
| | N | ECL Threshold Value Concordance Method | RCDF Method | 0.35 ug/mL | Agreement Rate Concordance Method | RCDF Method |
| **Overall** | 1736 | | | **89.4%** | 91.2% | 91.6% |

Note: 1) Agreement rate for each serotype is determined using 0.35 µg/mL as the threshold for the WHO ELISA assay and 3 different threshold values for the Pn ECL assay. 2) The bolded agreement rate value indicates that the corresponding test of imbalance in the discordance between the two assays is statistically significant (P-Value < 0.05).

Given: (1) the proximity of the aggregate Pn ECL threshold values to the WHO ELISA threshold of 0.35 µg/mL (0.35 µg/mL using the concordance method, and 0.38 µg/mL using the RCDF method); (2) that the serotype specific Pn ECL threshold values were within 1.60-fold of 0.35 µg/mL for each of the 15 serotypes; and (3) that the agreement rates between assays were only slightly improved when using the serotype specific threshold values for the Pn ECL as compared to using the 0.35 µg/mL threshold, the single Pn ECL threshold value of 0.35 µg/mL can reasonably be applied to each of the 15 evaluated serotypes.

For each serotype, the variability of the Pn ECL v2.0 assay was either comparable to that of the WHO ELISA, or notably less than that of the WHO ELISA (serotypes 4, 5, 6A and 14).

## 2.3.4. Discussion on clinical pharmacology

The set-up of the bridging study was adequate and was in line with guidance by WHO and the scientific advices received in March 2010 (EMEA/H/SA/1492/1/2010/PED/III) and May 2017 (EMEA/H/SA/1492/1/FU/1/2017/III). In the scientific advice of 2017, the general approach for using immunobridging was agreed.

Overall, the IgG concentrations obtained using the Pn ECL v2.0 and WHO ELISA assays were similar throughout the range of response, as for 14 of the 15 serotypes the average difference in antibody concentration ranged between -22% and 29%. Serotype 5 resulted in approximately 50% higher concentrations in the Pn ECL assay compared to the WHO ELISA, the reason for this is unclear. This could result in overestimation of the immune response for serotype 5 when using Pn ECL assay. Based on the presented data, it can be agreed that the single Pn ECL threshold value of 0.35 µg/mL can be applied to each of the 15 evaluated serotypes, especially considering the fact that the agreement rates between assays were only slightly, <8%, improved when using the serotype specific threshold values for the Pn ECL as compared to using the 0.35 µg/mL threshold. In addition, the threshold of 0.35 µg/mL is a conservative threshold, considering that there is consensus that the protective level of antibody as measured by ELISA lies between 0.18 and 0.35 µg/ml (Plotkin, 2010 Clinical and Vaccine Immunology). However, whether this threshold also applies for the new serotypes included in this vaccine, is currently unknown. Information on breakthrough disease/vaccine failure for IPD, AOM and pneumonia will be provided in PSURs, which will provide indications on efficacy.

The PnECL assay was adequately bridged to the WHO ELISA, indicating comparability of the measurements between the PnECL assay and the WHO ELISA. Therefore, a link to the surrogate of protection of 0.35 µg/mL has been established.

### 2.3.5. Conclusions on clinical pharmacology

The evaluation of the protective effect of V114 is based on bridging clinical immunogenicity results to PCV13. This strategy has been accepted by CHMP in scientific advice procedure EMEA/H/SA/1492/1/2010/PED/III.

There are no dedicated PK studies. This can be accepted, as PK studies are generally not required for vaccines.

The applicant has utilised two assays to characterise the vaccine-induced immune response: Pn ECL to measure IgGs and MOPA, which measures functional antibodies as the assay is designed to mimic the opsonophagocytosis process. The Pn ECL measures all antibodies against specific serotypes. Both assays were validated and shown to be fit for purpose. In addition, the PnECL assay was bridged to the WHO ELISA, confirming a link between the immune responses generated by V114 vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevenar. The surrogate of protection of 0.35 µg/mL can be used to infer protection against IPD. However, for the new serotypes included in the vaccine it needs to be confirmed, using adequate post marketing studies, whether the 0.35 µg/mL threshold is indeed indicative for efficacy. Information on this will be provided in spontaneous reports of breakthrough disease/vaccine failure. In addition, it needs to be taken into consideration that for pneumonia and AOM no correlate or surrogate of protection exists. These indications were granted to PCV13 based on non-inferiority of immune response to PCV7. Efficacy has been shown for PCV13 for these indications post-marketing, however, the strategy of non-inferiority testing for V114 to PCV13 introduces the possibility of biocreep for the shared serotypes as there is no known correlate of protection.

## *2.4. Clinical efficacy*

An overview of the clinical studies included in the present submission is provided in Table 1. The submission consists of a total of 7 phase 3 studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, and V114-031) and 1 phase 2 study (V114-008). Studies V114-025 (3-dose regimen) and V114-029 (4-dose regimen) are considered pivotal as they provide the main evidence for immunogenicity and safety in the target population.

### 2.4.1. Main studies

The MAH submitted eight studies (1 Phase 2 and 7 Phase 3 studies) to support the extension of indication of V114. Two studies were considered pivotal by the MAH: Study V114-025 and V114-029. The methods of these 2 studies are described below, where possible the presentation of methods has been integrated.

### Methods

**V114-025**

This was a phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days). V114 or Prevenar 13™ was administered to full-term participants at approximately 2, 4, and 11 to 15 months of age and to preterm infants at approximately 2, 3, 4, and 11 to 15 months of age.

**V114-029**

This was a phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability and immunogenicity of a 4-dose regimen of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days). V114 or PCV13 was administered at approximately 2, 4, 6, and 12 to 15 months of age.

***CHMP's comment***

Both pivotal studies were active-comparator controlled, randomized, double-blind studies, which is appreciated.

## Study participants

Both studies enrolled healthy male and female infants at approximately 2 months of age, from 42 to 90 days (inclusive) who had a legally acceptable representative who understood the study procedures, alternate treatments available, and risks involved with the study and voluntarily agreed to participate.

In addition to several standard exclusion criteria for vaccine trials, the main exclusion criteria for both studies were:

- History of IPD (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.
- Had a known hypersensitivity to any component of the PCV, any component of the licensed paediatric vaccines to be administered concomitantly in the study, or any diphtheria toxoid-containing vaccine.
- Had any contraindication to the concomitant study vaccines being administered in the study.
- Had a recent febrile illness (rectal temperature ≥38°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours prior to receipt of study vaccine.
- Had received a dose of any pneumococcal vaccine prior to study entry.

***CHMP's comment***

The study populations included healthy infants 6 to 12 weeks of age, which is the main population in which V114 will be administered. This is acceptable.

In- and exclusion criteria are adequately defined and seem appropriate.

## Treatments

During **Study V114-025**, V114 or PCV13 was administered to full-term participants at approximately 2, 4, and 11 to 15 months of age and to preterm infants at approximately 2, 3, 4, and 11 to 15 months of age (time from birth, not corrected for due date), see Table 4. All participants were also administered concomitant paediatric vaccines (i.e., INFANRIX™ hexa and Rotarix™) during the study.

**Table 4 Study Interventions V114-025**

| Arm Name | Intervention Name | Dosage Level(s) | Route | Vaccination Regimen [a] |
|---|---|---|---|---|
| V114 | V114 | 0.5 mL | IM | Single dose at Visits 1, 3, and 5 |
| V114 | Rotarix™ [b] | 1.5 mL | Oral | Single dose at Visits 1 and 3 |
| V114 | INFANRIX™ hexa | 0.5 mL | IM | Single dose at Visits 1, 2, 3, and 5 |
| Prevenar 13™ | Prevenar 13™ | 0.5 mL | IM | Single dose at Visits 1, 3, and 5 |
| Prevenar 13™ | Rotarix™ [b] | 1.5 mL | Oral | Single dose at Visits 1 and 3 |
| Prevenar 13™ | INFANRIX™ hexa | 0.5 mL | IM | Single dose at Visits 1, 2, 3, and 5 |

IM = intramuscular;

[a] Vaccination regimen specified in the table was for full-term infant participants. For preterm infant participants (<37 weeks gestational age), the vaccination regimen was as follows: V114 or Prevenar 13™ will be administered at Visits 1, 2, 3, and 5.

[b] Rotarix™ was not administered to participants enrolled at sites in the Russian Federation.

During **Study V114-029**, V114 or PCV13 was administered at approximately 2, 4, 6, and 12 to 15 months of age, see Table 5. Participants also received the following paediatric vaccines: RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™.

**Table 5 Study Interventions V114-029**

| Arm Name | Intervention Name | Dosage | Route of Admin. | Vaccination Regimen |
|---|---|---|---|---|
| V114 | V114 | 0.5 mL | IM | Single dose at Visits 1, 2, 3, and 5 |
| | RotaTeq™ | 2 mL | Oral | Single dose at Visits 1, 2, and 3 |
| | Pentacel™ | 0.5 mL | IM | Single dose at Visits 1, 2, and 3 |
| | RECOMBIVAX HB™* | 0.5 mL | IM | Single dose at Visits 1, 2, and 3 |
| | VAQTA™ | 0.5 mL | IM | Single dose at Visit 5 |
| | M-M-R™II | 0.5 mL | SC | Single dose at Visit 5 |
| | VARIVAX™ | 0.5 mL | SC | Single dose at Visit 5 |
| | HIBERIX™ | 0.5 mL | IM | Single dose at Visit 5 |
| PCV13 | PCV13 | 0.5 mL | IM | Single dose at Visits 1, 2, 3, and 5 |
| | RotaTeq™ | 2 mL | Oral | Single dose at Visits 1, 2, and 3 |
| | Pentacel™ | 0.5 mL | IM | Single dose at Visits 1, 2, and 3 |
| | RECOMBIVAX HB™* | 0.5 mL | IM | Single dose at Visits 1, 2, and 3 |
| | VAQTA™ | 0.5 mL | IM | Single dose at Visit 5 |
| | M-M-R™II | 0.5 mL | SC | Single dose at Visit 5 |
| | VARIVAX™ | 0.5 mL | SC | Single dose at Visit 5 |
| | HIBERIX™ | 0.5 mL | IM | Single dose at Visit 5 |

Admin=administration; IM=intramuscular; SC=subcutaneous.
*For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ was administered at Visits 1 and 3.

***CHMP's comment***

The dosing regimen of V114 used during the studies represent the 2 proposed dosing regimens included in the SmPC: a 2-dose primary series followed by a booster and a 3-dose primary series followed by a booster. The proposed dosing regimens are identical to the comparator PCV13.

The choice of PCV13 as comparator was agreed by CHMP, as it has the highest number of serotypes in common with V114 (EMEA/H/SA/1492/1/2010/PED/III).

The administration of V114 concomitantly with vaccines administered in the frame of routine child vaccination programs as offered in several European countries is appreciated. This is in line with the scientific advice given.

## Objectives

### V114-025

Primary Immunogenicity Objectives

- To compare the anti-pneumococcal polysaccharide (PnPs) serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following the toddler dose (Postdose 3 for full-term infants; Postdose 4 for preterm infants) for participants administered V114 versus participants administered PCV13.
    - Hypothesis 1: V114 is non-inferior to PCV13 for the 13 shared serotypes between V114 and PCV13 based on response rates at 30 days post toddler dose (PTD), using a non-inferiority margin of -10% (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates of V114 minus Prevenar 13™ should be greater than -0.1).
    - Hypothesis 2: V114 is superior to PCV13 for the 2 serotypes unique to V114 based on the response rates at 30 days PTD, using a superiority margin of 10%. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates of V114 minus Prevenar 13™ to be greater than 0.1).
- To compare anti-PnPs serotype-specific IgG geometric mean concentrations (GMCs) at 30 days PTD for participants administered V114 versus participants administered PCV13.
    - Hypothesis 3: V114 is non-inferior to PCV13 for the 13 shared serotypes between V114 and PCV13 based on anti-PnPs serotype-specific IgG GMCs at 30 days PTD, using a non-inferiority margin of 0.5 for the GMC ratio. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ PCV13] to be greater than 0.5.)
    - Hypothesis 4: V114 is superior to PCV13 for the 2 serotypes unique to V114 based on anti-PnPs serotype-specific IgG GMCs at 30 days PTD, using a superiority margin of 2.0 for the GMC ratio. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/PCV13] to be greater than 2.0.)

Secondary Immunogenicity Objectives

- To compare the antigen-specific response rate to each antigen included in INFANRIX™ hexa at 30 days PTD for participants administered V114 concomitantly with INFANRIX™ hexa versus participants administered Prevenar 13™ concomitantly with INFANRIX™ hexa.
    - Hypothesis 5: INFANRIX™ hexa administered concomitantly with V114 is non-inferior to INFANRIX™ hexa administered concomitantly with Prevenar 13™ at 30 days PTD dose for each antigen included in INFANRIX™ hexa.

- To compare anti-rotavirus immunoglobulin A (IgA) geometric mean titers (GMTs) at 30 days after the completion of the primary series (Postdose 2 for full-term infants; Postdose 3 for preterm infants) for participants administered V114 concomitantly with Rotarix™ versus participants administered Prevenar 13™ concomitantly with Rotarix™.
    - Hypothesis 6: Rotarix™ administered concomitantly with V114 is non-inferior to Rotarix™ administered concomitantly with Prevenar 13™ based on GMTs at 30 days post primary series (PPS).
- To evaluate the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PPS by each vaccination group.
- To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) GMTs and response rate at 30 days PTD by each vaccination group.
- To evaluate the anti-PnPs serotype-specific IgG response rates to the 2 unique serotypes in V114 compared with the lowest IgG response rate in any of 13 shared serotypes in PCV13 at 30 days PTD.

**V114-029**

Primary Immunogenicity Objectives

- To compare the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following dose 3 (PPS) for participants administered V114 versus participants administered PCV13.
    - Hypothesis 1: V114 is non-inferior to PCV13 for the 13 shared serotypes between V114 and PCV13 based on response rates at 30 days following PPS, using a non-inferiority margin of -10%. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates [V114 minus PCV13] to be greater than -0.1).
    - Hypothesis 2: V114 is non-inferior to PCV13 for the 2 unique V114 serotypes based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in PCV13, excluding serotype 3, at 30 days PPS, using a non-inferiority margin of -10%. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates [V114 minus PCV13] to be greater than -0.1)
- To compare anti-PnPs serotype-specific IgG GMCs at 30 days PPS for participants administered V114 versus participants administered PCV13.
    - Hypothesis 3: V114 is non-inferior to PCV13 for the 13 shared serotypes between V114 and PCV13 based on anti-PnPs serotype-specific IgG GMCs at 30 days PPS, using a non-inferiority margin of 0.5 for the GMC ratio. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ PCV13] to be greater than 0.5.)
    - Hypothesis 4: V114 is non-inferior to PCV13 for the 2 serotypes unique to V114 based on the anti-PnPs serotype specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in PCV13, excluding serotype 3, at 30 days PPS, using a non-inferiority margin of 0.5 for the GMC ratio. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ PCV13) to be greater than 0.5)

- To compare anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 (PTD) for participants administered V114 versus participants administered PCV13.
    - Hypothesis 5: V114 is non-inferior to PCV13 for the 13 shared serotypes between V114 and PCV13 based on anti-PnPs serotype-specific IgG GMCs at 30 days PTD, using a non-inferiority margin of 0.5 for the GMC ratio. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ PCV13) to be greater than 0.5.)
    - Hypothesis 6: V114 is non-inferior to PCV13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in PCV13, excluding serotype 3, at 30 days PTD, using a non-inferiority margin of 0.5 for the GMC ratio. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ PCV13) to be greater than 0.5.)

Secondary Objectives

- To compare the antigen specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days PPS for participants administered V114 concomitantly with Pentacel™ versus participants administered PCV13 concomitantly with Pentacel™.
    - Hypothesis 7: Pentacel™ administered concomitantly with V114 is non-inferior to Pentacel™ administered concomitantly with PCV13 at 30 days PPS for each antigen included in Pentacel™.
- To compare the response rate to anti-hepatitis A antigen at 30 days PTD for participants administered V114 concomitantly with VAQTA™ versus participants administered PCV13 concomitantly with VAQTA™.
    - Hypothesis 8: VAQTA™ administered concomitantly with V114 is non-inferior to VAQTA™ administered concomitantly with PCV13 at 30 days PTD.
- To compare the response rate to each antigen included in M-M-R™II at 30 days PTD for participants administered V114 concomitantly with MM-R™II versus participants administered PCV13 concomitantly with M-MR™II.
    - Hypothesis 9: M-M-R™II administered concomitantly with V114 is non-inferior to M-M-R™II administered concomitantly with PCV13 at 30 days PTD for each antigen included in M-MR™II.
- To compare the response rate to anti-varicella antigen at 30 days PTD for participants administered V114 concomitantly with VARIVAX™ versus participants administered PCV13 concomitantly with VARIVAX™.
    - Hypothesis 10: VARIVAX™ administered concomitantly with V114 is non-inferior to VARIVAX™ administered concomitantly with PCV13 at 30 days PTD.
- To compare the response rate to anti-PRP antigen at 30 days PTD for participants administered V114 concomitantly with HIBERIX™ versus participants administered PCV13 concomitantly with HIBERIX™.
    - Hypothesis 11: HIBERIX™ administered concomitantly with V114 is non-inferior to HIBERIX™ administered concomitantly with PCV13 at 30 days PTD.

- To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days PPS for participants administered V114 versus participants administered PCV13.
    - Hypothesis 12: V114 is superior to PCV13 for the 2 unique V114 serotypes based on the response rates at 30 days PPS.
    - Hypothesis 13: V114 is superior to PCV13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs at 30 days PPS.
- To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days PTD for participants administered V114 versus participants administered PCV13.
    - Hypothesis 14: V114 is superior to PCV13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs at 30 days following Dose 4.
- To compare the anti-PnPs serotype 3 IgG responses at 30 days PPS for participants administered V114 versus participants administered PCV13.
    - Hypothesis 15: V114 is superior to PCV13 for serotype 3 based on the response rates at 30 days PPS.
    - Hypothesis 16: V114 is superior to PCV13 for serotype 3 based on anti-PnPs IgG GMCs at 30 days PPS.
- To compare the anti-PnPs serotype 3 IgG GMCs at 30 days PTD for participants administered V114 versus participants administered PCV13.
    - Hypothesis 17: V114 is superior to PCV13 for serotype 3 based on anti-PnPs IgG GMCs at 30 days PTD.
- To evaluate the anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PPS by each vaccination group.

***CHMP's comment***

A surrogate of protection has been determined for IPD: 0.35 µg/mL. This is a population-derived IgG antibody threshold value that was based on the meta-analysis of 3 clinical studies investigating effectiveness of the 7-valent Prevenar. There is general consensus that the protective level of antibody lies between 0.18 and 0.35 µg/mL. The surrogate of protection of 0.35 µg/mL has been used to infer efficacy during the MAA procedure of PCV13. Efficacy trials are not considered feasible and therefore demonstration of non-inferiority to the licensed PCV13 for the 13 common serotypes was agreed. However, with respect to pneumonia or AOM no correlates of protection exist. PCV13 has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed post-marketing. However, no exact vaccine efficacy estimate was determined, nor the immune response required to achieve protection. Therefore, non-inferiority testing introduces the possibility of biocreep. In addition, for the two unique serotypes it is unknown what the clinical impact of a superior immune response will be.

The non-inferiority margin of -0.1 for the difference (V114 minus PCV13) in response rate and 0.5 for the GMC ratio (V114/PCV13) for the 13 shared serotypes has been agreed in the scientific advice (EMEA/H/SA/1492/1/FU/1/2017/III) and is identical to the margin used during MAA of PCV13, during which PCV7 was the active comparator.

Based on the study objectives for both pivotal studies, the immune response generated by V114 can be adequately compared to the immune response generated by PCV13. The proportion of participants

achieving IgG threshold value of ≥0.35 µg/mL will be compared between V114 group and the PCV13 group both 30 days post primary vaccination series and post-toddler dose in study **V114-025** and only post primary series in study **V114-029**. IgG GMCs will be compared between V114 group and the PCV13 group 30 days post primary vaccination series, prior to the toddler dose and 30 days post toddler dose. In addition, OPA GMTs and response rate can be compared between V114 group and the PCV13 group 30 days post primary vaccination series, prior to the toddler dose and 30 days post toddler dose. Finally, response to concomitantly administered childhood vaccines can be compared between the 2 groups. The assessment will focus on the totality of evidence, which should be sufficiently convincing to ensure CHMP that V114 is likely to be efficacious in children.

For study **V114-025**, the primary immunogenicity objective focusses on the vaccine response rate and IgG GMCs 30 days post toddler dose. It is debatable whether this should be the primary objective, considering the WHO guideline states that the primary analysis should be based on vaccine response rates and IgG GMCs post primary vaccine series, also taking into consideration the fact that IPD occurs frequently with severe disease course in infants <1 year of age. However, as the MAH has investigated both the immune response post toddler dose and post primary vaccination series both immune responses will be taken into consideration.

For study **V114-029**, the primary immunogenicity objective focusses on vaccine response rate and IgG GMCs 30 days post primary vaccination and IgG GMCs 30 days post toddler dose, which is appreciated. However, vaccine response rate at 30 days post-toddler dose, which is also considered valuable information, was not included in the objectives.

Study V114-025 investigates superiority of the 2 unique serotypes, while study V114-029 determines non-inferiority of the 2 unique serotypes by comparing to the lowest IgG GMC of any of the shared serotypes (except serotype 3). The latter is based on WHO guideline that indicates comparison of the unique serotypes to the lowest response of the shared serotypes and is preferred. The comparison to the lowest response indicates that at least a substantial response is generated known to be efficacious in other serotypes, however, it is unknown what the clinical relevance of this non-inferiority margin is.

The assessment of OPA antibody IgG GMTs are considered supportive to the IgG GMCs and response rate. There is no correlate of protection known for OPA antibodies in children, therefore the clinical impact of the response induced is unknown.

## Outcomes/endpoints

The endpoints measured for both studies include:

- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PPS, immediately pre-toddler dose and 30 days PTD.
- Antibody response to concomitantly administered vaccinations:
    - diphtheria toxoid, tetanus toxoid, pertussis toxin (PT), pertussis filamentous hemagglutinin (FHA), pertussis pertactin (PRN), Haemophilus influenzae type b polyribosylribitol phosphate (Hib-PRP), hepatitis B surface antigen (HBsAg), poliovirus serotypes 1, 2, and 3 at 30 days PPS and PTD of V114 or PCV13. **Study V114-025**
    - Anti-rotavirus IgA response at 30 days PPS of V114 or PCV13. **Study V114-025**
    - diphtheria toxoid, tetanus toxoid, PT, FHA, pertussis fimbrae types 2/3 (FIM 2/3), PRN, poliovirus serotypes 1, 2 and 3, Hib-PRP at 30 days PPS of V114 or PCV13. **Study V114-029**

    - Antibody responses to hepatitis A antigen, measles, mumps, rubella virus, varicella-zoster virus, and PRP at 30 days PTD of V114 or PCV13. **Study V114-029**

- Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PPS, immediately pre-toddler dose and 30 days PTD.

***CHMP's comment***

In general, the chosen endpoints are considered acceptable and adequate to address the study objectives. The use of serotype specific IgG for primary immunogenicity analyses is endorsed, as an IgG titre of 0.35 µg/mL is a surrogate of protection. Assessment will be based on totality of immunogenicity findings based on all relevant parameters, therefore in-depth assessment of the immune response is appreciated. Totality of all immunogenicity results will be assessed.

## Sample size

V114-025

The targeted sample size was 1180 participants, 590 in each vaccination group. The sample size was chosen to ensure sufficient power to evaluate both primary and secondary hypotheses. The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated with respect to IgG GMCs and response rates for the 13 shared serotypes and superiority is demonstrated with respect to IgG GMCs and response rates for the 2 unique serotypes at 30 days PTD (post dose 3).

With this study sample size and the assumptions described below, the overall power for the primary hypotheses is >95% at a 1-sided 2.5% alpha level for demonstrating non-inferiority of V114 to PCV13 for the 13 shared serotypes and superiority for the 2 unique serotypes for V114 formulations. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%.

The following assumptions were applied:

- For all hypothesis: an approximately 75% evaluability rate at post toddler dose as observed in previous Phase 2 V114 paediatric studies;
- V114 is noninferior to PCV13 for the 13 shared serotypes and superior to PCV13 for the 2 unique serotypes based on IgG response rate, defined as the proportion of participants with a titer at or above the threshold value of ≥0.35 µg/mL at 30 days PTD (*Hypothesis 1 and 2*):
    - Non-inferiority margin of -0.1 for the difference (V114-PCV13) for the 13 shared serotypes.
    - Superiority margin of 0.1 for the difference (V114-PCV13) for the 2 unique serotypes.
    - Underlying serotype-specific IgG response rates are 95% at 30 days PTD in the V114 group and 95% for the 13 serotypes in PCV13 and 2% for the 2 unique serotypes in the PCV13 group.
- V114 is noninferior to PCV13 for the 13 shared serotypes and superior to PCV13 for the 2 unique serotypes based on IgG GMCs at 30 days PTD (*Hypothesis 3 and 4*):
    - Non-inferiority margin of 0.5 (V114/PCV13) for the 13 shared serotypes.
    - Superiority margin of 2.0 (V114/PCV13) for the 2 unique serotypes.

- Standard Deviation (SD) of IgG GMCs in log scale is 1.1 as those observed in previous MSD studies.
- The true GMT ratio (V114/PCV13) for IgG GMCs is 1.0 for the 13 shared serotypes and 10.0 for the 2 unique serotypes.

For the hypotheses driven secondary endpoints, the power is 90.9% and >95% for each of the 2 non-inferiority hypotheses when INFANRIX™ hexa and Rotarix™ administered concomitantly with V114 or PCV13, respectively. This is based on the assumptions of approximately 80% evaluability rate at PPS for Rotarix™ and 75% evaluability rate at PTD for INFANRIX™ hexa. The assumed response rates, GMT, and non-inferiority margins are listed in Table 6.

**Table 6 Summary of Endpoints and Power for Concomitant Vaccine Antigens V114-025**

| | Antigen | Endpoint | Time Point | Assumed Response Rate or Standard Deviation | NI Margin | Power |
|---|---|---|---|---|---|---|
| INFANRIX™ hexa | Diphtheria toxoid | % ≥0.1 IU/mL | PTD | 95% | -10% | 90.9% |
| | Tetanus toxoid | % ≥0.1 IU/mL | PTD | 97% | -5% | |
| | Pertussis – PT | % ≥5 EU/mL | PTD | 90% | -10% | |
| | Pertussis – FHA | % ≥5 EU/mL | PTD | 90% | -10% | |
| | Pertussis – PRN | % ≥5 EU/mL | PTD | 90% | -10% | |
| | Hib-PRP | % ≥0.15 µg/mL | PTD | 90% | -10% | |
| | HBsAg | % ≥10 mIU/mL | PTD | 95% | -10% | |
| | Poliovirus 1 | % with Nab ≥1:8 dilution | PTD | 97% | -5% | |
| | Poliovirus 2 | % with Nab ≥1:8 dilution | PTD | 97% | -5% | |
| | Poliovirus 3 | % with Nab ≥1:8 dilution | PTD | 97% | -5% | |
| Rotarix™ | Rotavirus | GMT Ratio | PPS | SD = 1.7 | 2-Fold | >95% |

EU = endotoxin unit; FHA = filamentous hemagglutinin; GMT = geometric mean titer; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; IU = international unit; Nab = neutralizing antibodies; NI = non-inferiority; PPS = post primary series; PRN = pertactin; PRP = polyribosylribitol phosphate; PT = pertussis toxin; PTD = post-toddler dose; SD = standard deviation (in log scale).

Due to the larger serum requirements of the MOPA assay, functional antibody activity (as measured by the OPA GMTs) will be assessed in the first 20% of all participants with sufficient serum volume at PPS to evaluate OPA responses (OPA Subset). Additionally, evaluation of OPA responses will be conducted at the Pretoddler Dose and PTD for all participants who had OPA performed at PPS and for whom there is sufficient volume.

V114-029

The overall sample size will be approximately 1720 with 860 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses. The study will be considered to have met its primary objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PPS (post dose 3) and for IgG GMCs at 30 days PTD (post dose 4).

With this study sample size and the assumptions listed below, the overall power for all the primary hypotheses is >95% to demonstrate non-inferiority of V114 to PCV13 for the 13 shared serotypes and the 2 unique serotypes for V114. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%, to demonstrate superiority for the 2 unique V114 serotypes is >95%, and to demonstrate the superiority for the serotype 3 IgG response rates and IgG GMCs at 30 days PD3 is >95%, and IgG GMCs at 30 days PD4 is 94%.

The following assumptions were applied:

- For all hypothesis: an approximately 80% evaluability rate at PPS and approximately 75% evaluability rate at PTD.
    - V114 is noninferior to PCV13 for the 13 shared serotypes and the 2 unique serotypes based on IgG response rate at 30 days PPS (Hypothesis 1 & 2). A non-inferiority margin of -0.1 for the difference (V114 minus PCV13) in the 13 shared serotypes. A serotype-specific true response rate for 15 pneumococcal serotypes in V114 of 0.95 for all serotypes except 3, 6B, 23F and 33F for which the response rate is 0.90.
    - V114 is noninferior to PCV13 for the 13 shared serotypes and the 2 unique serotypes based on IgG GMCs at 30 days PPS (Hypothesis 3 & 4). A non-inferiority margin of 0.5 for the GMC ratio (V114/PCV13) in the 13 shared serotypes. A true GMC ratio of 1.0 for the 13 shared serotypes and for the 2 unique serotypes between V114 and the lowest GMC of any of the shared serotypes in PCV13, excluding serotype 3. The standard deviation of the natural log concentrations is 1.1 for each of the 15 pneumococcal serotypes in V114.
    - V114 is noninferior to PCV13 for the 13 shared serotypes and the 2 unique serotypes based on IgG GMCs at 30 days PTD (Hypothesis 5 & 6). The standard deviation of the natural log concentrations is 1.1 for each of the 15 pneumococcal serotypes in V114. A true GMC ratio of 1.0 for the 13 shared serotypes and and for the 2 unique serotypes between V114 and the lowest GMC of any of the shared serotypes in PCV13, excluding serotype 3.
- Secondary Immunogenicity Endpoints/Hypotheses (Hypothesis 7 to 11):
    - This study has >90% power at a 1-sided 2.5% alpha-level to demonstrate Pentacel™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ administered concomitantly with V114 is non-inferior to these vaccines administered concomitantly with PCV13 based on the response rate of antigens included in Pentacel™ at 30 days PD3 and antigens included in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. This power assumes the same underlying response rate in both V114 group and PCV13 group for each antigen. Detailed assumptions for concomitant antigens are provided in Table 7.

**Table 7 Summary of Endpoints and Power for Concomitant Vaccine Antigens V114-029**

| Concomitant Vaccine | Antigen | Endpoint | Timepoint | NI Margin (δ) (V114-Prevnar 13™) | Evaluability Rate | Assumed True Response Rates | Power |
|---|---|---|---|---|---|---|---|
| Pentacel™ | Diphtheria toxoid | % ≥ 0.1 IU/mL | PD3 | -10% | 80% | 0.90 | >95% |
| | Tetanus toxoid | % ≥ 0.1 IU/mL | PD3 | -5% | 80% | 0.97 | |
| | Pertussis – PT | % ≥ 5 EU/mL | PD3 | -10% | 80% | 0.90 | |
| | Pertussis – FHA | % ≥ 5 EU/mL | PD3 | -10% | 80% | 0.90 | |
| | Pertussis – FIM 2/3 | % ≥ 20 EU/mL | PD3 | -10% | 80% | 0.90 | |
| | Pertussis – PRN | % ≥ 5 EU/mL | PD3 | -10% | 80% | 0.90 | |
| | Poliovirus 1 | % with NAb>=1:8 dilution | PD3 | -5% | 80% | 0.97 | |
| | Poliovirus 2 | % with NAb>=1:8 dilution | PD3 | -5% | 80% | 0.97 | |
| | Poliovirus 3 | % with NAb>=1:8 dilution | PD3 | -5% | 80% | 0.97 | |
| | Hib-PRP | % ≥ 0.15 µg/mL | PD3 | -10% | 80% | 0.90 | |
| VAQTA™ | Hepatitis A | % ≥ 10 mIU/mL | PD4 | -10% | 70% | 0.95 | >95% |
| M-M-R™II | Measles | % ≥ 255 mIU/mL | PD4 | -5% | 75% | 0.95 | >90% |
| | Mumps | % ≥ 10 mumps Ab units/mL | PD4 | -5% | 75% | 0.95 | |
| | Rubella | % ≥ 10 IU/mL | PD4 | -5% | 75% | 0.95 | |
| VARIVAX™ | VZV | % ≥ 5 gpELISA units/ml | PD4 | -10% | 70% | 0.90 | >95% |
| HIBERIX™ | Hib-PRP | % ≥ 0.15 µg/mL | PD4 | -10% | 65% | 0.95 | >95% |

EU = endotoxin unit; FHA = filamentous hemagglutinin; FIM = fimbriae types 2 and 3; gpELISA = glycoprotein enzyme-linked immunosorbent assay; mIU = milli International Units; NAb=neutralizing antibodies; NI = non-inferiority; PD = postdose; PRN = pertactin; PRP = polyribosylribitol phosphate; PT = pertussis toxin; VZV = varicella-zoster virus.

- V114 is superior to PCV13 for the 2 unique serotypes based on the proportion of participants with serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PPS (post dose 3) (Hypothesis 12). A superiority margin of 0.1 for the difference (V114 minus PCV13). A serotype-specific true response rate for the 2 V114 unique serotypes of 0.95 for 22F and 0.90 for 33F vs 0.02 for PCV13.
- V114 is superior to PCV13 for the 2 unique serotypes based on serotype-specific IgG GMCs at 30 days PD3 and 30 days PTD (post dose 4) (Hypothesis 13 &14). A superiority margin of 2.0 for the GMC ratio (V114/PCV13). A true GMC ratio of 10.0. The standard deviation of the natural log concentrations is 1.1.
- V114 is superior to PCV13 for serotype 3 based on the proportion of participants with serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PPS (post dose 3) (Hypothesis 15). A superiority margin of 0 for the difference (V114 minus PCV13). A true response rate for serotype 3 of 0.95 in the V114 group vs 0.76 in the PCV13 group.
- V114 is superior to PCV13 for serotype 3 based on serotype-specific IgG GMCs at 30 days PPS (post dose 3) (>95% power) and 30 days PTD (post dose4) (94% power) (Hypothesis 16 & 17). A superiority margin of 1.2 for the GMC ratio (V114/PCV13). True GMC ratios of 1.94 at 30 days PPS and 1.38 at 30 days PTD. The standard deviation of the natural log concentrations is of 0.75 at 30 days PPS and 0.73 at 30 days PTD.

Due to the larger serum requirements of the MOPA, functional antibody activity (as measured by OPA GMTs) will be assessed in the first 20% of all participants with sufficient serum volume at PD3 to evaluate OPA responses (OPA Subset). Additionally, evaluation of OPA responses will be conducted at Predose 4 and PD4 for 50% of the participants who had OPA performed at PD3, for whom there is sufficient volume.

***CHMP's comment***

The main driver for the sample size calculation of the pivotal studies was to achieve sufficient power to meet immunogenicity objectives. The underlying assumptions appear plausible.
The sample size accounts for 25% non-evaluability at post-toddler dose, even though this is the PP population, this exclusion rate is considered high. As non-evaluability might be linked to immunogenicity, handling of non-evaluable subjects in the analysis deserved further attention (see statistical methods).
Multiplicity is controlled for the primary endpoints.

As stated above, the non-inferiority margins have been agreed in the scientific advice (EMEA/H/SA/1492/1/FU/1/2017/III) and are identical to the margin used during MAA of PCV13, during which PCV7 was the active comparator.

The interpretation of the immune response generated by V114 for the 2 unique serotypes is hampered by the fact that the clinical relevance of this response is unknown. However, non-inferiority criteria on IgG response rate posed for the 2 unique serotypes based on the lowest response generated by the shared serotypes (excluding serotype 3) at least indicates that a substantial and potentially clinically relevant response was generated.

Measuring of OPA GMTs in approximately 20% of subjects will provide sufficient insight into the immune response generated by V114 and PCV13.

## Randomisation

For both pivotal studies, treatment allocation occurred centrally using interactive response technology (IRT) system. Participants were assigned randomly in a 1:1 ratio to V114 or PCV13.

For **Study V114-025**, randomization was stratified based on gestational age <37 weeks (yes/no); No preterm infants will be enrolled at sites in the Russian Federation.

In Study **V114-029** no stratification factors were used.

***CHMP's comment***

Randomization using a central IRT system is acceptable.

For study V114-025 randomisation was stratified for gestational age which is endorsed, as dosing regimen was different between term- and preterm infants.

No stratification by gestational age was performed during study V114-029. Stratification by gestational age would have been appreciated. However, considering the study showed a comparable distribution in both study arms, no additional information is requested.

No stratification for centre has been performed, due to small number of participants that would be included in analyses from each centre. Upon request the MAH performed additional sensitivity analyses adjusting the primary analyses for region. No substantial differences were observed, indicating a minor impact of region on immunogenicity.

## Blinding (masking)

Both studies were double blind and used a similar method of blinding:

V114 and PCV13 will be prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator who are involved in the clinical evaluation of the participants will remain blinded to the group assignments.

Because V114 and PCV13 have a different appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing, and administering these study vaccines. The paediatric vaccines being provided in the study will also be prepared and administered by unblinded study site staff for consistency even though these vaccines are being provided open label for this study.

To avoid bias, the unblinded study personnel will have no further contact with study participants for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow-up procedures. Additionally, blinded site personnel will not be present in the examination room when study vaccines are administered. Contact between participants and unblinded study personnel after vaccination administration is strictly prohibited. Blinded site personnel will be responsible for all safety and immunogenicity follow-up procedures after vaccine administration.

***CHMP's comment***

Both pivotal trials were double-blind.

Blinding measures were taken to keep participants (legal guardians/parents), clinical staff and study-site personnel blinded to the study vaccine allocation. In principle, the measures to ensure blinding are adequate. However, the administrator of the study vaccines was not blinded, and could theoretically

inform participants about the vaccine administered. As both vaccines are active, the likelihood and potential impact are considered limited.

## Statistical methods

Analysis population:

Both studies defined similar analysis populations:

The Per-Protocol (PP) population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s).

A supportive analysis using the Full Analysis Set (FAS) population will also be performed for the primary immunogenicity endpoints and selected secondary endpoints for the evaluation of concomitant vaccines. The FAS population consists of all randomized participants who received at least one PCV vaccination and have a serology result relevant to the immunogenicity endpoint and time point being analyzed. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population.

Safety analyses were based on all participants as treated population (APaT) population, which included all participants who received at least 1 dose of study intervention. Participants were included in the intervention group according to the intervention they actually received.

Analysis method:

A detailed analysis strategy for immunogenicity endpoints is presented in Table 8 for study V114-025.

**Table 8 Analysis Strategy for Immunogenicity Variables V114-025**

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach[†] | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Primary Endpoint (H1 – H2)** | | | | |
| Serotype-specific IgG response rates at 30 days PTD | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed. |
| | S | | FAS | |
| **Primary Endpoint (H3 – H4)** | | | | |
| Serotype-specific IgG GMCs at 30 days PTD | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed. |
| | S | | FAS | |
| **Secondary Endpoint (H5)** | | | | |
| Antigen-specific response rates for all antigens included in INFANRIX™ hexa at 30 days PTD of V114 or PCV13 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed. |
| | S | | FAS | |
| **Secondary Endpoint (H6)** | | | | |
| Anti-rotavirus IgA GMT at 30 days PPS of V114 or PCV13 | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed. |
| | S | | FAS | |
| **Other Secondary Endpoints** | | | | |
| Serotype-specific IgG response rates and GMCs for the 15 serotypes contained in V114 at 30 days PPS | P | Descriptive Statistics (estimate, 95% CI) | PP | Missing data will not be imputed. |

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach† | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| Serotype-specific OPA GMTs and response rates at 30 days PTD | P | Descriptive Statistics (estimate, 95% CI) | PP | Missing data will not be imputed. |
| Serotype-specific IgG response rates for the 2 unique serotypes in V114 at 30 days PTD | P | Miettinen and Nurminen (estimate, 95% CI) | PP | Missing data will not be imputed. |

CI = confidence interval; FAS = Full Analysis Set; GMC = geometric mean concentration; GMT = geometric mean titer; H = hypothesis; IgA = Immunoglobulin A; IgG = Immunoglobulin G; OPA = opsonophagocytic activity; PD = postdose; PnPs = pneumococcal polysaccharide; PP = Per-Protocol; PPS = post primary series; PTD = post toddler dose.
† P = Primary approach; S = Supportive approach.
‡ Estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

A detailed analysis strategy for immunogenicity endpoints is presented in Table 9 for study V114-029.

**Table 9 Analysis Strategy for Immunogenicity Variables V114-029**

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach† | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Primary Endpoints (H1 and H2)** | | | | |
| Proportion of participants with serotype-specific IgG ≥0.35 µg/mL at 30 days PD3 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Primary Endpoints (H3 and H4)** | | | | |
| Serotype-specific IgG GMCs at 30 days PD3 | P | t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Primary Endpoints (H5 and H6)** | | | | |
| Serotype-specific IgG GMCs at 30 days PD4 | P | t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H7)** | | | | |
| Antigen-specific response rates for all antigens included in Pentacel™ at 30 days PD3 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| Antigen-specific GMCs for all pertussis antigens included in Pentacel™ at 30 days PD3 | P | t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H8)** | | | | |
| Anti-hepatitis A response rate at 30 days PD4 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H9)** | | | | |
| Antigen-specific response rates for all antigens included M-M-R™II at 30 days PD4 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H10)** | | | | |
| Anti-varicella response rate at 30 days PD4 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H11)** | | | | |
| Anti-PRP response rate at 30 days PD4 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| | S | | FAS | |
| **Secondary Endpoints (H12)** | | | | |
| Proportion of participants with serotype-specific IgG ≥0.35 µg/mL at 30 days PD3 for the 2 unique V114 serotypes | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach[†] | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Secondary Endpoints (H13)** | | | | |
| Serotype-specific IgG GMCs at 30 days PD3 for the 2 unique V114 serotypes | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| **Secondary Endpoints (H14)** | | | | |
| Serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| **Secondary Endpoints (H15)** | | | | |
| Proportion of participants with anti-serotype 3 IgG ≥0.35 µg/mL at 30 days PD3 | P | Miettinen and Nurminen (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| **Secondary Endpoints (H16)** | | | | |
| Serotype 3 IgG GMCs at 30 days PD3 | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| **Secondary Endpoints (H17)** | | | | |
| Serotype 3 IgG GMCs at 30 days PD4 | P | t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value) | PP | Missing data will not be imputed |
| **Other Secondary Endpoints** | | | | |
| Anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3. | P | Descriptive Statistics (estimate, 95% CI) | PP | Missing data will not be imputed |

CI = confidence interval; FAS = Full Analysis Set; GMC = Geometric Mean Concentration; GMT = Geometric Mean Titer; IgG = Immunoglobulin G; OPA= opsonophagocytic activity; PD = postdose; PnPs = pneumococcal polysaccharide; PP = Per-Protocol; PRP = polyribosylribitol phosphate.

[†] P = Primary approach; S = Supportive approach.

[‡] Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) will be calculated using t-distribution with the variance estimate from a linear model utilizing the log- transformed antibody titers as the response and a single term for vaccination group.

Multiplicity

**V114-025**

The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated with respect to IgG GMCs and response rates for the 13 shared serotypes and superiority is demonstrated with respect to IgG GMCs and response rates for the 2 unique serotypes at 30 days PTD. All hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha level. This approach controls the 1-sided type-I error rate at 0.025; thus, no multiplicity adjustment is required.

The study will be considered to have met its secondary objective for a specific concomitant vaccine if non-inferiority is demonstrated for all the antigens included in that concomitant vaccine.

**V114-029**

The study will be considered to have met its primary objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. All hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha level. This approach controls the 1-sided type-I error rate at 0.025, thus no multiplicity adjustment is required.

The study will be considered to have met its secondary objective for a specific concomitant vaccine if non-inferiority is demonstrated for all the antigens included in that concomitant vaccine. The study will be considered to have met its secondary objective for the superiority hypotheses for the 2 unique V114 serotypes if superiority is demonstrated for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. The study will be considered to have met its secondary objective for the superiority hypotheses for serotype 3 if superiority is demonstrated for IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4.

***CHMP's comment***

The use of the PP to conclude on non-inferiority, with corresponding supportive analyses based on the FAS is supported, to allow conclusions on non-inferiority.

Missing data are not imputed. The sample size accounts for 25% non-evaluability at post-toddler dose, which is considered relatively high. Non-evaluability might be linked to immunogenicity, therefore exclusion of non-evaluable subjects in the immunogenicity analysis should be further substantiated, and sensitivity analyses where missing are imputed using plausible assumptions were requested during the pre-submission meeting. Upon request during the pre-submission meeting, additional analyses were provided (supplementary document 07W0MX) in the all randomized population for the primary and key secondary endpoints. These additional analyses are appreciated. However, still randomized participants who did not have serology results at the time point for the analysis were not included in the analysis. The MAH argued that the reasons for missing serology results were generally balanced between vaccination groups. In addition, the MAH argued that the assay results were not available to the investigators at the time of clinical visits, so the missing data are unlikely to be dependent on the immunogenicity outcomes, and therefore it is reasonable to assume that the missing data are missing completely at random. Therefore, the MAH decided that no data were imputed for these analyses. We do not agree with the argument that the fact that assay results were not available to the investigator provides sufficient argument to assume missing completely at random, it does however make it likely that there was no purposive selection. However, the percentage of missing serology results from the FAS was relatively small and comparable over the groups as shown below.

| Timing | Study V114-025 | | Study V114-029 | |
|---|---|---|---|---|
| | V114 (N=591) | PCV13 (N=593) | V114 (N=860) | PCV13 (N=860) |
| Missing serology results for IgG analysis | | | | |
| 30 days PPS | 2 (0.3%) | 12 (2.0%) | 62 (7.2%) | 65 (7.6%) |
| Prior to toddler dose | 22 (3.7%) | 22 (3.7%) | 67 (7.8%) | 63 (7.3%) |
| 30 days PTD | 18 (3.0%) | 18 (3.0%) | 51 (5.9%) | 48 (5.6%) |

As there are also no strong effect modifiers known that impact immunogenicity results, and results were consistent between the PP and the FAS (see results), relying on the missing completely at random assumption unlikely has strong impact on the results. Therefore, this issue is not further pursued.

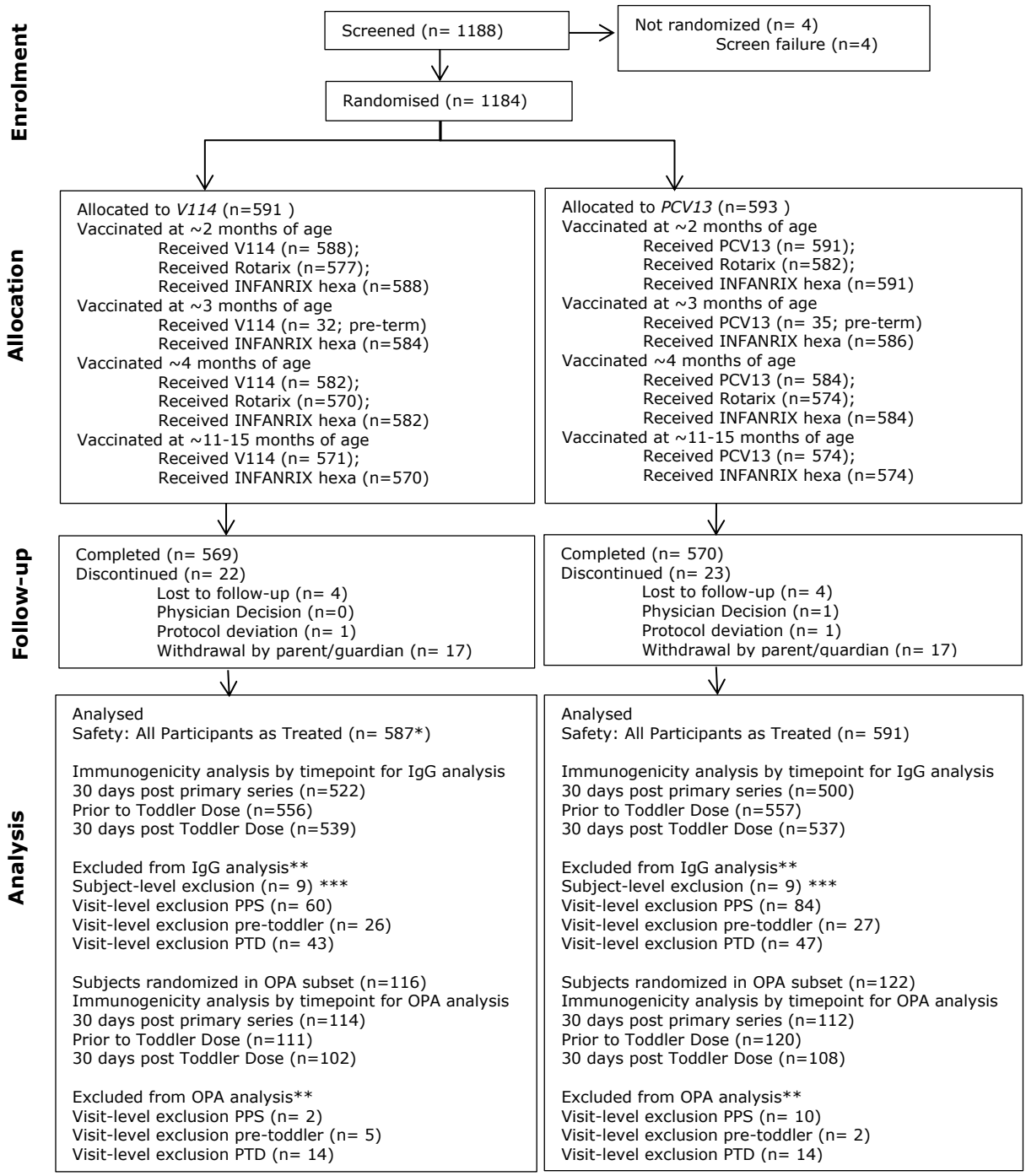
Considering the fact that all primary objectives should be met prior to study being successful and all hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha level, for the primary hypothesis alpha is adequately controlled. However, for study V114-025 the study will be considered to have met its secondary objective for a specific concomitant vaccine if non-inferiority is demonstrated for all the antigens included in that concomitant vaccine, either INFARIX or ROTARIX. For study V114-029 multiple hypothesis tests for secondary endpoints have been formulated, without a strategy to control type I error over these outcomes. Therefore, type I error is not adequately controlled in the strict sense over the secondary endpoints. Therefore, the results will be descriptive.

The between-treatment difference of the proportion of anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PTD (V114 minus Prevenar 13™) and its 95% confidence interval (CI) will be calculated using unstratified Miettinen and Nurminen method. Coverage probabilities are generally close to the nominal level of 95%.

# Results

## Participant flow

### V114-025




*One participant was cross-treated with study medication and was excluded form APaT population
**Subjects may have more than 1 reason for exclusion. Subjects are displayed in all applicable categories.
***Subject level exclusion results in exclusion from analyses at all timepoints

***CHMP's comment***

The participant flow is comparable in both treatment groups. The majority of enrolled participants were vaccinated (more than 99% of participants) and also completed the study (more than 95% of participants) in both groups. Low numbers of participants discontinued the study (22 participants [3.7%] vs 23 participants [3.9%] in the V114 vs the PCV13 group), with withdrawal by parent/guardian being the most reported reason; 17 subjects (2.9%) in both treatment groups.

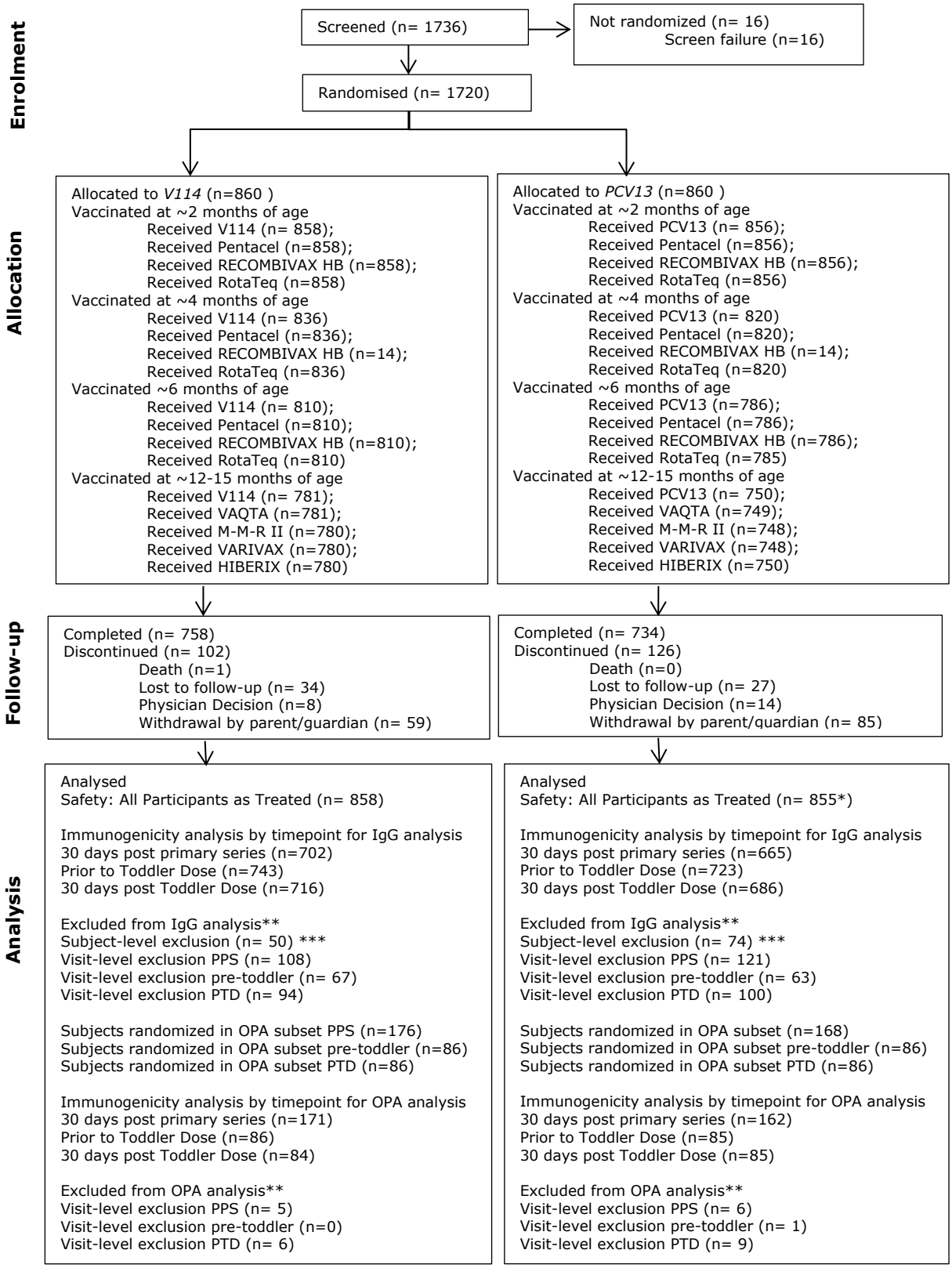
In both treatment groups, 1 Protocol deviation led to discontinuation of the study.

The majority of participants, >84%, were included in the PP population in both treatment groups at each timepoint. Exclusion from immunogenicity analysis was divided into subject level exclusion and visit-level exclusion. Subject-level exclusion resulted in exclusion from all immunogenicity analyses at all timepoints and was identical in both treatment groups (n=9) with "missed at least one vaccination of PCV during the primary infant series" being the reported reason for exclusion.

Visit-level exclusion at 30 days PPS was somewhat lower in the V114 group compared to the PCV13 group, n=60 (10.2%) vs N=84 (14.2%) respectively. The most commonly reported reason for visit-level exclusion in both treatment groups was blood draw out of window, with 25 subjects in the V114 group (4.2%) and 23 subjects in the PCV13 group (3.9%), and vaccination out of window, with 19 subjects in the V114 group (3.2%) and 31 subjects in the PCV13 group (5.2%). Generally, the reasons for exclusion were balanced over the groups, with more subjects out of window in the PCV13 group.

Visit-level exclusions at both pre-toddler dose and PTD were comparable between the V114 and PCV13 group, with 26 of participants (4.4%) and 43 of participants (7.3%) being excluded in the V114 group compared to 27 (4.6%) and 47 (7.9%) in the PCV13 group. The most commonly reported reasons for visit-level exclusion was missing serology results at pre-toddler dose and missed PCV at toddler dose (includes participants who discontinued the study) and missing serology results.

**V114-029**




*One participant was cross-treated with study medication and was excluded form APaT population
**Subjects may have more than 1 reason for exclusion. Subjects are displayed in all applicable categories.
***Subject level exclusion results in exclusion from analyses at all timepoints

***CHMP's comment***

The participant flow is comparable in both treatment groups. The majority of enrolled participants were vaccinated (> 99% of participants) and also completed the study (> 85% of participants) in both groups. More than 10% of participants discontinued the study (102 participants [11.9%] vs 126 participants [14.7%] in the V114 vs the PCV13 group), with withdrawal by parent/guardian being the most reported reason in both treatment groups, with 59 participants (6.9%) in the V114 group vs 85 participants (9.9%) in the PCV13 group.

The majority of participants, >77%, were included in the PP population in both treatment groups at each timepoint.

Exclusion from immunogenicity analysis was divided into subject level exclusion and visit-level exclusion. Subject-level exclusion resulted in exclusion from all immunogenicity analyses at all timepoints and was numerically lower in the V114 group (n=50, 5.8%) vs the PCV13 group (n=74, 8.6%), with missed at least one vaccination of PCV during the primary infant series being the reported reason for exclusion.

Visit-level exclusion at 30 days PPS was somewhat lower in the V114 group compared to the PCV13 group, n=108 (12.6%) vs N=121 (14.1%) respectively. The most commonly reported reason for visit-level exclusion in both treatment groups was blood draw out of window, with 31 subjects in the V114 group (3.1%) and 41 subjects in the PCV13 group (4.8%), and missed serology results, with 62 subjects in the V114 group (7.2%) and 65 subjects in the PCV13 group (7.6%). Generally, the reasons for exclusion were balanced over the groups.

Visit-level exclusions at both pre-toddler dose and PTD were comparable between the V114 and PCV13 group, with 67 of participants (7.8%) and 94 of participants (10.9%) being excluded in the V114 group compared to 63 (7.3%) and 100 (11.6%) in the PCV13 group. The most commonly reported reasons for visit-level exclusion was missing serology results at pre-toddler dose and missed PCV at toddler dose (includes participants who discontinued the study) and missing serology results.

## Recruitment

### V114-025

The study was conducted at 58 sites in 9 countries; 3 sites in Australia, 6 sites in Belgium, 3 sites in the Czech Republic, 6 sites in Estonia, 13 sites in Germany, 4 sites in Greece, 9 sites in Poland, 3 sites in the Russian Federation and 11 sites in Spain.

First subject first visit: 04 September 2019, Last subject last visit: 05 August 2021.

### V114-029

The study was conducted at 75 centers in 3 countries; 6 sites in Puerto Rico, 4 sites in Thailand, 5 sites in Turkey and 61 sites in the Unites States.

First subject first visit: 13 June 2019, Last subject last visit: 24 May 2021.

***CHMP's comment***

The pivotal studies were performed more or less simultaneous, which is acceptable.

It is appreciated that one of the pivotal studies was performed mainly in Europe. Of note, the studies were performed during the COVID pandemic. COVID impacted study conduct, which is discussed below.

## Conduct of the study

### V114-025

*Amendments*

There were 2 amendments to the original study protocol (dd. 22 February 2019). Amendment 1 (24 July 2019) included country specific changes for the Russian Federation, not Rotarix would be administred and no pre-term infants would be enrolled. Amendment 2 (16 March 2021) aimed to expand the visit windows for Visit 4 (PPS blood draw) and Visit 6 (PTD blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This change was made in response to the COVID-19 global pandemic which impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions.

*Protocol deviations*

Important protocol deviations were reported for 270 (22.8%) participants in the study. Of these, 186 participants (15.7%) had protocol deviations that were considered clinically important, see Table 10. The most frequently reported clinically important protocol deviations were categorized under Trial Procedures, as the participant's immunogenicity blood sample being drawn outside the protocol-defined window. The protocol deviations were comparably distributed between intervention groups.

**Table 10 Summary of Important Protocol Deviations Considered to be Clinically Important reported in >1% of participants - V114-025**

| | **V114 N=591** | | **PCV13 N=593** | | **Total N=1184** | |
|---|---|---|---|---|---|---|
| | **N** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Participants with clinically important protocol deviation | 78 | (13.2) | 108 | (18.2) | 86 | (15.7) |
| **Prohibited Medications** | **13** | **(2.2)** | **16** | **(2.7)** | **29** | **(2.4)** |
| Participant received a non-study live vaccine or non-live vaccine during the time period prohibited per protocol.[a] | 8 | (1.4) | 14 | (2.4) | 22 | (1.9) |
| **Study Intervention** | **5** | **(0.8)** | **13** | **(2.2)** | **18** | **(1.5)** |
| Participant was administered improperly stored study intervention.[b] | 4 | (0.7) | 11 | (1.9) | 15 | (1.3) |
| **Trial Procedures** | **64** | **(10.8)** | **86** | **(14.5)** | **150** | **(12.7)** |
| Immunogenicity blood sample was not drawn or the sample could not be tested for any immune responses due to an error by the site | 16 | (2.7) | 20 | (3.4) | 36 | (3.0) |
| Participant's immunogenicity blood sample was drawn outside the protocol- defined window. | 30 | (5.1) | 41 | (6.9) | 71 | (6.0) |
| Participant's study vaccination was administered outside the protocol- defined window for the vaccination prior to the immunogenicity blood sample. | 20 | (3.4) | 35 | (5.9) | 55 | (4.6) |

Every participant is counted a single time for each applicable row and column.
[a] Clinically important if participant received vaccine prohibited per protocol immediately prior to an immunogenicity assessment and for that assessment only.
[c] Clinically important if participant received improperly stored study intervention immediately prior to an immunogenicity assessment and for that assessment only.

***CHMP's comment***

The study conduct was overall acceptable. The protocol amendments are not considered to impact subject well-being. The visit windows for Visit 4 (PPS blood draw) and Visit 6 (PTD blood draw) were expanded by 18 days. As this was done for both treatment arms, this is not expected to affect the difference between arms if the distribution of visits later in the window was comparable over the arms. It could potentially impact the measurement of the immune response, however, considering the relatively short expansion of the window by 18 days no clinically relevant impact is expected.

The MAH has comprehensively monitored the protocol deviations. Important protocol deviations were reported by 186 participants (15.7%) during the study, most of which were deviations in trial procedures, with blood drawn outside protocol-defined window being most commonly reported, for 5.1% in the V114 group vs 6.9% in the PCV13 group, followed by study vaccination administered outside window, for 3.4% in the V114 group vs 5.9% in the PCV13 group. The percentage of clinically important protocol deviations were comparable between the V114 and PCV13 group (13.2% versus 18.2%).

**V114-029**

*Amendments*

There were 2 amendments to the original study protocol (dd. 30 January 2019). Amendment 1 (28 February 2020) was included to more closely align with guidelines for the assessment of immune responses to PCVs from the World Health Organization, the 2 unique V114 serotypes will be evaluated for non-inferiority to the immune response of the lowest of any of the shared serotypes in PCV13, excluding serotype 3. For these comparisons, PCV13 serotype 3 immune responses will be excluded as the immunological profile of serotype 3 is not consistent with the performance of other PCV13 vaccine serotypes. Amendment 2 (16 March 2021) aimed to expand the visit windows for Visit 3 (dose 3 vaccination), Visit 4 (PPS blood draw) and Visit 6 (PTD blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This change was made in response to the COVID-19 global pandemic which impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions. This amendment also includes the addition of 3 secondary hypotheses relating to the demonstration of superiority for serotype 3 immune responses.

*Protocol deviations*

Important protocol deviations were reported for 477 (27.7%) participants in the study. Of these, 239 participants (13.9%) had protocol deviations that were considered clinically important, see Table 11. The most frequently reported clinically important protocol deviations were related to trial procedures (e.g., study vaccination administered outside the protocol-defined window). The protocol deviations were comparably distributed between intervention groups.

**Table 11 Summary of Important Protocol Deviations Considered to be Clinically Important reported in >1% of participants - V114-029**

| | **V114 N=860** | | **PCV13 N=860** | | **Total n=1720** | |
|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Participants with one or more important protocol deviations considered to be clinically important | 121 | (14.1) | 118 | (13.7) | 239 | (13.9) |
| **Prohibited Medications** | **27** | **(3.1)** | **35** | **(4.1)** | **62** | **(3.6)** |
| Participant was administered a non-study live vaccine or non-live vaccine during the time period prohibited per protocol. | 20 | (2.3) | 27 | (3.1) | 47 | (2.7) |
| Participant was administered a non-study pneumococcal vaccine. | 6 | (0.7) | 6 | (0.7) | 12 | (0.7) |
| **Trial Procedures** | **104** | **(12.1)** | **102** | **(11.9)** | **206** | **(12.0)** |
| Participant's immunogenicity blood sample was drawn outside the protocol- defined window as follows: Visit 3: 6 months of age to 1 day prior to 7 months of age (+14 days); Visit 4: Day 28 to Day 60 Post dose 3; Visit 6: Day 28 to Day 60 Post dose 4. | 42 | (4.9) | 51 | (5.9) | 93 | (5.4) |
| Participant's study vaccination was administered outside the protocol defined window for the vaccination prior to the immunogenicity blood sample as follows: Visit 3 (Dose 3): 6 months of age to 1 day prior to 7 months of age (+14 days); Visit 5 (Dose 4): 12 months of age to 1 day prior to 16 months of age. | 61 | (7.1) | 51 | (5.9) | 112 | (6.5) |
| Every participant is counted a single time for each applicable row and column. | | | | | | |

***CHMP's comment***

The study conduct was overall acceptable. In protocol amendment 1 testing of superiority of the 2 unique serotypes was moved to a secondary objective, while primary objectives of non-inferiority of the 2 unique serotypes to the lowest of any of the shared serotypes were included. The objective of non-inferiority is more closely matched to the WHO guideline, which is appreciated. It ensures that any immune response generated by the 2 unique serotypes is substantial and potentially clinically relevant. In addition, the newly proposed primary endpoint is considered more stringent, as superiority of the new serotypes compared to PCV13, and in effect placebo for these serotypes, is more easily achieved than non-inferiority to any of the shared serotypes. The addition of 2 secondary endpoints investigating the superiority of serotype 3 during protocol amendment 2 is acceptable. Testing for superiority once non-inferiority has been demonstrated is acceptable. As both amendments were implemented prior to the last visit and database lock it would not affect the type I error.

The visit windows for Visit 3 (dose 3 vaccination) was extended by 14 days and the visit windows for Visit 4 (PPS blood draw) and Visit 6 (PTD blood draw) were expanded by 18 days. As this was done for both treatment arms, this is not expected to affect the difference between arms if the distribution of visits later in the window was comparable over the arms. It could potentially impact the induction and measurement of the immune response, however, considering the relatively short expansion of the window by 14 to 18 days no clinically relevant impact is expected.

The MAH has comprehensively monitored the protocol deviations. Important protocol deviations were reported by in total 239 participants (13.9%) during the study, most of which were deviations in trial procedures, with study vaccination administered outside protocol-defined window being most commonly reported, for 7.1% in the V114 group vs 5.9% in the PCV13 group, followed by blood drawn outside protocol-defined window, for 4.9% in the V114 group vs 5.9% in the PCV13 group. The percentage of clinically important protocol deviations were comparable between the V114 and PCV13 group (14.1% versus 13.7%).

## Baseline data

Although the proportions of participants by race and ethnicity varied across the studies due to the countries where these studies were conducted, the demographic characteristics were generally comparable between intervention groups in each study, see Table 12.

In study **V114-025**, the median age of participants at the time of consent was 8.0 weeks (range: 6 to 12 weeks). Approximately half of the participants were male, most participants were White; and the majority of participants were of non-Hispanic or Latino ethnicity. Approximately 6% of participants were preterm born infants (<37 weeks gestational age at birth).

In study **V114-029**, the median age of participants at the time of consent was 8.0 weeks (range: 6 to 12 weeks). Approximately 52% of the participants were male; 55% were white, and 26% were Asian. The majority (>74%) of participants were of non-Hispanic or Latino ethnicity. Approximately 9% of participants were preterm born infants (gestational age <37 weeks).

**Table 12 Participant Characteristics V114-025 and V114-029**

| | V114-025 | | | | V114-029 | | | |
|---|---|---|---|---|---|---|---|---|
| | V114 | | PCV13 | | V114 | | PCV13 | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 588 | | 591 | | 858 | | 856 | |
| **Sex** | | | | | | | | |
| Male | 305 | (51.9) | 306 | (51.8) | 461 | (53.7) | 429 | (50.1) |
| Female | 283 | (48.1) | 285 | (48.2) | 397 | (46.3) | 427 | (49.9) |
| **Age (Weeks)** | | | | | | | | |
| 6 | 77 | (13.1) | 60 | (10.2) | 75 | (8.7) | 80 | (9.3) |
| 7 | 80 | (13.6) | 82 | (13.9) | 100 | (11.7) | 98 | (11.4) |
| 8 | 161 | (27.4) | 152 | (25.7) | 276 | (32.2) | 252 | (29.4) |
| 9 | 151 | (25.7) | 162 | (27.4) | 281 | (32.8) | 289 | (33.8) |
| 10 | 53 | (9.0) | 75 | (12.7) | 90 | (10.5) | 96 | (11.2) |
| 11 | 43 | (7.3) | 39 | (6.6) | 28 | (3.3) | 32 | (3.7) |
| 12 | 23 | (3.9) | 21 | (3.6) | 8 | (0.9) | 9 | (1.1) |
| Mean | 8.4 | | 8.5 | | 8.4 | | 8.4 | |
| SD | 1.5 | | 1.5 | | 1.2 | | 1.3 | |
| Median | 8.0 | | 9.0 | | 8.0 | | 8.0 | |
| Range | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | |
| **Race** | | | | | | | | |
| American Indian Or Alaska Native | 4 | (0.7) | 5 | (0.8) | 6 | (0.7) | 13 | (1.5) |
| Asian | 4 | (0.7) | 5 | (0.8) | 223 | (26.0) | 226 | (26.4) |
| Black Or African American | 4 | (0.7) | 3 | (0.5) | 52 | (6.1) | 53 | (6.2) |
| Multiple | 5 | (0.9) | 7 | (1.2) | 98 | (11.4) | 80 | (9.3) |
| White | 571 | (97.1) | 571 | (96.6) | 472 | (55.0) | 480 | (56.1) |
| Native Hawaiian or Other Pacific Islander | | | | | 6 | (0.7) | 4 | (0.5) |
| Missing | | | | | 1 | (0.1) | 0 | (0.0) |
| **Ethnicity** | | | | | | | | |
| Hispanic Or Latino | 66 | (11.2) | 65 | (11.0) | 206 | (24.0) | 203 | (23.7) |
| Not Hispanic Or Latino | 522 | (88.8) | 524 | (88.7) | 639 | (74.5) | 643 | (75.1) |
| Not Reported | 0 | (0.0) | 1 | (0.2) | 11 | (1.3) | 5 | (0.6) |
| Unknown | 0 | (0.0) | 1 | (0.2) | 2 | (0.2) | 5 | (0.6) |
| **Gestational Age (Weeks)** | | | | | | | | |
| < 37 Weeks | 32 | (5.4) | 36 | (6.1) | 74 | (8.6) | 76 | (8.9) |
| ≥ 37 Weeks | 556 | (94.6) | 555 | (93.9) | 784 | (91.4) | 780 | (91.1) |
| SD=standard deviation. | | | | | | | | |

***CHMP's comment***

The baseline characteristics in the pivotal studies were balanced across treatment groups in both studies. Both studies were comparable with respect to gender and age of the participants included. Differences were observed concerning race and ethnicity, reflective of the countries in which the studies were performed. However, the included population seems to be sufficiently representative for the European population.
Overall, the intended population is well represented.

## Numbers analysed

For both studies primary immunogenicity analyses were conducted using the per protocol (PP) population, with supportive immunogenicity analyses conducted on the full analysis set (FAS) population for the primary immunogenicity endpoints and secondary immunogenicity endpoints that were associated with a hypothesis test.

**V114-025**

Safety analyses were based on all participants as treated population (APaT) population, which included 1178 randomized participants (V114, 587 participants; PCV13, 591 participants) who received at least 1 dose of study intervention. All participants received the study intervention to which they were randomized. One participant in the V114 group was cross-treated with study medication and is excluded from the APaT population, see Table 13.

**Table 13 Summary of analyses sets Study V114-025**

| Population | V114 | PCV13 |
|---|---|---|
| Subjects randomized | 591 | 593 |
| At least 1 dose of study intervention | 588 (99.5%) | 591 (99.7%) |
| APaT | 587 (99.3%) | 591 (99.7%) |
| Subjects included in IgG analyses by timepoint (PP population) | | |
| 30 Days post primary series (Dose 2) | 522 (88.3%) | 500 (84.3%) |
| Prior to toddler dose (Dose 3) | 556 (94.1%) | 557 (93.9%) |
| 30 Days post toddler dose (PTD, Dose 3) | 539 (91.2%) | 537 (90.6%) |
| Subjects included in OPA analyses by timepoint (PP population) | | |
| Randomized in OPA subset | 116 | 122 |
| 30 days post primary series | 114 (98.3%) | 112 (91.8%) |
| Prior to toddler dose | 111 (95.7%) | 120 (98.4%) |
| 30 days post toddler dose | 102 (87.9%) | 108 (88.5%) |

**V114-029**

Safety analyses were based on all participants as treated population (APaT) population, which included 1713 randomized participants (V114, 858 participants; PCV13, 855 participants) who received at least 1 dose of study intervention. All participants received the study intervention to which they were randomized. One participant in the PCV13 group was cross-treated with study medication and is excluded from the APaT population, see Table 14.

**Table 14 Summary of analyses sets Study V114-029**

| Population | V114 | PCV13 |
|---|---|---|
| Subjects randomized | 860 | 860 |
| At least 1 dose of study intervention | 858 (99.8%) | 856 (99.5%) |
| APaT | 858 (99.8%) | 855 (99.4%) |
| Subjects included in IgG analyses by timepoint (PP population) | | |
| 30 Days post primary series (Dose 3) | 702 (81.6%) | 665 (77.3%) |
| Prior to toddler dose (Dose 4) | 743 (86.4%) | 723 (84.1%) |
| 30 Days post toddler dose (PTD, Dose 4) | 716 (83.3%) | 686 (79.8%) |
| Subjects included in OPA analyses by timepoint (PP population) | | |
| Randomized in OPA subset 30 days post primary series (Dose 3) | 176 | 168 |
| Randomized in OPA subset prior to toddler dose and 30 days PTD | 86 | 86 |
| 30 days post primary series | 171 (97.2%) | 162 (96.4%) |
| Prior to toddler dose | 86 (100.0%) | 85 (98.8%) |
| 30 days post toddler dose | 84 (97.7%) | 85 (98.8%) |

***CHMP's comment***

The definitions of the analysis populations are acceptable.
Of all subjects randomized, most exclusions from the IgG analysis are observed at 30 days post primary series, and slightly more exclusions were present in the PCV13 group, with 88% versus 84% included for V114 and PCV13 for study V114-025 and 82% versus 77% for study V114-029 included. A very strong relation between exclusion from the IgG analysis and the immunogenicity results is unlikely, therefore major impact of the disbalance on the immunogenicity results is unlikely.

## Outcomes and estimation

### ***V114-025***

*Primary Immunogenicity endpoints*

As can be observed in Figure 1, V114 met noninferiority criteria for the 13 shared serotypes and met superiority criteria for the 2 unique serotypes (22F and 33F), as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35 µg/mL (response rates) at 30 days PTD in the per protocol population.

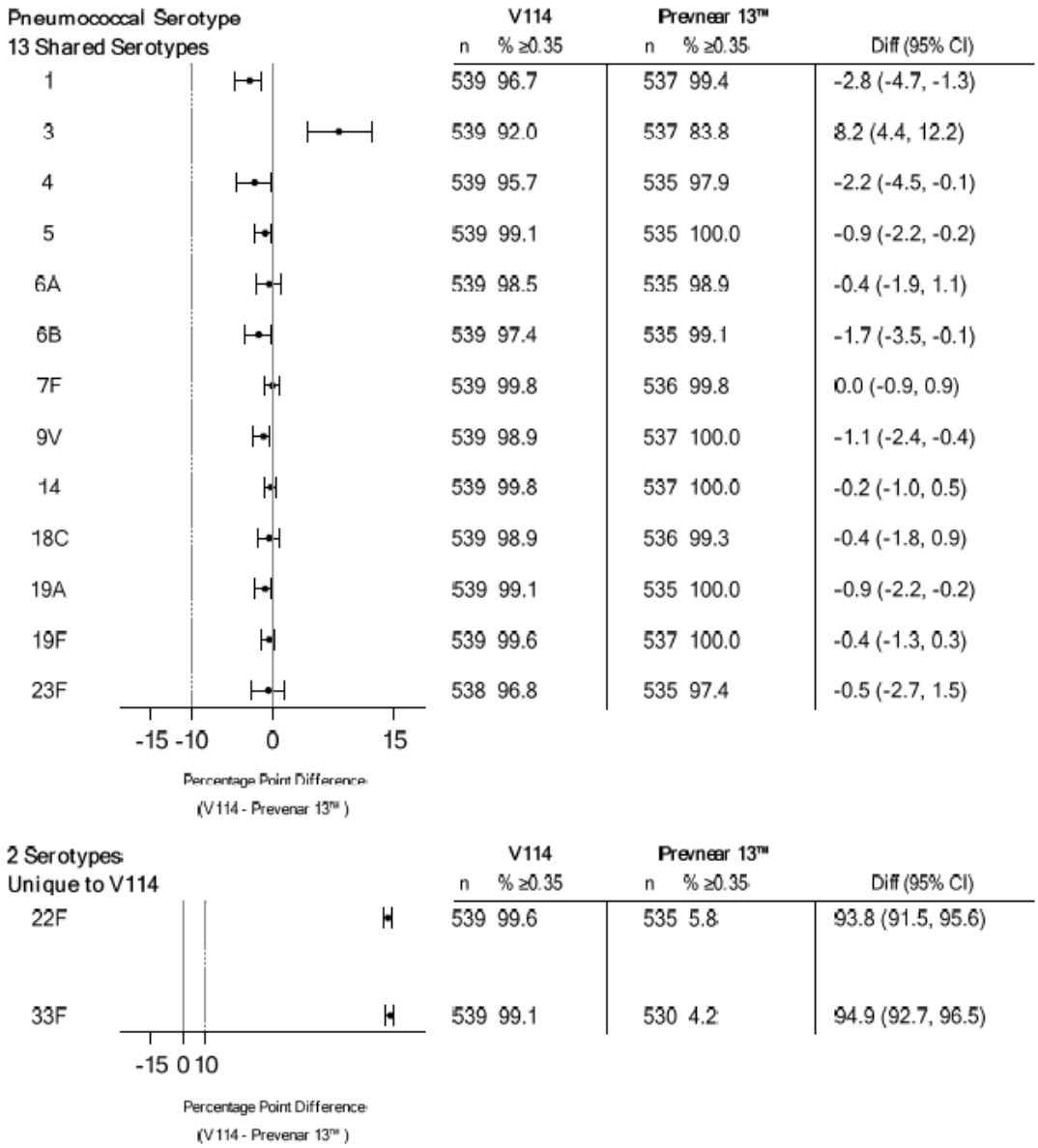



**Figure 1 Forest Plot of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Post Toddler Dose (PP population) – V114-025**

Serotype-specific IgG response rates at 30 days PTD in the FAS population were consistent with those observed in the PP population.

V114 met noninferiority criteria for the 13 shared serotypes and superiority criteria for the 2 unique serotypes (22F and 33F) as assessed by the serotype-specific IgG GMCs at 30 days PTD.

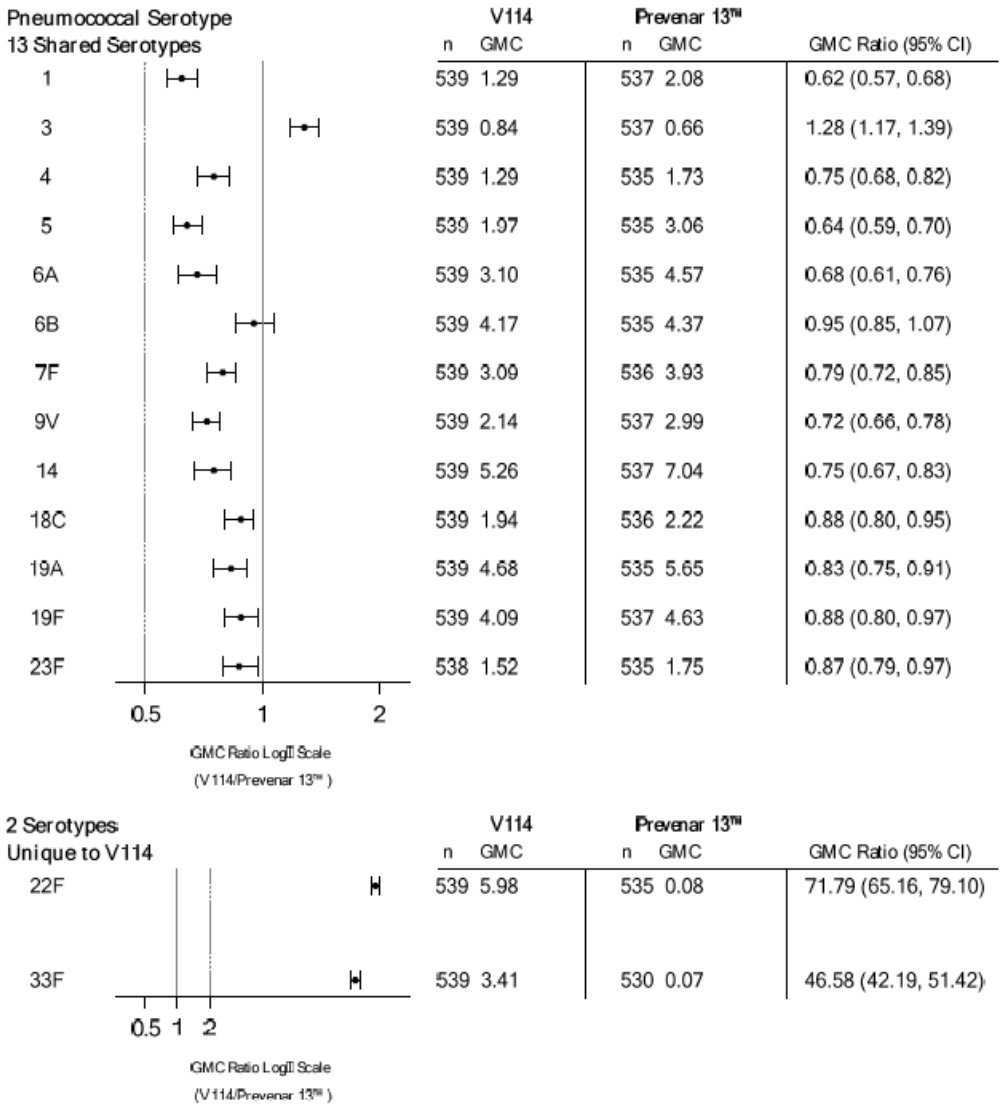



**Figure 2 Forest Plot of IgG GMC Ratios at 30 Days Post Toddler Dose (PP) - V114-025**

Serotype-specific IgG GMCs at 30 days PTD in the FAS population were consistent with those observed in the PP population. In addition, when only full-term infants are analysed, the resulst are consistent with the overall PP population.

The distribution of immune responses at 30 days PTD (as displayed by RCDCs) was generally comparable between intervention groups for the 13 shared serotypes and higher for the 2 unique serotypes (22F and 33F) in the V114 group, consistent with the results observed for serotype-specific IgG GMCs.

***CHMP's comment***

The primary immunogenicity objectives were met as non-inferiority to PCV13 for the 13 shared serotypes and superiority for the 2 unique serotypes in V114 were shown at 30 days PTD both for IgG response rate and IgG GMCs.

Excluding serotype 3, 30 days PTD, >95% of participants had achieved an IgG threshold value of ≥0.35 µg/mL for the 12 shared serotypes in the V114 group compared to >97% of participants in the PCV13 group. For serotype 3, 92.0% of participants achieved an IgG threshold value of ≥0.35 µg/mL in the V114 group compared to 83.8% in the PCV13 group. These results indicate that for the shared serotypes, the response rate was comparable between the V114 and PCV13 group 30 days post toddler dose. The surrogate of protection was achieved by the vast majority of participants indicating good protection against IPD.

For the 2 unique serotypes, as expected the response rate was significantly higher in the V114 group compared to the PCV13 group, with >99% of participants achieving an IgG threshold value of ≥0.35 µg/mL in the V114 group, compared to <6% in the PCV13 group. The response rate of >99% for both unique serotypes is not worse than the lowest response rate seen in the PCV13 group for the 13 shared serotypes. These results indicate a substantial immune response is generated for the 2 unique serotypes, which is likely to offer protection against IPD.

Analysis performed using the FAS population, provided similar results to the analysis performed on the PP population, indicating robustness of the results. In addition, the results including only full-term infants are comparable with the overall PP population. Considering that only full-term infants actually received the 2-dose primary series, the MAH was asked to include only full-term infants in the presentation of the immunogenicity data on the 2-dose primary series in the SmPC in section 5.1. The MAH has complied to the request.

Excluding serotype 3, 30 days PTD, the IgG GMCs ranged from 1.29 to 5.26 for the 12 shared serotypes in the V114 group compared to 1.73 to 7.04 in the PCV13 group, leading to GMC ratios that ranged from 0.62 to 0.95. For serotype 3, the IgG GMC in the V114 group was 0.88 compared to 0.62 in the PCV13 group. These results indicate that even though the non-inferiority margin of ≥0.5 was met for all 13 shared serotypes as assessed by the serotype-specific IgG GMCs at 30 days PTD that IgG GMCs at 30 days PTD were lower in the V114 group compared to the PCV13 group (Figure 2). Only serotype 3 and 6B had an upper bound of the 2-sided 95% CI that did contain 1.00. Four of the shared serotypes, 1, 5, 6A and 9V, had a lower bound of the 2-sided 95% CI that was lower than 0.67. For all serotypes the IgG GMCs were well above 0.35 µg/mL. As there is only a surrogate of protection available for IPD and not for pneumonia or AOM it is difficult to interpret the clinical impact of these lower titres on the protection against pneumonia and AOM. Especially considering the fact that for protection against pneumonia and AOM higher antibody responses are thought to be necessary compared to protection against IPD as the protection should take place at the mucosal level or the ear instead of blood. There is an ongoing AOM vaccine-efficacy clinical trial, which will evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal AOM. In addition, PSURs, including information on breakthrough disease/vaccine failure, serotype distribution and incidence of IPD will provide an indication on efficacy against the new serotypes included in the vaccine, as frequency of IPD caused by these serotypes is expected to decline after V114 uptake. In addition, this will provide insight into impact of the lower titers on immune persistence as frequency of IPD is reported per age category.

For the 2 unique serotypes, as expected the IgG GMCs were substantially higher in the V114 group compared to the PCV13 group, with IgG GMCs being 5.98 for serotype 22F and 3.41 for serotype 33F in the V114 group compared to 0.08 and 0.07 respectively in the PCV13 group. The IgG GMCs for both unique serotypes are higher than the IgG GMCs seen in the PCV13 group for the 13 shared serotypes, even excluding serotype 3. This again indicates a substantial immune response for the 2 serotypes, which likely confers protection against IPD as the IgG GMCs are above 0.35 µg/mL. For pneumonia and AOM the results are more difficult to interpret, however, as the immune response is substantial, it is likely that some protection against pneumonia and AOM caused by the 2 unique serotypes is still achieved.

*Secondary Immunogenicity Endpoints: concomitant vaccines*

Immune responses to INFANRIX™ hexa administered concomitantly with V114 met noninferiority criteria, as assessed by the proportions of participants meeting antigenspecific response rate to each antigen in INFANRIX™ hexa at 30 days PTD, see Table 15. Immune responses to INFANRIX™ hexa administered concomitantly with V114 in the FAS population were consistent with those observed in the PP population.

**Table 15 Proportions of Participants Meeting Specified INFANRIX™ hexa Antigen Responses at 30 Days Post Toddler Dose (PP) – V114-025**

| Antigen | Endpoint | NI Margin | V114 (N=588) | PCV13 (N=591) | Percentage Point Difference (V114 – PCV13) | |
|---|---|---|---|---|---|---|
| | | | Percentage (m/n) | Percentage (m/n) | Estimate (95% CI)[ab] | p-value[ab] (1- sided) |
| Diphtheria toxoid | % ≥ 0.1 IU/mL | -10% | 99.3 (533/537) | 99.8 (532/533) | -0.6 (-1.7, 0.4) | <0.001 |
| Tetanus toxoid | % ≥ 0.1 IU/mL | -5% | 99.6 (535/537) | 100.0 (533/533) | -0.4 (-1.3, 0.3) | <0.001 |
| Pertussis - PT | % ≥ 5 EU/mL | -10% | 99.4 (534/537) | 99.6 (531/533) | -0.2 (-1.3, 0.9) | <0.001 |
| Pertussis - FHA | % ≥ 5 EU/mL | -10% | 99.8 (536/537) | 100.0 (533/533) | -0.2 (-1.0, 0.5) | <0.001 |
| Pertussis - PRN | % ≥ 5 EU/mL | -10% | 99.6 (535/537) | 100.0 (533/533) | -0.4 (-1.3, 0.3) | <0.001 |
| Hib-PRP | % ≥ 0.15 µg/mL | -10% | 98.5 (516/524) | 98.1 (513/523) | 0.4 (-1.3, 2.1) | <0.001 |
| HBsAg | % ≥ 10 mIU/mL | -10% | 99.2 (518/522) | 100.0 (521/521) | -0.8 (-2.0, -0.0) | <0.001 |
| Poliovirus 1 | % with NAb≥1:8 dilution | -5% | 100.0 (526/526) | 100.0 (521/521) | 0.0 (-0.7, 0.7) | <0.001 |
| Poliovirus 2 | % with NAb≥1:8 dilution | -5% | 100.0 (525/525) | 100.0 (525/525) | 0.0 (-0.7, 0.7) | <0.001 |
| Poliovirus 3 | % with NAb≥1:8 dilution | -5% | 100.0 (531/531) | 99.8 (522/523) | 0.2 (-0.5, 1.1) | <0.001 |

[a] Estimated difference, CI, and p-value are based on the Miettinen & Nurminen method.
[b] A conclusion of non-inferiority of INFANRIX™ hexa administered concomitantly with V114 to INFANRIX™ hexa administered concomitantly with PCV13 is based on the lower bound of the 2-sided 95% CI for the difference in percentages (V114 - PCV13) being greater than the specified non-inferiority margin (1-sided p-value <0.025).
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; NI=non-inferiority; m=Number of participants with the indicated response. Note: Per protocol, the toddler dose was administered at ~11 to 15 months of age.
CI=confidence interval; EU=endotoxin unit; FHA=filamentous hemagglutinin; HBsAg=hepatitis B surface antigen; Hib=haemophilus influenzae type b; IU=international unit; Nab=neutralizing antibodies; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin.

Immune response to Rotarix™ administered concomitantly with V114 met noninferiority criteria, as assessed by anti-rotavirus IgA GMTs at 30 days PPS, see Table 16. Immune response to Rotarix™ administered concomitantly with V114 in the FAS population was consistent with that observed in the PP population.

**Table 16 Anti-rotavirus IgA GMTs at 30 Days Post Primary Series (PP) – V114-025**

| Antigen | V114 (N=588) | | PCV13 (N=591) | | GMT Ratio[a] (V114 / PCV13) | |
|---|---|---|---|---|---|---|
| | n | GMT | n | GMT | Estimate (95% CI)[ab] | p-value[ab] (1-sided) |
| Rotavirus | 520 | 45.39 | 503 | 47.07 | 0.96 (0.80, 1.16) | <0.001 |

[a] GMT ratio, CI, and p-value are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.
[b] A conclusion of non-inferiority of Rotarix™ administered concomitantly with V114 to Rotarix™ administered concomitantly with PCV13 is based on the lower bound of the 2-sided 95% CI for the GMT ratio (V114/PCV13) being >0.5 (1-sided p-value <0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis. Note: Per protocol, the final dose of the primary series was administered at ~4 months of age.
CI=confidence interval; GMT=geometric mean titer (U/mL); IgA=immunoglobulin A; U=units.

***CHMP's comment***

The noninferiority criteria were met for the immune response to each antigen in both vaccines. The immune response to both concomitantly administered vaccines was comparable between the V114 and PCV13 group, indicating that the generation of the immune response was not impacted differently by the 2 vaccines.

*Secondary Immunogenicity Endpoints: Responses at 30 days PPS*

Serotype-specific IgG response rates and IgG GMCs, see Table 17, were comparable for most of the 13 shared serotypes between the intervention groups at 30 days PPS. Serotype-specific IgG response rates and IgG GMCs were higher for the 2 unique serotypes (22F and 33F) in V114 recipients compared with PCV13 recipients at 30 days PPS.

**Table 17 Analysis of IgG GMCs at 30 Days Post Primary Series (PP)- -V114-025**

| **Pneumococcal Serotype** | **V114 (N=588)** | | **PCV13 (N=591)** | | **GMC Ratio[a] (V114 / PCV13) Estimate (95% CI)[a]** |
|---|---|---|---|---|---|
| | **n** | **GMC** | **n** | **GMC** | |
| 13 Shared Serotypes (Non-inferiority) | | | | | |
| 1 | 522 | 1.30 | 500 | 1.62 | 0.80 (0.73, 0.88) |
| 3 | 522 | 0.88 | 500 | 0.48 | 1.85 (1.70, 2.02) |
| 4 | 522 | 1.41 | 500 | 1.30 | 1.08 (0.98, 1.19) |
| 5 | 522 | 0.89 | 500 | 1.06 | 0.84 (0.74, 0.94) |
| 6A | 522 | 0.64 | 500 | 1.42 | 0.45 (0.40, 0.52) |
| 6B | 522 | 0.43 | 499 | 0.36 | 1.18 (1.00, 1.41) |
| 7F | 522 | 2.04 | 500 | 2.46 | 0.83 (0.76, 0.91) |
| 9V | 522 | 1.23 | 500 | 1.43 | 0.86 (0.77, 0.96) |
| 14 | 522 | 3.87 | 500 | 5.14 | 0.75 (0.66, 0.86) |
| 18C | 522 | 1.17 | 500 | 1.37 | 0.85 (0.77, 0.95) |
| 19A | 522 | 1.71 | 500 | 2.20 | 0.78 (0.70, 0.87) |
| 19F | 522 | 2.63 | 500 | 3.40 | 0.77 (0.70, 0.85) |
| 23F | 522 | 0.76 | 499 | 0.62 | 1.22 (1.07, 1.40) |
| 2 Serotypes Unique to V114 (Superiority) | | | | | |
| 22F | 522 | 2.76 | 500 | 0.05 | 57.69 (51.20, 65.00) |
| 33F | 522 | 0.31 | 500 | 0.05 | 6.24 (5.46, 7.14) |

[a] GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis. Note: Per protocol, the final dose of the primary series was administered at ~4 months of age.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

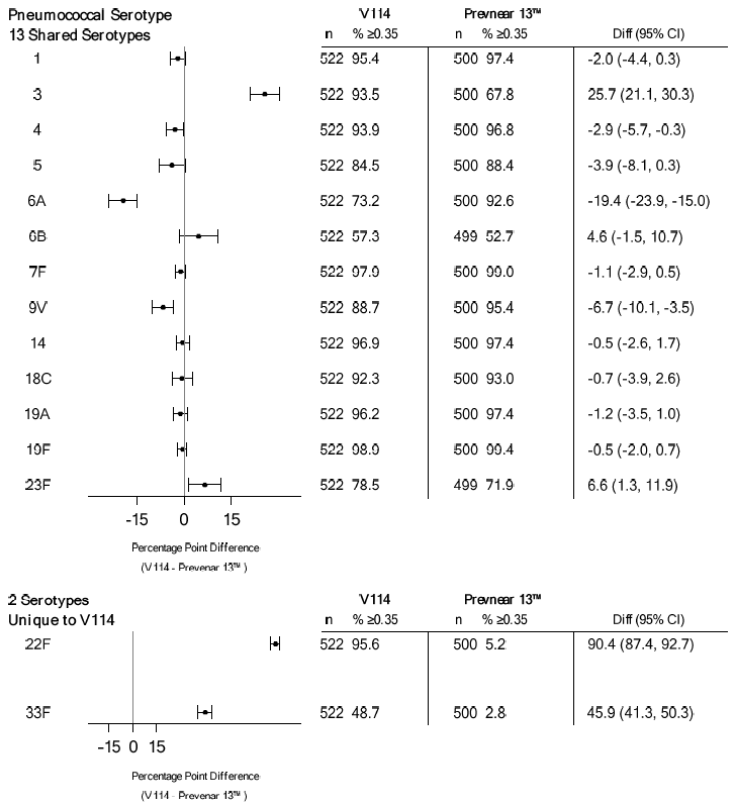



**Figure 3 Forest Plot of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Post Primary – V114-025**

***CHMP's comment***

At 30 days PPS, for the 13 shared serotypes the proportion of participants achieving IgG ≥0.35 µg/mL ranged from 57.3% (serotype 6B) to 98.9% (serotype 19F) in the V114 group compared to the range from 52.7% (serotype 6B) to 99.4% (serotype 19F) in the PCV13 group. Noninferiority criteria were met for all serotypes except 6A, as the percentage point difference between V114 and PCV13 was -19.4, with even the upper bound of the confidence interval below -10% (-23.9, -15.0). The response rate to serotype 3 was higher in the V114 group compared to the PCV13 group (25.7 (21.1, 30.3). As expected the response rate for the 2 unique serotypes was higher in the V114 group compared to the PCV13 group, with response rate for 22F being 95.6% vs 5.2% and for 33F being 48.7% vs 2.8%. The response rate for the 2 unique serotypes fell within the 10% difference for the lowest response rate in the PCV13 group (48.7% for serotype 33F in the V114 compared to 52.7% for serotype 6B in the PCV13 group). Of note, for serotype 33F the response rate and IgG GMC observed at 30 days PPS are much lower compared to 30 days PTD. The fact that the mean (0.31 µg/mL) is slightly less than 0.35 µg/mL is in line with the proportion of participants achieving ≥0.35 µg/mL being less than 50%; the observed response rate being 48.7%.

Similarly, the noninferiority criteria for IgG GMCs were met for all shared serotypes except serotype 6A, with GMC ratio V114/PCV13 ranging from 0.75 (serotype 14) to 1.85 (serotype 3). The GMC ratio for serotype 6A was 0.45 (0.40, 0.52). The clinical impact of the reduced IgG GMCs for serotype 6A is likely limited as the percentage of participants achieving the IgG threshold value of ≥0.35 µg/mL was 93.7% in the V114 compared to 98.6% in the PCV13 group at 30 days PPS. For the 2 unique serotypes, the IgG GMCs were higher in the V114 group compared to the PCV13 group: for 22F the IgG GMCs were 2.76 vs 0.05 and for 33F 0.31 vs 0.05.

*Immune Responses over time: IgG GMCs*

Serotype-specific IgG GMCs for the 13 shared serotypes declined from 30 days PPS to the pretoddler dose, and then increased from the pretoddler dose to 30 days PTD, at levels higher than those measured at 30 days PPS for most serotypes in both intervention groups, see Table 18. The pattern of serotype-specific immune responses over time was comparable in both groups for most of the 13 shared serotypes.

In the V114 group, IgG GMCs for the unique serotype 22F declined from 30 days PPS to the pretoddler dose, and then increased from the pretoddler dose to 30 days PTD, see Table 18. In the V114 group, serotype 33F increased from 30 days PPS and the pretoddler dose, and then increased from the pretoddler dose to 30 days PTD. Minimal changes in immune responses to these serotypes 22F and 33F were observed in the PCV13 group.

**Table 18 Summary of IgG Antibody Responses (PP)- -V114-025**

| | | | V114 (N=588) | | | PCV13 (N=591) | | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **Endpoint** | **Timepoint** | **n** | **Response** | **95% CI[a]** | **n** | **Response** | **95% CI[a]** |
| 13 Shared Serotypes | | | | | | | | |
| 1 | GMC | 30 Days PPS | 522 | 1.30 | (1.22, 1.38) | 500 | 1.62 | (1.51, 1.72) |
| | | Prior to the Toddler Dose | 556 | 0.23 | (0.22, 0.24) | 557 | 0.36 | (0.34, 0.38) |
| | | 30 Days PTD | 539 | 1.29 | (1.22, 1.37) | 537 | 2.08 | (1.96, 2.20) |
| 3 | GMC | 30 Days PPS | 522 | 0.88 | (0.83, 0.93) | 500 | 0.48 | (0.45, 0.51) |
| | | Prior to the Toddler Dose | 556 | 0.20 | (0.18, 0.21) | 557 | 0.10 | (0.09, 0.10) |
| | | 30 Days PTD | 539 | 0.84 | (0.79, 0.90) | 537 | 0.66 | (0.62, 0.70) |
| 4 | GMC | 30 Days PPS | 522 | 1.41 | (1.31, 1.52) | 500 | 1.30 | (1.22, 1.39) |
| | | Prior to the Toddler Dose | 556 | 0.22 | (0.21, 0.24) | 557 | 0.23 | (0.22, 0.24) |
| | | 30 Days PTD | 539 | 1.29 | (1.20, 1.38) | 535 | 1.73 | (1.62, 1.85) |
| 5 | GMC | 30 Days PPS | 522 | 0.89 | (0.82, 0.97) | 500 | 1.06 | (0.98, 1.16) |
| | | Prior to the Toddler Dose | 556 | 0.56 | (0.53, 0.59) | 557 | 0.69 | (0.65, 0.73) |
| | | 30 Days PTD | 539 | 1.97 | (1.85, 2.10) | 535 | 3.06 | (2.87, 3.27) |
| 6A | GMC | 30 Days PPS | 522 | 0.64 | (0.58, 0.71) | 500 | 1.42 | (1.30, 1.55) |
| | | Prior to the Toddler Dose | 556 | 0.24 | (0.22, 0.26) | 557 | 0.37 | (0.35, 0.40) |
| | | 30 Days PTD | 539 | 3.10 | (2.86, 3.36) | 535 | 4.57 | (4.25, 4.90) |
| 6B | GMC | 30 Days PPS | 522 | 0.43 | (0.38, 0.49) | 499 | 0.36 | (0.32, 0.41) |
| | | Prior to the Toddler Dose | 556 | 0.31 | (0.28, 0.34) | 557 | 0.25 | (0.23, 0.28) |
| | | 30 Days PTD | 539 | 4.17 | (3.84, 4.54) | 535 | 4.37 | (4.04, 4.73) |
| 7F | GMC | 30 Days PPS | 522 | 2.04 | (1.91, 2.18) | 500 | 2.46 | (2.31, 2.62) |
| | | Prior to the Toddler Dose | 556 | 0.55 | (0.52, 0.58) | 557 | 0.72 | (0.69, 0.76) |
| | | 30 Days PTD | 539 | 3.09 | (2.92, 3.27) | 536 | 3.93 | (3.70, 4.16) |
| 9V | GMC | 30 Days PPS | 522 | 1.23 | (1.13, 1.34) | 500 | 1.43 | (1.33, 1.55) |
| | | Prior to the Toddler Dose | 556 | 0.31 | (0.29, 0.33) | 557 | 0.40 | (0.37, 0.42) |
| | | 30 Days PTD | 539 | 2.14 | (2.02, 2.28) | 537 | 2.99 | (2.83, 3.17) |
| 14 | GMC | 30 Days PPS | 522 | 3.87 | (3.52, 4.25) | 500 | 5.14 | (4.65, 5.68) |
| | | Prior to the Toddler Dose | 556 | 0.91 | (0.84, 0.99) | 557 | 1.70 | (1.58, 1.84) |
| | | 30 Days PTD | 539 | 5.26 | (4.88, 5.66) | 537 | 7.04 | (6.58, 7.54) |
| 18C | GMC | 30 Days PPS | 522 | 1.17 | (1.09, 1.26) | 500 | 1.37 | (1.27, 1.48) |
| | | Prior to the Toddler Dose | 556 | 0.27 | (0.25, 0.28) | 557 | 0.27 | (0.26, 0.29) |
| | | 30 Days PTD | 539 | 1.94 | (1.83, 2.06) | 536 | 2.22 | (2.09, 2.36) |
| 19A | GMC | 30 Days PPS | 522 | 1.71 | (1.58, 1.84) | 500 | 2.20 | (2.03, 2.38) |
| | | Prior to the Toddler Dose | 556 | 0.37 | (0.34, 0.41) | 557 | 0.48 | (0.44, 0.52) |
| | | 30 Days PTD | 539 | 4.68 | (4.36, 5.02) | 535 | 5.65 | (5.29, 6.03) |
| 19F | GMC | 30 Days PPS | 522 | 2.63 | (2.44, 2.83) | 500 | 3.40 | (3.18, 3.63) |
| | | Prior to the Toddler Dose | 556 | 0.36 | (0.33, 0.39) | 557 | 0.52 | (0.49, 0.56) |
| | | 30 Days PTD | 539 | 4.09 | (3.82, 4.38) | 537 | 4.63 | (4.35, 4.93) |
| 23F | GMC | 30 Days PPS | 522 | 0.76 | (0.69, 0.84) | 499 | 0.62 | (0.56, 0.68) |
| | | Prior to the Toddler Dose | 554 | 0.17 | (0.16, 0.18) | 554 | 0.14 | (0.13, 0.15) |
| | | 30 Days PTD | 538 | 1.52 | (1.42, 1.63) | 535 | 1.75 | (1.62, 1.88) |

| Serotype | Endpoint | Timepoint | V114 (N=588) | | | PCV13 (N=591) | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Response | 95% CI[a] | n | Response | 95% CI[a] |
| 2 Serotypes Unique to V114 | | | | | | | | |
| 22F | GMC | 30 Days PPS | 522 | 2.76 | (2.53, 3.01) | 500 | 0.05 | (0.04, 0.05) |
| | | Prior to the Toddler Dose | 556 | 0.88 | (0.83, 0.93) | 557 | 0.05 | (0.05, 0.06) |
| | | 30 Days PTD | 539 | 5.98 | (5.61, 6.36) | 535 | 0.08 | (0.08, 0.09) |
| 33F | GMC | 30 Days PPS | 522 | 0.31 | (0.27, 0.34) | 500 | 0.05 | (0.05, 0.05) |
| | | Prior to the Toddler Dose | 556 | 0.61 | (0.56, 0.66) | 557 | 0.04 | (0.04, 0.05) |
| | | 30 Days PTD | 539 | 3.41 | (3.19, 3.65) | 530 | 0.07 | (0.07, 0.08) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, the final dose of the primary series was administered at ~4 months of age, and the toddler dose was administered at ~11 to 15 months of age.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

The distribution of serotype-specific IgG concentrations (as displayed by RCDCs) for the 13 shared serotypes increased from 30 days PPS to 30 days PTD in both intervention groups, see Figure 4 and Figure 5. In the V114 group, the distribution of serotypes 22F and 33F IgG concentrations (as displayed by RCDCs) increased from 30 days PPS to 30 days PTD; minimal to no changes in immune responses to these unique serotypes were observed in the PCV13 group, see Figure 5.

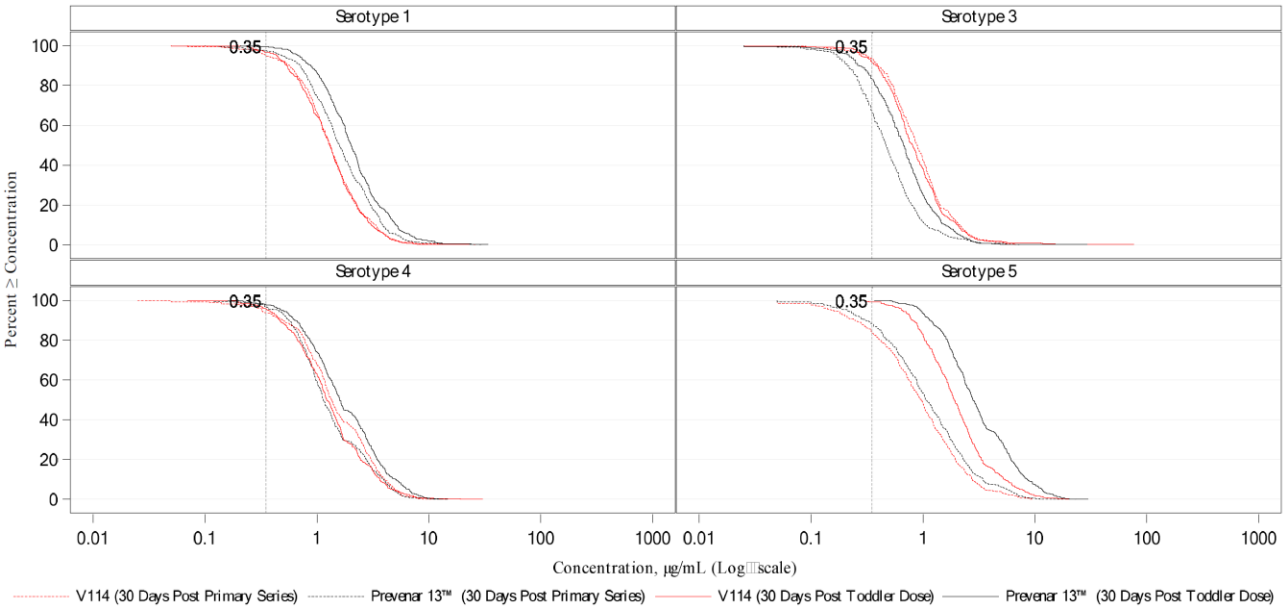



**Figure 4 RCDCs of IgG Concentrations 30 Days Post Primary Series and 30 Days Post Toddler Dose for serotype 1, 3, 4 and 5 (PP) - V114-025**

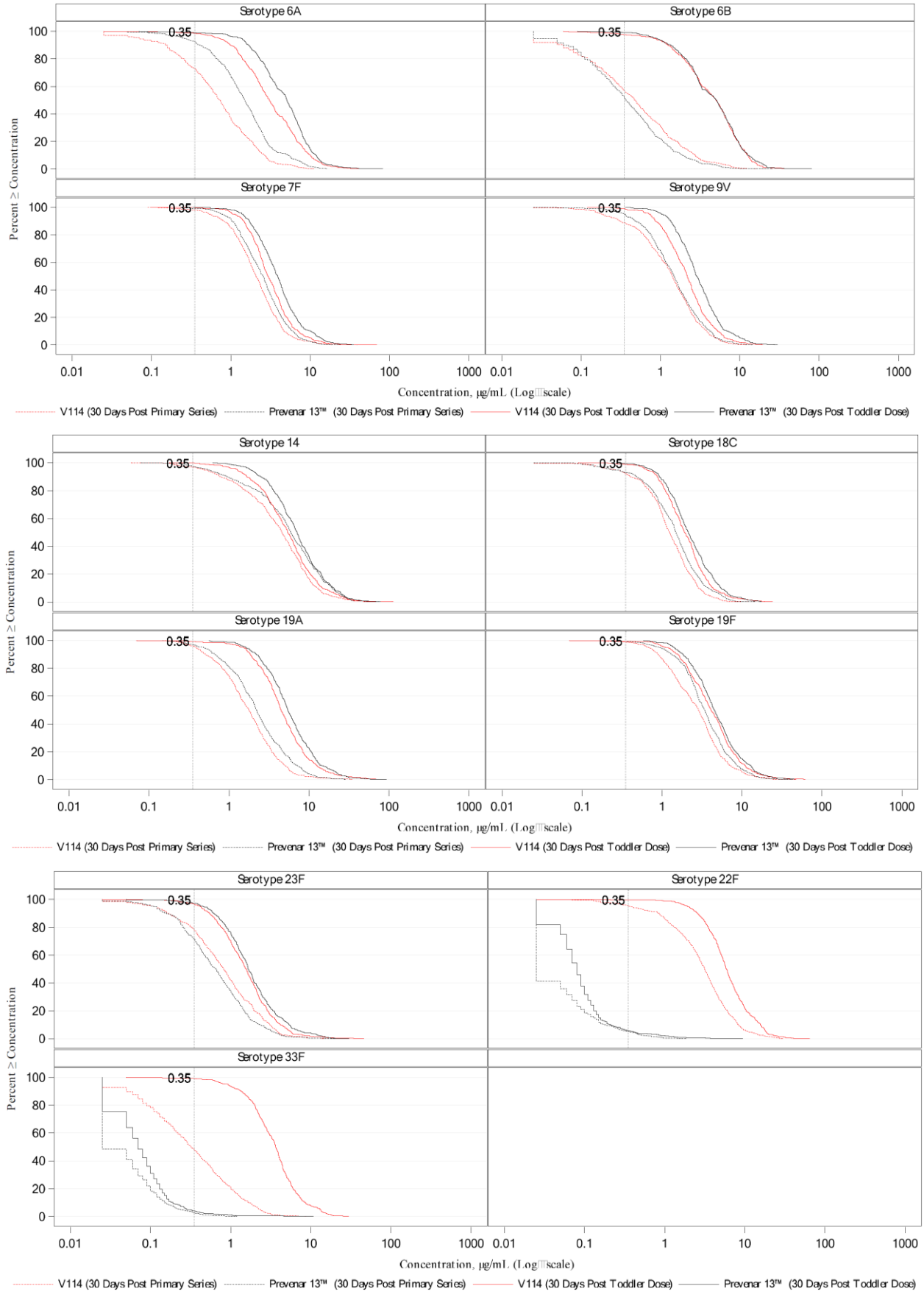



**Figure 5 RCDCs of IgG Concentrations 30 Days Post Primary Series and 30 Days Post Toddler Dose for serotype 6A, 6B, 7F,9V,14, 18C, 19A, 19F, 23F, 22F and 33F (PP) - V114-025**

***CHMP's comment***

For all serotypes the IgG GMCs decreased over time from 30 days PPS to pre-toddler dose, except 33F in the V114 group. This potentially indicates that for serotype 33F the peak immune response has not been reached at 30 days post primary series. A slow immune response has been observed in literature for serotype 6B (Spijkerman et al. JAMA 2013, Zhao et al. Front Microbiol 2022). OPA GMTs also showed an increase in the V114 group, pointing to natural exposure, however, no such increase was seen in the PCV13 group as would have been expected since exposure would be expected to occur in similar rates for both treatment arms. Therefore, this requires and explanation by the MAH, which should include a discussion on timing of the measurement as it might be that immune response to 33F still increases after 30 days.

The results indicate that as expected, for most serotypes, antibody concentration decreases over time. The toddler dose has a substantial impact and increases IgG GMCs to levels comparable to or higher than PPS. This indicates that immune memory is generated.

When looking at the RCDCs of the 13 shared serotypes, all serotypes showed a similar pattern for the V114 group and the PCV13 group, although the curves for V114 generally fall below the curve for PCV13. Visually, the curves are comparable, indicating that the response induced in both groups is comparable. It is also clear that the threshold level of 0.35 µg/mL is achieved by the majority of participants both PPS and PTD for most serotypes. In addition, the data of the RCDCs indicate that IgG concentrations decline at a similar rate after vaccination with V114 and PCV13 and consequently also the response rates. Given that the initial concentrations were lower with V114, it could be assumed that the protective effect of V114 might wane earlier compared to PCV13. Since no data after a longer period are available, this issue can currently not be answered but has to be referred to post marketing.

In conclusion, V114 generates an immune response that achieves the threshold of 0.35 µg/mL, both PPS and PTD for all serotypes for the majority of patients. For 11 out of the 13 shared serotypes, the response achieved in the V114 group is lower compared to the response in the PCV13 group. As the response is somewhat lower compared to PCV13, more serotypes (8 vs 5) fall below the threshold of 0.35 µg/mL immediately prior to the toddler dose. The clinical impact of this is unknown. After the toddler dose, a substantial immune response is generated in both arms, and the IgG GMCs levels generated are comparable to or higher than levels achieved PPS.

*Immune Responses over time: Functional antibodies over time*

The pattern of functional immune responses (as assessed by serotype-specific OPA responses) over time and the distribution of OPA titres (as displayed by RCDCs) were generally comparable between intervention groups and were consistent with that observed for serotype-specific IgG responses, see Table 19.

### Table 19 Summary of OPA Antibody Titer over time – V114-025

| Serotype | Timepoint | V114 (N=116) | | | PCV13 (N=122) | | |
|---|---|---|---|---|---|---|---|
| | | n | Response | 95% CI[a] | n | Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | |
| 1 | 30 Days PPS | 114 | 36.4 | (28.1, 47.2) | 112 | 43.7 | (33.9, 56.5) |
| | Prior to the Toddler Dose | 108 | 7.3 | (6.2, 8.6) | 117 | 8.2 | (6.8, 9.9) |
| | 30 Days PTD | 101 | 136.8 | (107.2, 174.6) | 108 | 164.6 | (127.9, 211.8) |
| 3 | 30 Days PPS | 114 | 162.1 | (141.5, 185.6) | 110 | 119.9 | (100.8, 142.6) |
| | Prior to the Toddler Dose | 107 | 72.1 | (61.3, 84.7) | 116 | 36.1 | (29.9, 43.7) |
| | 30 Days PTD | 98 | 321.5 | (277.2, 372.9) | 103 | 303.0 | (253.2, 362.6) |
| 4 | 30 Days PPS | 113 | 1168.6 | (991.5, 1377.5) | 110 | 1098.6 | (932.6, 1294.3) |
| | Prior to the Toddler Dose | 106 | 147.0 | (112.2, 192.7) | 116 | 122.2 | (95.5, 156.3) |
| | 30 Days PTD | 97 | 2231.7 | (1770.5, 2813.1) | 99 | 3206.4 | (2626.6, 3914.1) |
| 5 | 30 Days PPS | 114 | 140.2 | (108.7, 180.9) | 112 | 180.8 | (142.0, 230.3) |
| | Prior to the Toddler Dose | 111 | 56.4 | (44.0, 72.3) | 120 | 67.4 | (54.5, 83.4) |
| | 30 Days PTD | 102 | 791.6 | (640.9, 977.8) | 108 | 947.9 | (784.3, 1145.7) |
| 6A | 30 Days PPS | 112 | 955.7 | (798.4, 1143.9) | 112 | 1290.0 | (1069.0, 1556.6) |
| | Prior to the Toddler Dose | 104 | 321.7 | (261.7, 395.5) | 112 | 424.7 | (339.9, 530.6) |
| | 30 Days PTD | 98 | 3274.9 | (2734.5, 3921.9) | 99 | 5387.2 | (4388.9, 6612.5) |
| 6B | 30 Days PPS | 114 | 577.6 | (443.1, 752.9) | 110 | 481.6 | (365.0, 635.5) |
| | Prior to the Toddler Dose | 110 | 158.9 | (118.7, 212.6) | 118 | 83.1 | (64.6, 106.8) |
| | 30 Days PTD | 94 | 2439.9 | (1936.1, 3074.7) | 95 | 3182.4 | (2500.9, 4049.7) |
| 7F | 30 Days PPS | 113 | 4033.7 | (3429.4, 4744.6) | 112 | 5343.8 | (4328.0, 6598.0) |
| | Prior to the Toddler Dose | 111 | 1097.9 | (925.3, 1302.8) | 120 | 1781.8 | (1530.0, 2075.1) |
| | 30 Days PTD | 97 | 6300.9 | (5363.9, 7401.7) | 100 | 10071.4 | (8327.2, 12181.0) |
| 9V | 30 Days PPS | 113 | 455.9 | (366.1, 567.7) | 111 | 532.7 | (440.1, 644.7) |
| | Prior to the Toddler Dose | 105 | 256.7 | (206.5, 319.2) | 113 | 241.0 | (193.6, 300.0) |
| | 30 Days PTD | 97 | 1904.4 | (1584.8, 2288.4) | 103 | 2616.6 | (2133.3, 3209.4) |
| 14 | 30 Days PPS | 113 | 1247.9 | (950.8, 1637.9) | 109 | 1692.4 | (1357.6, 2109.9) |
| | Prior to the Toddler Dose | 108 | 324.1 | (248.9, 421.9) | 118 | 473.7 | (387.6, 578.9) |
| | 30 Days PTD | 99 | 2633.8 | (2102.6, 3299.2) | 100 | 2582.1 | (2089.5, 3190.9) |
| 18C | 30 Days PPS | 114 | 732.5 | (630.5, 851.0) | 112 | 849.3 | (713.0, 1011.6) |
| | Prior to the Toddler Dose | 111 | 131.3 | (110.7, 155.7) | 118 | 186.8 | (156.2, 223.5) |
| | 30 Days PTD | 98 | 1968.6 | (1676.4, 2311.7) | 103 | 2091.8 | (1789.1, 2445.7) |
| 19A | 30 Days PPS | 114 | 524.5 | (425.0, 647.4) | 112 | 706.0 | (565.7, 881.0) |
| | Prior to the Toddler Dose | 110 | 128.0 | (99.3, 165.0) | 119 | 161.5 | (125.9, 207.3) |
| | 30 Days PTD | 101 | 2995.6 | (2556.5, 3510.0) | 104 | 4254.3 | (3649.3, 4959.5) |
| 19F | 30 Days PPS | 114 | 774.0 | (668.0, 896.8) | 112 | 840.3 | (720.5, 980.0) |
| | Prior to the Toddler Dose | 109 | 109.4 | (92.8, 128.9) | 118 | 143.2 | (120.2, 170.5) |
| | 30 Days PTD | 98 | 1793.9 | (1535.3, 2096.1) | 103 | 2012.3 | (1677.0, 2414.6) |
| 23F | 30 Days PPS | 110 | 945.6 | (744.4, 1201.1) | 110 | 1068.5 | (830.4, 1374.8) |
| | Prior to the Toddler Dose | 108 | 321.6 | (235.7, 438.8) | 114 | 408.7 | (301.2, 554.5) |
| | 30 Days PTD | 97 | 4517.8 | (3685.1, 5538.8) | 99 | 7987.6 | (6149.3, 10375.5) |
| 2 Serotypes Unique to V114 | | | | | | | |
| 22F | 30 Days PPS | 112 | 1745.6 | (1494.9, 2038.2) | 111 | 9.1 | (7.6, 11.0) |
| | Prior to the Toddler Dose | 110 | 274.8 | (202.7, 372.5) | 112 | 18.4 | (12.9, 26.2) |
| | 30 Days PTD | 98 | 2405.2 | (1980.5, 2921.0) | 96 | 24.5 | (16.0, 37.7) |
| 33F | 30 Days PPS | 113 | 912.7 | (599.5, 1389.5) | 111 | 26.6 | (19.1, 37.0) |
| | Prior to the Toddler Dose | 111 | 4022.9 | (3401.5, 4757.9) | 119 | 1488.5 | (1158.6, 1912.2) |
| | 30 Days PTD | 96 | 14268.4 | (11680.1, 17430.2) | 101 | 1875.6 | (1477.4, 2381.3) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, the final dose of the primary series was administered at ~4 months of age, and the toddler dose was administered at ~11 to 15 months of age.
CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity.

***CHMP's comment***

Opsonophagocytic antibodies are functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing. No correlate of protection is known for OPA antibodies in children, therefore the clinical impact of the response induced is unknown.

It is agreed with the MAH that overall, the results of OPA GMTs are consistent with the results as observed for IgG GMCs.

OPA GMTs decrease over time from PPS to pretoddler dose for all serotypes, except 33F. After the toddler dose an increase in OPA GMTs was seen for all serotypes. PTD, OPA GMTs increased over the levels observed PPS for all serotypes in both treatment groups. This indicates that immune memory is present.

When comparing OPA GMTs between V114 and PCV13 at PPS, the OPA titers of the 13 shared serotypes were generally comparable between the 2 treatment arms. Immediately prior to the toddler dose, OPA GMTs were substantially decreased from PPS for all serotypes. PTD, levels increased and were comparable between the 2 treatment arms for 9 out of 13 shared serotypes. Four serotypes, 6A, 7F, 19A and 23F, were somewhat lower in the V114 arm compared to the PCV13 arm. Interestingly, no difference was observed between the 2 treatment arms in OPA GMTs for serotype 3.

An increase in OPA titers from 30 days PPS to immediately prior to toddler dose for serotype 33F was observed in the PCV13 group, which is not reflected in an increase in IgG GMCs. No clear explanation exists, however, it could be related to non-specific background interference in combination with increasing IgM due to maturation of the immune system. The observed increase is several magnitudes lower than the response seen in the V114 group. Finally, no further substantial increase is seen between pre-toddler dose and toddler dose. For all other serotypes there is a correlation between IgG GMCs and OPA titers, as when IgG GMCs decrease, the OPA GMTs also decrease and vice versa.

The OPA GMTs for the 2 unique serotypes in the V114 group were consistently higher compared to the PCV13 arm, which is to be expected. The OPA GMTs for the 2 unique serotypes were higher compared to the OPA GMTs for serotypes 1 and 5, indicating that a robust response was generated.

***V114-029***

*Primary Immunogenicity endpoints*

V114 met noninferiority criteria for the 13 shared serotypes as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35 µg/mL (response rates) for each serotype at 30 days PPS (post dose 3). V114 met noninferiority criteria for the 2 unique serotypes as assessed by the response rate for serotypes 22F and 33F compared with the response rate for serotype 23F (lowest response rate of the shared serotypes in PCV13, excluding serotype 3) at 30 days PPS.

Serotype-specific IgG response rates at 30 days PPS and 30 days PTD in the FAS population were consistent with those observed in the PP population.

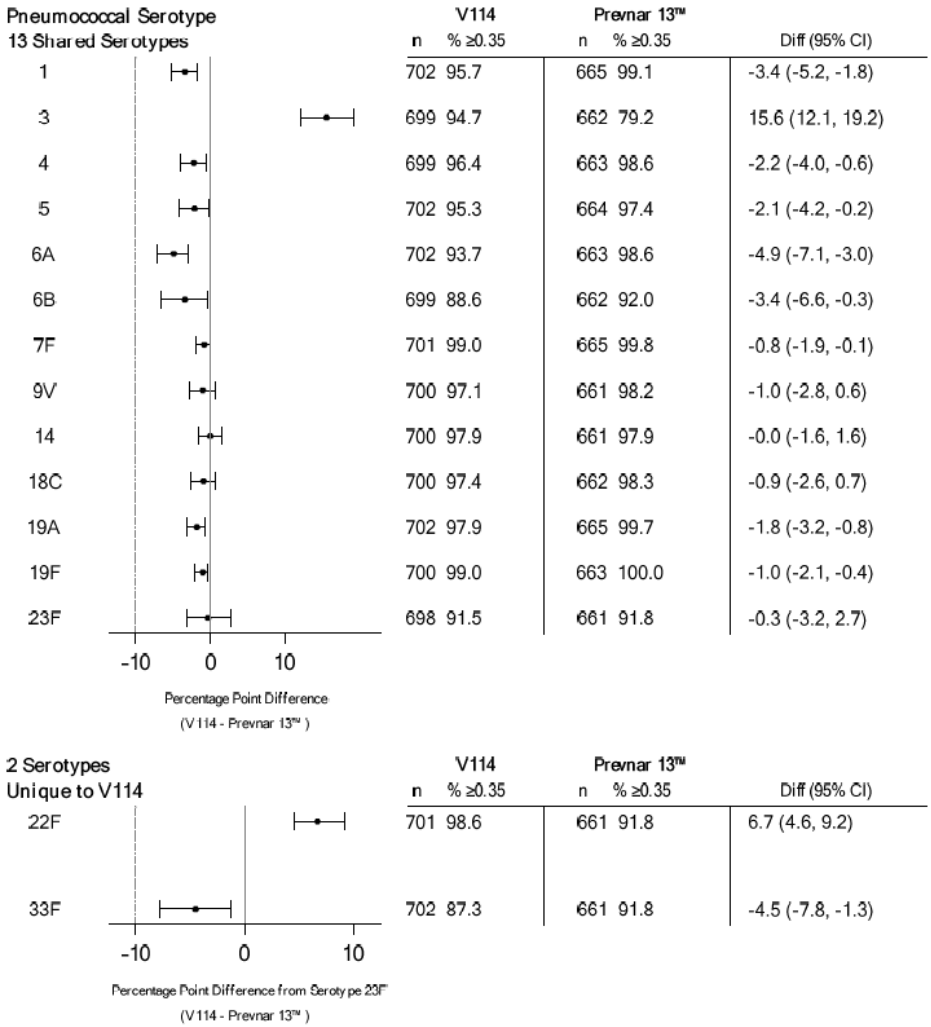



**Figure 6 Forest Plot of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days PPS (PP) – V114-029**

V114 met noninferiority criteria for 12 of the 13 shared serotypes (narrowly missing on serotype 6A) as assessed by serotype-specific IgG GMCs at 30 days PPS, see Figure 7. V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with the IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in PCV13, excluding serotype 3) at 30 days PPPS.

V114 met noninferiority criteria for the 13 shared serotypes as assessed by serotype-specific IgG GMCs at 30 days PD4, see Figure 7. V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in PCV13, excluding serotype 3) at 30 days PD4.

Serotype-specific IgG GMCs at 30 days PPS and 30 days PTD in the FAS population were consistent with those observed in the PP population.

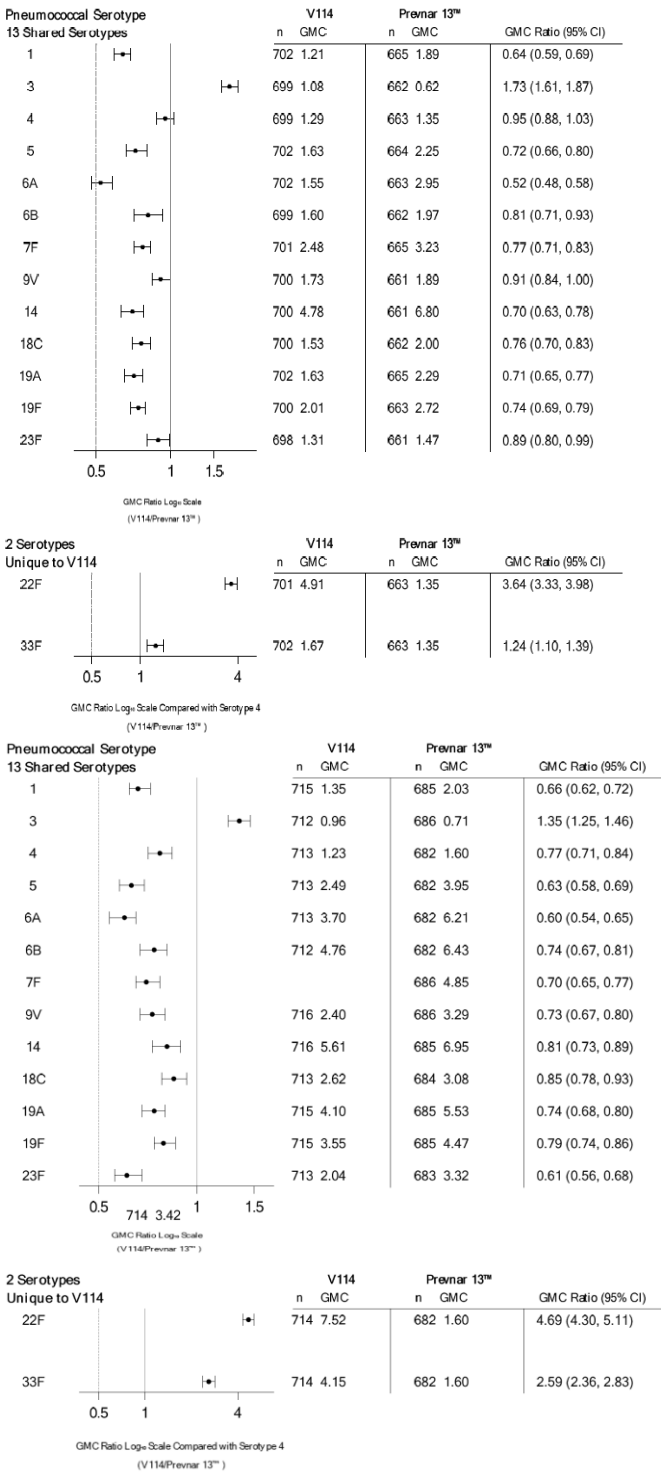



**Figure 7 Forest Plot of IgG GMC Ratios at 30 Days PPS (Left) and 30 Days PTD (Right) (PP) – V114-029**

***CHMP's comment***

At 30 days PPS, non-inferiority to PCV13 was shown based on IgG response rate for all serotypes and for 14 out of 15 serotypes (excluding serotype 6A) based on IgG GMC ratio. At 30 days PTD, all serotypes were non-inferior to PCV13 based on IgG GMCs. In principle the study failed, as the primary objectives were not all met, as IgG GMC for serotype 6A did not meet non-inferiority criteria based on IgG GMCs at 30 days PPS. However, as stated in the WHO guideline non-inferiority to antibody

response for each of the serotypes in the registered vaccine at both response rate and IgG GMCs is desirable, but not an absolute requirement.

At 30 days PPS, the vast majority of participants achieved the surrogate of protection in both treatment arms, indicating adequate protection against IPD. The proportion of participants achieving ≥0.35 µg/mL was comparable in both groups. The immune response generated by the 2 unique serotypes was also comparable to the lowest response rate generated by PCV13 (excluding serotype 3), which indicates a substantial immune response is generated which is likely to offer protection against IPD.

At 30 days PPS, the IgG GMC for serotype 6A in the V114 was 1.55 and 2.95 in the PCV13 group. This IgG GMC is still well above the 0.35 µg/mL threshold and is even higher compared to the response for other serotypes such as serotype 4 and 23F. The GMC ratio at 30 days PPS indicated that the immune response generated for each of the shared serotypes was lower in the V114 group compared to the response generated by PCV13, except for serotype 3, with the ratios ranging from 0.52 (serotype 6A) to 0.95 (serotype 4) and 1.73 (serotype 3). This is expected based on the fact that more serotypes are included in the vaccine, however, it does raise the question of immune persistence. For the 2 unique serotypes, the IgG GMCs were 4.91 for 22F and 1.67 for 33F, both of which were higher compared to the lowest IgG GMCs, serotype 4, of PCV13. For all serotypes the IgG GMCs were well above 0.35 µg/mL. As stated previously, there is only a surrogate of protection in place for IPD and not for pneumonia or AOM. This hampers the interpretation of the clinical impact of these lower titres on the protection against pneumonia and AOM. Especially considering the fact that for protection against AOM higher antibody responses are thought to be necessary compared to protection against IPD.

At 30 days PTD (dose 4), all serotypes met the non-inferiority margin and GMC ratios ranged from 0.60 to 0.85 for 12 of the shared serotypes, excluding serotype 3 (GMC ratio 1.35 [1.25, 1.46]). The IgG GMCs for the 2 unique serotypes are higher compared to the lowest response seen for PCV13 (excluding serotype 3). For all serotypes the IgG GMCs were well above 0.35 µg/mL. This indicates that after the 4$^{th}$ dose the immune response generated by V114 is comparable to the one generated by PCV13 for all serotypes.

The FAS population showed similar results as the PP population, indicating consistency and robustness of the results.

Overall, at both 30 days PPS and 30 days PTD the IgG GMC was well above the threshold of 0.35 µg/mL for all serotypes in both treatment arms, indicating a substantial immune response that is likely to confer protection.

*Secondary Immunogenicity Endpoints: concomitant vaccines*

Immune responses to licensed vaccines, including Pentacel, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™, administered concomitantly with PCV were comparable in the V114 and PCV13 groups.

- Immune responses to Pentacel™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants meeting specified antibody responses to antigens included in Pentacel™ (response rates) and as assessed by the antigen-specific GMCs of pertussis antigens contained in Pentacel™ at 30 days PPS.
- Immune responses to VAQTA™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥10 mIU/mL to anti-hepatitis A antigen (response rates) at 30 days PTD.

- Immune responses to M-M-R™II administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants meeting specified antibody responses to M-M-R™II antigens (response rates) at 30 days PTD.
- Immune responses to VARIVAX™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥5 gpELISA units/ml to anti-varicella antigen (response rates) at 30 days PTD.
- Immune responses to HIBERIX™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥0.15 µg/mL to anti-PRP antigen (response rates) at 30 days PTD.

Results in the FAS population were consistent with those observed in the PP population.

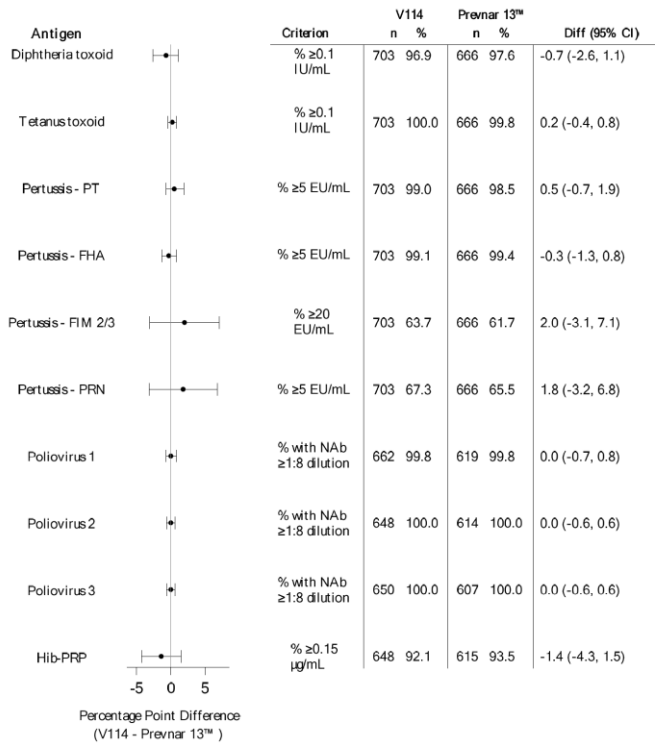



**Figure 8 Forest Plot of the Proportions of Participants Meeting Specified Pentacel™ Antigen Responses at 30 Days Postdose 3 (Left) and Proportions of Participants Meeting Specified VAQTA™, M-M-R™ II, VARIVAX™ and HIBERIX™ Antigen Responses at 30 Days Postdose 4 (Right) (PP) – V114-029**

***CHMP's comment***

The noninferiority criteria were met for the immune response to each antigen in all concomitantly administered vaccines. However, as the study formally failed to achieve the predefined primary endpoint, formally no further testing of secondary endpoints is justified.

The immune response to the concomitantly administered vaccines was comparable between the V114 and PCV13 group, indicating that the generation of the immune response was not impacted differently by the 2 treatment arms. All responses for the concomitant vaccines showed a within 5 percentage points difference between the treatment arms.

*Secondary Immunogenicity Endpoints: PCV*

V114 elicited immune responses that were higher than PCV13 for the 2 unique serotypes 22F and 33F and for shared serotype 3.

- V114 met the superiority criteria for serotypes 22F and 33F as assessed by the proportions of participants with IgG ≥0.35 µg/mL (response rates) for each serotype at 30 days PD3, as the lower bound of the 2-sided 95% CI for the difference in response rates (V114 minus PCV13) was greater than 10 percentage points for each serotype.
- V114 met the superiority criteria for serotypes 22F and 33F as assessed by the serotypespecific IgG GMC at 30 days PPS and 30 days PTD. The lower bound of the 2-sided 95% CI for serotypespecific IgG GMC ratio (V114/PCV13 was greater than 2.0 for each serotype.
- V114 met the superiority criteria for serotype 3 as assessed by the proportion of participants with IgG ≥0.35 µg/mL at 30 days PPS. The lower bound of the 2-sided 95% CI for the difference in response rates (V114 minus PCV13) was greater than 0 percentage points.
- V114 met the superiority criteria for serotype 3 as assessed by the serotype-specific IgG GMCs at 30 days PPS and 30 days PTD. The lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio (V114/PCV13) was greater than 1.2.

***CHMP's comment***

The immune response generated by V114 for the 2 unique serotypes is substantial. For both serotypes, at IgG GMCs reached the threshold of 0.35 µg/mL both 30 days PPS and 30 days PTD, with the vast majority (>87%) of participants achieving this threshold at both timepoints in the V114 group. It is acknowledged that this response was not generated by PCV13, as these serotypes are not included in PCV13.

The higher response to serotype 3 in the V114 group compared to the PCV13 group is acknowledged, as a greater proportion of participants achieve the threshold value of 0.35 µg/mL at both 30 days PPS and 30 day PTD compared to PCV13. However, as the study formally failed to achieve the predefined primary endpoint, no further statistical testing of secondary endpoints is justified. Secondary endpoints should be descriptive.

Considering no correlate of protection exists for the new serotypes, the clinical relevance of these findings is unknown.

*Immune Responses over time: IgG*

Serotype-specific IgG GMCs for the 13 shared serotypes declined from PD3 to predose 4 as expected, and subsequently increased from predose 4 to PD4, at levels higher than those measured at 30 days PD3 for most serotypes in both intervention groups. The pattern of serotype-specific immune responses over time were comparable between the intervention groups for the 13 shared serotypes.

In the V114 group, IgG GMCs for serotypes 22F and 33F declined from PD3 to predose 4, and increased from predose 4 to PD4 [Table 20]. Minimal responses were seen in the PCV13 group.

### Table 20 Summary of IgG Antibody Responses (PP) – V114-029

| Serotype | Endpoint | Timepoint | V114 (N=858) | | | PCV13 (N=856) | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Response | 95% CI[a] | n | Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | |
| 1 | GMC | 30 Days Postdose 3 | 702 | 1.21 | (1.15, 1.27) | 665 | 1.89 | (1.79, 2.00) |
| | | Prior to Dose 4 | 743 | 0.32 | (0.31, 0.34) | 722 | 0.50 | (0.48, 0.53) |
| | | 30 Days Postdose 4 | 715 | 1.35 | (1.27, 1.42) | 685 | 2.03 | (1.92, 2.14) |
| 3 | GMC | 30 Days Postdose 3 | 699 | 1.08 | (1.03, 1.14) | 662 | 0.62 | (0.59, 0.66) |
| | | Prior to Dose 4 | 742 | 0.28 | (0.27, 0.30) | 723 | 0.15 | (0.14, 0.16) |
| | | 30 Days Postdose 4 | 712 | 0.96 | (0.91, 1.01) | 686 | 0.71 | (0.67, 0.75) |
| 4 | GMC | 30 Days Postdose 3 | 699 | 1.29 | (1.22, 1.36) | 663 | 1.35 | (1.28, 1.43) |
| | | Prior to Dose 4 | 742 | 0.31 | (0.29, 0.32) | 723 | 0.34 | (0.33, 0.36) |
| | | 30 Days Postdose 4 | 713 | 1.23 | (1.16, 1.31) | 682 | 1.60 | (1.51, 1.71) |
| 5 | GMC | 30 Days Postdose 3 | 702 | 1.63 | (1.52, 1.74) | 664 | 2.25 | (2.09, 2.41) |
| | | Prior to Dose 4 | 742 | 0.79 | (0.75, 0.84) | 722 | 1.05 | (1.00, 1.11) |
| | | 30 Days Postdose 4 | 713 | 2.49 | (2.34, 2.64) | 682 | 3.95 | (3.71, 4.20) |
| 6A | GMC | 30 Days Postdose 3 | 702 | 1.55 | (1.44, 1.66) | 663 | 2.95 | (2.76, 3.15) |
| | | Prior to Dose 4 | 743 | 0.42 | (0.39, 0.45) | 722 | 0.69 | (0.66, 0.73) |
| | | 30 Days Postdose 4 | 713 | 3.70 | (3.46, 3.97) | 682 | 6.21 | (5.83, 6.62) |
| 6B | GMC | 30 Days Postdose 3 | 699 | 1.60 | (1.45, 1.76) | 662 | 1.97 | (1.80, 2.16) |
| | | Prior to Dose 4 | 742 | 0.56 | (0.52, 0.60) | 722 | 0.55 | (0.52, 0.59) |
| | | 30 Days Postdose 4 | 712 | 4.76 | (4.43, 5.10) | 682 | 6.43 | (6.02, 6.88) |
| 7F | GMC | 30 Days Postdose 3 | 701 | 2.48 | (2.35, 2.61) | 665 | 3.23 | (3.06, 3.40) |
| | | Prior to Dose 4 | 743 | 0.80 | (0.76, 0.84) | 722 | 1.05 | (1.00, 1.10) |
| | | 30 Days Postdose 4 | 714 | 3.42 | (3.22, 3.64) | 686 | 4.85 | (4.56, 5.16) |
| 9V | GMC | 30 Days Postdose 3 | 700 | 1.73 | (1.63, 1.83) | 661 | 1.89 | (1.77, 2.01) |
| | | Prior to Dose 4 | 742 | 0.49 | (0.46, 0.51) | 722 | 0.57 | (0.54, 0.60) |
| | | 30 Days Postdose 4 | 716 | 2.40 | (2.27, 2.55) | 686 | 3.29 | (3.10, 3.49) |
| 14 | GMC | 30 Days Postdose 3 | 700 | 4.78 | (4.44, 5.16) | 661 | 6.80 | (6.30, 7.33) |
| | | Prior to Dose 4 | 742 | 1.46 | (1.36, 1.57) | 722 | 2.35 | (2.21, 2.51) |
| | | 30 Days Postdose 4 | 716 | 5.61 | (5.21, 6.04) | 685 | 6.95 | (6.51, 7.43) |
| 18C | GMC | 30 Days Postdose 3 | 700 | 1.53 | (1.44, 1.61) | 662 | 2.00 | (1.88, 2.13) |
| | | Prior to Dose 4 | 740 | 0.43 | (0.41, 0.45) | 722 | 0.46 | (0.43, 0.48) |
| | | 30 Days Postdose 4 | 713 | 2.62 | (2.46, 2.78) | 684 | 3.08 | (2.88, 3.29) |
| 19A | GMC | 30 Days Postdose 3 | 702 | 1.63 | (1.54, 1.73) | 665 | 2.29 | (2.16, 2.44) |
| | | Prior to Dose 4 | 743 | 0.46 | (0.44, 0.50) | 722 | 0.65 | (0.60, 0.69) |
| | | 30 Days Postdose 4 | 715 | 4.10 | (3.88, 4.33) | 685 | 5.53 | (5.21, 5.87) |
| 19F | GMC | 30 Days Postdose 3 | 700 | 2.01 | (1.91, 2.11) | 663 | 2.72 | (2.59, 2.86) |
| | | Prior to Dose 4 | 742 | 0.46 | (0.44, 0.49) | 723 | 0.67 | (0.63, 0.70) |
| | | 30 Days Postdose 4 | 715 | 3.55 | (3.37, 3.75) | 685 | 4.47 | (4.23, 4.73) |
| 23F | GMC | 30 Days Postdose 3 | 698 | 1.31 | (1.22, 1.41) | 661 | 1.47 | (1.36, 1.59) |
| | | Prior to Dose 4 | 741 | 0.34 | (0.31, 0.36) | 721 | 0.37 | (0.34, 0.39) |
| | | 30 Days Postdose 4 | 713 | 2.04 | (1.91, 2.18) | 683 | 3.32 | (3.08, 3.58) |
| 2 Serotypes Unique to V114 | | | | | | | | |
| 22F | GMC | 30 Days Postdose 3 | 701 | 4.91 | (4.58, 5.26) | 660 | 0.05 | (0.05, 0.06) |
| | | Prior to Dose 4 | 743 | 1.51 | (1.43, 1.60) | 722 | 0.06 | (0.06, 0.07) |
| | | 30 Days Postdose 4 | 714 | 7.52 | (7.09, 7.98) | 682 | 0.11 | (0.10, 0.12) |
| 33F | GMC | 30 Days Postdose 3 | 702 | 1.67 | (1.51, 1.85) | 664 | 0.06 | (0.05, 0.06) |
| | | Prior to Dose 4 | 743 | 1.07 | (1.00, 1.14) | 722 | 0.05 | (0.05, 0.06) |
| | | 30 Days Postdose 4 | 714 | 4.15 | (3.89, 4.42) | 677 | 0.09 | (0.09, 0.10) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, dose 3 (last of primary series) was administered at ~6 months of age, and dose 4 (toddler dose) was administered at ~12 to 15 months of age.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

The distribution of immune responses at 30 days PD3 (as displayed by RCDCs) was generally comparable between intervention groups for the 13 shared serotypes and higher for the 2 unique serotypes in the V114 group, consistent with the results observed for serotype-specific IgG GMCs, see Figure 9 and Figure 10.

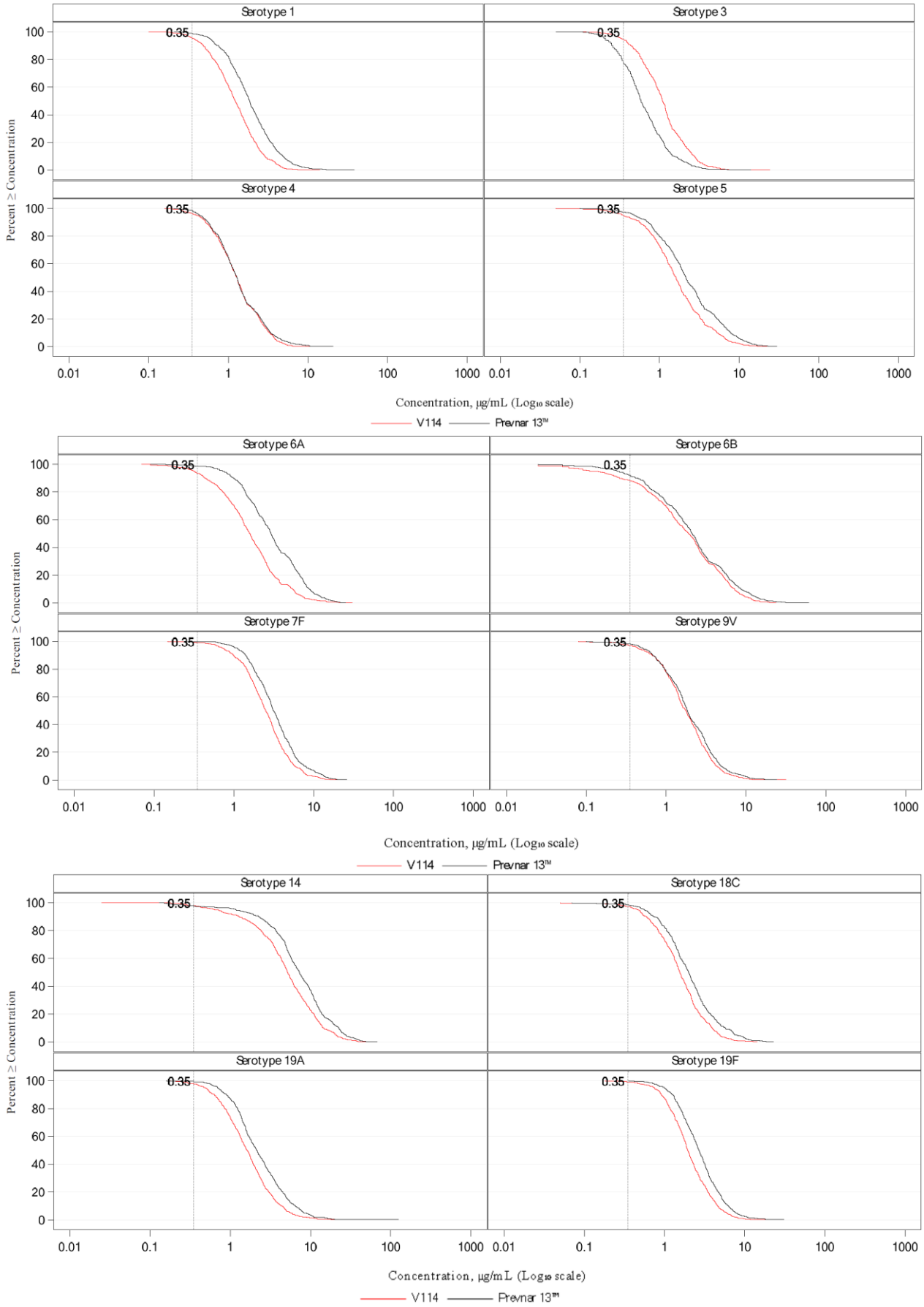



**Figure 9 RCDCs of IgG Concentrations 30 Days Post Primary Series (Post Dose 3) for serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A and 19F (PP) - V114-029**

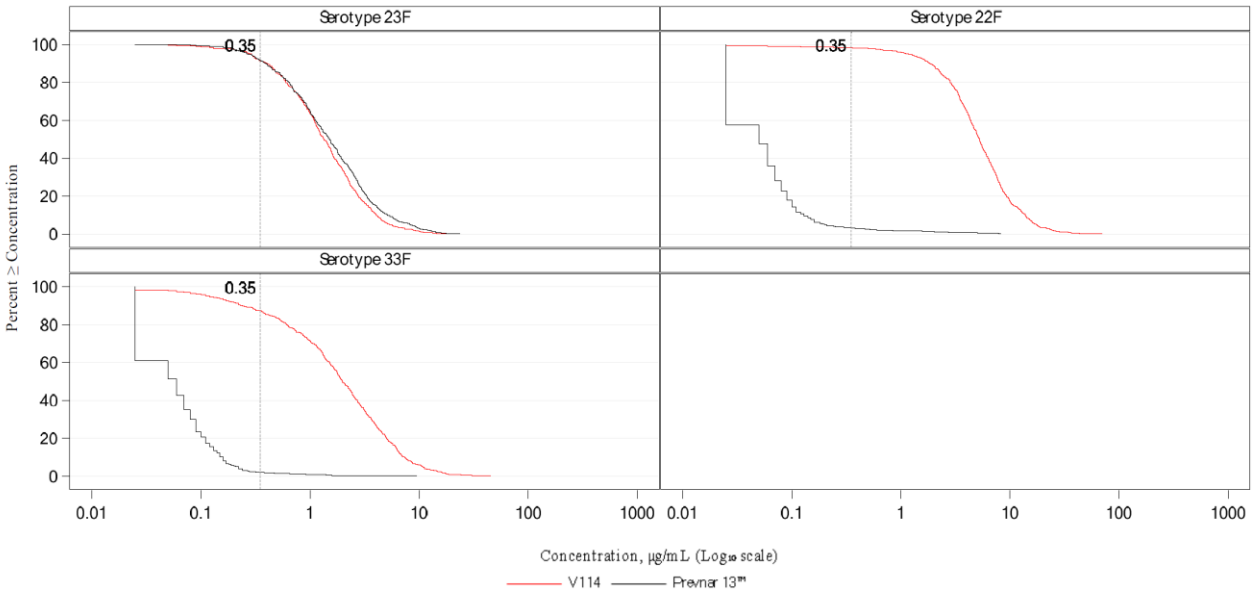



**Figure 10 RCDCs of IgG Concentrations 30 Days Post Primary Series (Post Dose 3) for serotype 23F, 22F and 33F (PP) - V114-029**

The response rate 30 days post toddler dose the response rate is presented in Table 21.

**Table 21 Summary of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Post Toddler Dose – PP population V114-029**

| Pneumococcal Serotype | V114 (N=858) | | PCV13 (N=856) | |
|---|---|---|---|---|
| | Observed response % (m/n) | 95% CI† | Observed response % (m/n) | 95% CI† |
| 13 Shared Serotypes | | | | |
| 1 | 96.6% (691/715) | (95.0, 97.8) | 99.4% (681/685) | (98.5, 99.8) |
| 3 | 94.0% (669/712) | (92.0, 95.6) | 86.9% (596/686) | (84.1, 89.3) |
| 4 | 95.1% (678/713) | (93.2, 96.6) | 97.5% (665/682) | (96.0, 98.5) |
| 5 | 99.2% (707/713) | (98.2, 99.7) | 99.9% (681/682) | (99.2, 100.0) |
| 6A | 98.7% (704/713) | (97.6, 99.4) | 99.3% (677/682) | (98.3, 99.8) |
| 6B | 98.7% (703/712) | (97.6, 99.4) | 99.3% (677/682) | (98.3, 99.8) |
| 7F | 99.6% (711/714) | (98.8, 99.9) | 99.9% (685/686) | (99.2, 100.0) |
| 9V | 99.4% (712/716) | (98.6, 99.8) | 99.7% (684/686) | (99.0, 100.0) |
| 14 | 99.3% (711/716) | (98.4, 99.8) | 99.6% (682/685) | (98.7, 99.9) |
| 18C | 99.7% (711/713) | (99.0, 100.0) | 99.6% (681/684) | (98.7, 99.9) |
| 19A | 99.9% (714/715) | (99.2, 100.0) | 99.9% (684/685) | (99.2, 100.0) |
| 19F | 99.7% (713/715) | (99.0, 100.0) | 99.7% (683/685) | (98.9, 100.0) |
| 23F | 98.6% (703/713) | (97.4, 99.3) | 99.0% (676/683) | (97.9, 99.6) |
| 2 Additional Serotypes in V114 | | | | |
| 22F | 99.6% (711/714) | (98.8, 99.9) | 7.2% (49/682) | (5.4, 9.4) |
| 33F | 98.9% (706/714) | (97.8, 99.5) | 6.2% (42/677) | (4.5, 8.3) |

† The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
Note: Per protocol, for studies V114-029 toddler dose of PCV administered at ~12 to 15 months of age.
CI=confidence interval; IgG=immunoglobulin G.

***CHMP's comment***

For all serotypes the IgG GMCs decreased over time from 30 days post dose 3, PPS, to pre-toddler dose. Thirty days after the toddler dose, the IgG GMCs achieved levels similar to PPS or higher in both treatment arms. This indicates that immune memory is generated.

At 30 days post toddler dose, the response rate in the V114 group for the 13 shared serotypes is comparable, within 5% difference, to the PCV13 group, except for serotype 3 which is higher in the V114 group. The response rate for the 2 new serotypes is higher in the V114 group compared to the PCV13 group and is with ≥98.9% comparable to the the 13 shared serotypes. Although the high response rate for the 2 new serotypes is considered reassuring, the clinical relevance is unknown and can only be further investigated in post marketing studies. The data on the response rate at 30 days PTD is considered relevant for the prescribers and upon request have been included in the SmPC.

When looking at the RCDCs of the 13 shared serotypes, all serotypes showed a similar pattern for the V114 group and the PCV13 group, although the curves for V114 generally fell below the curve for PCV13. Visually, the curves are comparable, indicating that the groups respond comparable. It is also clear that the threshold level of 0.35 µg/mL is achieved by the majority of participants PPS, which also holds true PTD (not shown). In addition, since the initial immune response induced by V114 is reduced compared to the response induced by PCV13, it could be assumed that the protective effect of V114 might wane earlier compared to PCV13, given that the decline in antibodies appears similar in both groups. The issue of persistence of protection can currently not be answered and has to be referred to post marketing.

In conclusion, V114 generates an immune response that achieves the threshold of 0.35 µg/mL, both PPS and PTD, for all serotypes for the majority of patients. For 12 out of the 13 shared serotypes (exception: serotype 3), the response achieved in the V114 group is lower compared to the response in the PCV13 group. As the response is somewhat lower compared to PCV13, more serotypes (4 vs 2) fall below the threshold of 0.35 µg/mL immediately prior to the toddler dose. The clinical impact of this is unknown. After the toddler dose, a substantial immune response is generated in both arms, and the IgG GMCs levels generated are comparable to or higher than levels achieved PPS.

*Immune Responses over time: Functional antibodies*

The pattern of functional immune responses over time, as assessed by serotype-specific OPA responses, was generally comparable between the intervention groups and was consistent with that observed for serotype-specific IgG responses.

**Table 22 Summary of OPA Antibody Responses Over Time (PP) – V114-029**

| Serotype | Endpoint | Timepoint | V114 (N=176) | | | PCV13 (N=168) | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Response | 95% CI[a] | n | Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | |
| 1 | GMT | 30 Days Postdose 3 | 170 | 56.9 | (46.1, 70.3) | 162 | 78.3 | (61.5, 99.5) |
| | | Prior to Dose 4 | 83 | 8.4 | (6.7, 10.5) | 81 | 17.0 | (12.3, 23.6) |
| | | 30 Days Postdose 4 | 84 | 138.5 | (105.4, 182.1) | 85 | 228.6 | (171.6, 304.7) |
| 3 | GMT | 30 Days Postdose 3 | 169 | 284.7 | (253.5, 319.8) | 158 | 210.6 | (188.2, 235.7) |
| | | Prior to Dose 4 | 84 | 106.4 | (87.3, 129.7) | 83 | 76.5 | (58.0, 100.8) |
| | | 30 Days Postdose 4 | 81 | 389.1 | (328.8, 460.6) | 85 | 455.9 | (393.7, 528.0) |
| 4 | GMT | 30 Days Postdose 3 | 169 | 1304.8 | (1139.6, 1494.0) | 159 | 1566.7 | (1381.8, 1776.4) |
| | | Prior to Dose 4 | 86 | 232.3 | (170.0, 317.4) | 85 | 350.5 | (254.2, 483.3) |
| | | 30 Days Postdose 4 | 84 | 2558.3 | (2034.4, 3217.1) | 82 | 3492.6 | (2817.6, 4329.4) |
| 5 | GMT | 30 Days Postdose 3 | 171 | 387.4 | (315.0, 476.3) | 162 | 510.8 | (415.9, 627.2) |
| | | Prior to Dose 4 | 86 | 128.2 | (94.6, 173.9) | 85 | 188.0 | (135.4, 261.0) |
| | | 30 Days Postdose 4 | 84 | 1062.9 | (830.1, 1361.0) | 85 | 1538.8 | (1216.9, 1945.7) |
| 6A | GMT | 30 Days Postdose 3 | 171 | 2072.1 | (1787.5, 2401.9) | 159 | 2743.4 | (2368.1, 3178.2) |
| | | Prior to Dose 4 | 83 | 648.4 | (503.3, 835.2) | 84 | 856.9 | (666.2, 1102.2) |
| | | 30 Days Postdose 4 | 84 | 5553.5 | (4397.8, 7012.8) | 83 | 7784.6 | (6115.9, 9908.7) |
| 6B | GMT | 30 Days Postdose 3 | 169 | 1932.5 | (1612.1, 2316.6) | 160 | 1963.7 | (1604.9, 2402.8) |
| | | Prior to Dose 4 | 86 | 446.7 | (327.0, 610.4) | 84 | 361.0 | (253.2, 514.8) |
| | | 30 Days Postdose 4 | 81 | 4641.8 | (3567.0, 6040.4) | 85 | 5897.0 | (4297.9, 8091.1) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7F | GMT | 30 Days Postdose 3 | 170 | 4973.2 | (4277.6, 5781.8) | 158 | 7335.1 | (6181.8, 8703.5) |
| | | Prior to Dose 4 | 86 | 2063.8 | (1643.3, 2591.8) | 85 | 2523.8 | (1938.9, 3285.3) |
| | | 30 Days Postdose 4 | 84 | 10098.6 | (8162.4, 12494.0) | 85 | 12301.9 | (9402.0, 16096.2) |
| 9V | GMT | 30 Days Postdose 3 | 168 | 1217.3 | (1040.2, 1424.6) | 162 | 1534.1 | (1305.5, 1802.8) |
| | | Prior to Dose 4 | 84 | 367.3 | (283.6, 475.6) | 85 | 552.1 | (418.7, 727.9) |
| | | 30 Days Postdose 4 | 84 | 2714.5 | (2229.0, 3305.7) | 84 | 4237.1 | (3356.3, 5349.2) |
| 14 | GMT | 30 Days Postdose 3 | 167 | 2400.7 | (1980.8, 2909.6) | 160 | 1853.1 | (1511.2, 2272.5) |
| | | Prior to Dose 4 | 86 | 816.6 | (604.3, 1103.7) | 85 | 963.0 | (751.4, 1234.3) |
| | | 30 Days Postdose 4 | 84 | 4558.1 | (3723.8, 5579.2) | 84 | 3010.5 | (2396.9, 3781.2) |
| 18C | GMT | 30 Days Postdose 3 | 171 | 1171.2 | (1022.7, 1341.4) | 162 | 1330.2 | (1158.3, 1527.5) |
| | | Prior to Dose 4 | 86 | 273.8 | (213.7, 350.7) | 85 | 333.6 | (260.1, 427.8) |
| | | 30 Days Postdose 4 | 84 | 2471.0 | (1960.5, 3114.5) | 85 | 3319.6 | (2785.5, 3956.1) |
| 19A | GMT | 30 Days Postdose 3 | 171 | 841.3 | (716.0, 988.6) | 162 | 1400.7 | (1205.5, 1627.4) |
| | | Prior to Dose 4 | 86 | 240.3 | (168.5, 342.6) | 84 | 340.1 | (239.6, 482.6) |
| | | 30 Days Postdose 4 | 84 | 3370.4 | (2835.8, 4005.8) | 84 | 5584.6 | (4557.7, 6842.7) |
| 19F | GMT | 30 Days Postdose 3 | 171 | 703.9 | (614.2, 806.6) | 162 | 850.6 | (744.5, 971.9) |
| | | Prior to Dose 4 | 85 | 205.5 | (159.6, 264.6) | 85 | 269.9 | (206.3, 353.1) |
| | | 30 Days Postdose 4 | 84 | 2286.4 | (1843.5, 2835.5) | 85 | 2626.7 | (2119.7, 3255.1) |
| 23F | GMT | 30 Days Postdose 3 | 167 | 2078.9 | (1779.2, 2428.9) | 158 | 3668.8 | (3069.2, 4385.6) |
| | | Prior to Dose 4 | 82 | 914.6 | (686.2, 1219.1) | 82 | 1271.2 | (910.4, 1775.0) |
| | | 30 Days Postdose 4 | 83 | 6098.6 | (4730.6, 7862.2) | 85 | 13677.9 | (10178.0, 18381.2) |
| 2 Serotypes Unique to V114 | | | | | | | | |
| 22F | GMT | 30 Days Postdose 3 | 170 | 1849.3 | (1606.9, 2128.2) | 155 | 9.1 | (7.9, 10.4) |
| | | Prior to Dose 4 | 82 | 545.2 | (412.4, 720.7) | 82 | 25.1 | (15.4, 40.8) |
| | | 30 Days Postdose 4 | 84 | 3387.1 | (2733.9, 4196.4) | 77 | 22.1 | (13.5, 36.1) |
| 33F | GMT | 30 Days Postdose 3 | 170 | 8262.6 | (6585.3, 10367.1) | 155 | 119.6 | (83.2, 171.8) |
| | | Prior to Dose 4 | 86 | 6144.5 | (4957.1, 7616.3) | 85 | 1413.2 | (968.5, 2062.1) |
| | | 30 Days Postdose 4 | 84 | 20663.3 | (16633.3, 25669.6) | 82 | 1764.6 | (1243.2, 2504.7) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, dose 3 was administered at ~6 months of age and dose 4 was administered at ~12 to 15 months of age.
CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity.

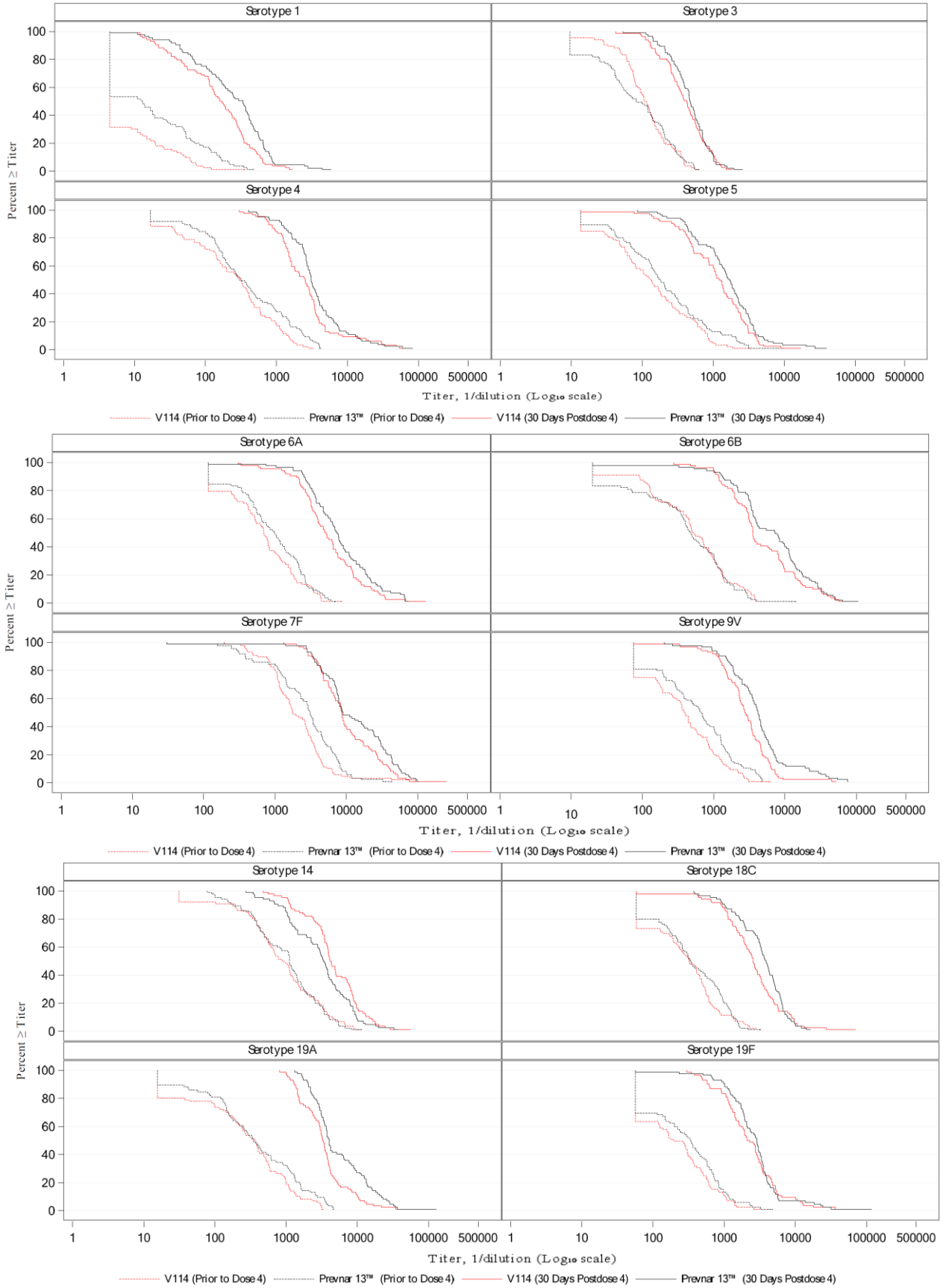



**Figure 11 RCDCs of OPA Titers Prior to Dose 4 and 30 Days Postdose 4 for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A and 19F (PP) – V114-029**

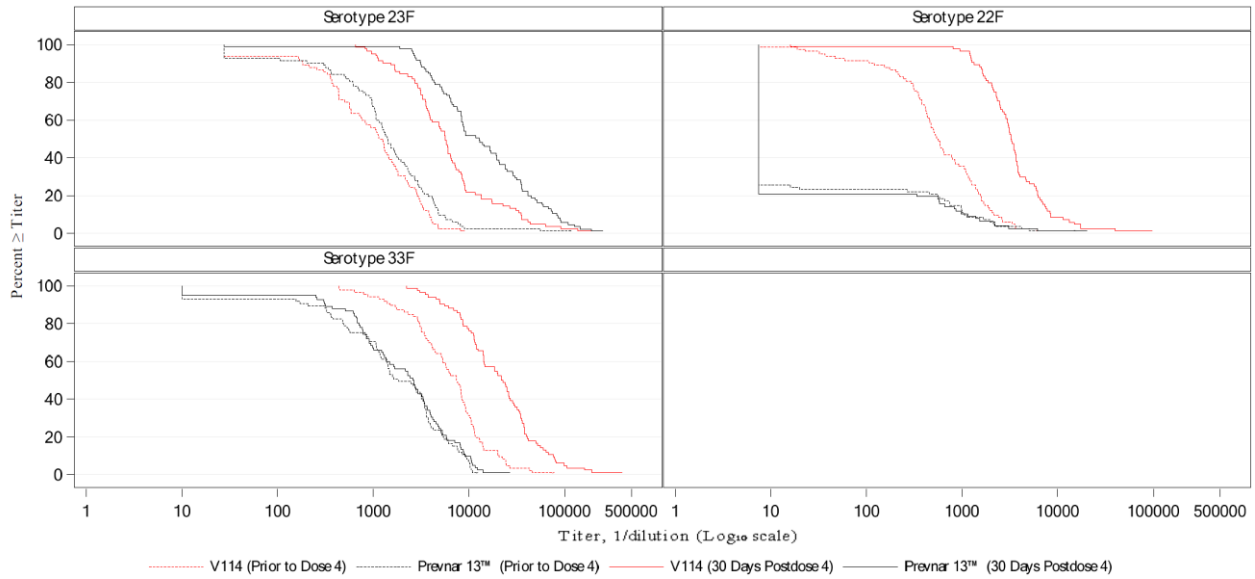



**Figure 12 RCDCs of OPA Titers Prior to Dose 4 and 30 Days Postdose 4 for serotypes 23F, 22F and 33F (PP) – V114-029**

***CHMP's comment***

The results of the functional OPA antibodies are consistent with the results as observed for IgG GMCs, which is appreciated. No correlate of protection is known for OPA antibodies in children, therefore the clinical impact of the response induced is unknown.

In the V114 group, OPA GMTs decrease over time from PPS to pretoddler dose for all serotypes. After the toddler dose an increase in OPA GMTs was seen for all serotypes. PTD, OPA GMTs increased over the levels observed PPS for all serotypes in both treatment groups. This indicates that immune memory is present.

When comparing OPA GMTs between V114 and PCV13 at PPS, the OPA titres of the 13 shared serotypes were generally comparable between the 2 treatment arms. Immediately prior to the toddler dose, OPA GMTs were substantially decreased from PPS for all serotypes, except for serotype 33F in the PCV13 group. PTD, levels increased and were comparable between the 2 treatment arms for 10 out of 13 shared serotypes. Three serotypes, 9V, 19A and 23F, were somewhat lower in the V114 arm compared to the PCV13 arm. Interestingly, no difference in serotype 3 OPA antibodies was seen between V114 and PCV13 30 days PTD.

An increase in OPA titres from 30 days PPS to immediately prior to toddler dose was observed for serotype 33F in the PCV13 group, which is not reflected in an increase in IgG GMCs. No clear explanation exists, however, it could be related to non-specific background interference in combination with increasing IgM due to maturation of the immune system. The observed increase is several magnitudes lower than the response seen in the V114 group. In addition, no further substantial increase is seen between pre-toddler dose and toddler dose. For all other serotypes there is a correlation between IgG GMCs and OPA titres, as when IgG GMCs decrease, the OPA GMTs also decrease and vice versa.

The OPA GMTs for the 2 unique serotypes in the V114 group were consistently higher compared to the PCV13 arm, which is to be expected. The OPA GMTs for the 2 unique serotypes were higher compared to the lowest OPA GMTs, serotype 1, indicating that a robust response was generated.

## Ancillary analyses

### Sex, Race and Ethnicity

*V114-025*

The primary immunogenicity endpoint was summarized by intervention group for each subgroup with ≥5% of the total number of randomized participants in each intervention group. Serotype-specific IgG response rates and GMCs at 30 days PTD for all 15 serotypes in male and female participants, in the race subgroup (White) and in ethnicity subgroups (Hispanic or Latino and non-Hispanic or Latino) were consistent with the results observed in the overall population, an example for sex is provided in Figure 13.

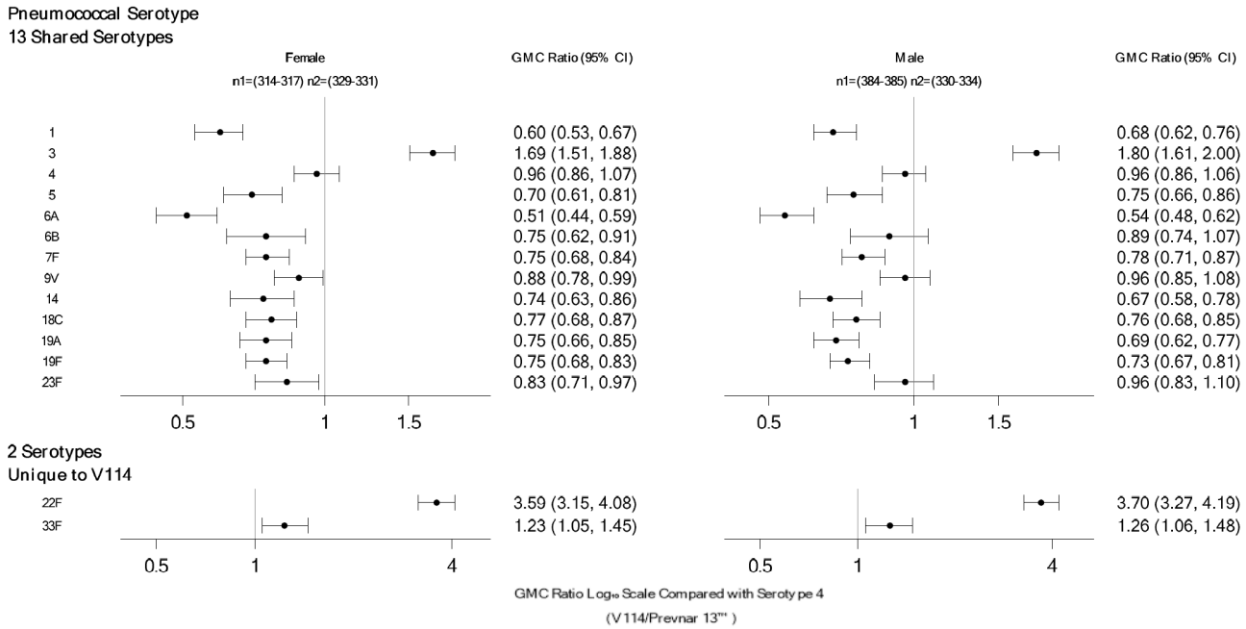



**Figure 13 Forest Plot of IgG GMC Ratios at 30 Days Post Toddler Dose by Sex (PP) – V114-025**

*V114-029*

The primary immunogenicity endpoint was summarized by intervention group for each subgroup with ≥5% of the total number of randomized participants in each intervention group. Serotype-specific IgG GMCs and response rates at 30 days PD3 and serotype-specific IgG GMCs at 30 days PD4 for all 15 serotypes in both male and female participants, within race subgroups (black, white, Asian, and multiple races) and in both ethnicity subgroups (Hispanic or Latino and non-Hispanic or Latino) were generally consistent with the results observed in the overall population, an example for sex is provided in Figure 14.

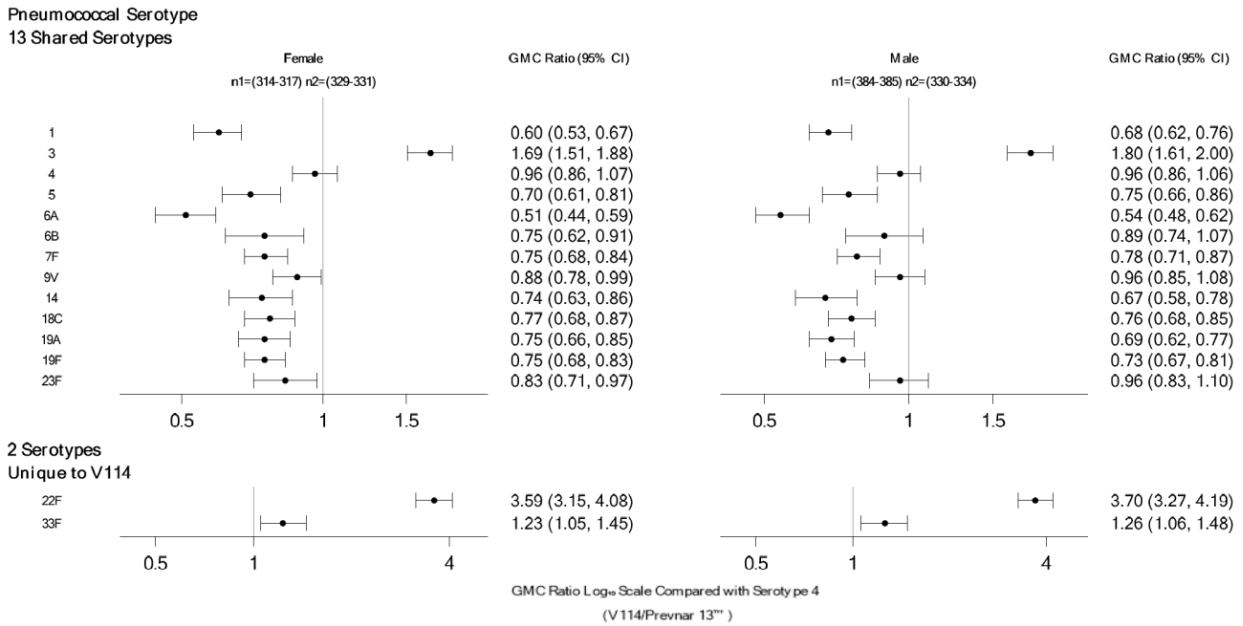



**Figure 14 Forest Plot of IgG GMC Ratios at 30 Days Postdose 3 by Sex (PP) – V114-029**

***CHMP's comment***

In both pivotal studies, it was shown that V114 was immunogenic in both male and female participants as assessed by IgG GMCs and response rates for all 15 serotypes contained in the vaccine 30 days PPS and IgG GMCs 30 days PTD. The forest plots and IgG GMCs of female and male participants were largely comparable to the overall PP population. Although slight differences could be observed, no clear trend was seen. The same holds true for the subgroups for race and ethnicity, as slight differences in immune response could be observed between the subgroups, however no clear trends were observed. For study V114-025 no subgroup analyses for race other than White was performed, as for other races the threshold of ≥5% of participants was not met.

Overall, the results of the subgroup analyses are consistent with results observed with other vaccinations and do not raise concerns.

Of note, term/preterm will be discussed separately in the analysis performed across trials.

## Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 23 Summary of Efficacy for trial V114-025**

| **Title: A Phase 3, Multicenter, Randomized, Double-blind, Active-comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Infants (PNEU PED EU-1)** | |
|---|---|
| Study identifier | Protocol Number: P025V114<br>IND: 14115<br>EudraCT: 2018-003787-31 |
| Design | A randomized, active-controlled, parallel-group, multi-site, double-blind (with in-house blinding) study of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days). |

| | | | |
|---|---|---|---|
| | Duration of main phase:<br><br><br>Duration of Run-in phase:<br>Duration of Extension phase: | | First Participant First Visit: 04-SEP-2019<br>Last Participant Last Visit: 05-AUG-2021<br>Approximately 23 months<br>not applicable<br>not applicable |
| Hypothesis | Non-inferiority, superiority | | |
| Treatments groups | V114 | | Term infants: Injection of 0.5 mL IM at 2, 4 and 11-15 mo of age<br>Pre-term infants: Injection of 0.5 ML IM at 2, 3, 4 and 11-15 mo of age<br>591 participants randomized<br>588 participants vaccinated (99.5%)<br>569 participants completed the study (96.3%) |
| | PCV13 | | Term infants: Injection of 0.5 mL IM at 2, 4 and 11-15 mo of age<br>Pre-term infants: Injection of 0.5 ML IM at 2, 3, 4 and 11-15 mo of age<br>593 participants randomized<br>591 participants vaccinated (99.7%)<br>570 participants completed the study (96.1%) |
| Endpoints and definitions | Primary endpoints | Immuno-genicity | • Serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days following the toddler dose (PTD). |
| | Secondary endpoints | <label> | • Antibody responses to:<br>• diphtheria toxoid<br>• tetanus toxoid<br>• pertussis toxin<br>• pertussis filamentous hemagglutinin<br>• pertactin<br>• Haemophilus influenzae type b polyribosylribitol phosphate<br>• Hepatitis B surface antigen<br>• poliovirus serotypes 1, 2, and 3<br>at 30 days PTD of V114 or PCV13.<br>• Anti-rotavirus IgA response at 30 days PPS of V114 or PCV13.<br>• Serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PPS.<br>• Serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PTD. |
| Database lock | 24-AUG-2021 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | PP population: all randomized participants without deviations from the protocol that could have substantially affected the results of the immunogenicity endpoints.<br>Timepoint: 30 Days PTD. |
| Results | • V114 met noninferiority criteria for the 13 shared serotypes, as assessed by the proportions of participants meeting the threshold value of ≥0.35 µg/mL (response rate) and serotype-specific IgG GMCs at 30 days PTD.<br>• V114 met superiority criteria for the 2 serotypes (22F and 33F) unique to V114, as assessed by response rate and serotype-specific IgG GMCs at 30 days PTD. |
| Notes | Thirty days PTD, excluding serotype 3, the proportion of participants achieving 0.35 µg/mL was >95% in the V114 compared to >97% in the PCV13 group. For serotype 3, 92.0% of participants were responders, compared to 83.8% in the PCV13 group. For the 2 unique serotypes, >99% of participants were responders compared to <6% in the PCV13 group.<br><br>For the 13 shared serotypes, except serotype 3, IgG GMCs were lower in the V114 group compared to the PCV13 group. For 11 out of 13 shared serotypes the upper bound of the 2-sided 95% CI did not contain 1.00. The IgG GMCs for the 2 unique serotypes were substantially higher in the V114 group compared to the PCV13 group.<br><br>For all serotypes the IgG GMCs were well above 0.35 µg/mL and the vast majority of participants achieved this threshold indicating protection against IPD. As there is only a surrogate of protection in place for IPD and not for pneumonia or AOM it is difficult to interpret the clinical impact of these lower titres on the protection against pneumonia and AOM. |
| **Analysis description** | **Secondary analysis** |

| | |
|---|---|
| Analysis population and time point description | PP population: all randomized participants without deviations from the protocol that could have substantially affected the results of the immunogenicity endpoints.<br>Timepoints: 30 Days PPS and 30 days PTD. |
| Results | • Immune responses to INFANRIX™ hexa administered concomitantly with V114 met noninferiority criteria, as assessed by the proportions of participants meeting the antigen-specific response rate to each antigen in INFANRIX™ hexa at 30 days PTD.<br>• Immune response to Rotarix™ administered concomitantly with V114 met noninferiority criteria, as assessed by anti-rotavirus IgA GMTs at 30 days PPS.<br>• Serotype-specific IgG response rates and IgG GMCs were comparable for most of the 13 shared serotypes between the intervention groups and were higher for the 2 unique serotypes (22F and 33F) in V114 recipients compared with PCV13 recipients at 30 days PPS.<br>• The pattern of functional immune responses (as assessed by serotype-specific OPA responses) over time and the distribution of OPA titers (as displayed by RCDCs) were generally comparable between intervention groups and were consistent with that observed for serotype-specific IgG responses |
| Notes | The immune response to both concomitantly administered vaccines was comparable between the V114 and PCV13 group, indicating that the generation of the immune response was not impacted differently by the 2 vaccines.<br><br>At 30 days PPS, serotype 6A does not meet non-inferiority criteria for both response rate and IgG GMCs, as the response rate is 73.2% in the V114 group compared to 92.6% in the PCV13 group and IgG GMC is 0.64 µg/mL in the V114 group compared to 1.42 in the PCV13 group. For all other shared serotypes, non-inferiority criteria are met. For all shared serotype the IgG GMCs are well above the threshold of 0.35 µg/mL. For the 2 unique serotypes, the immune response is higher in the V114 group compared to PCV13, with a response rate of 95.6% and 48.7% in the V114 group compared to 5.2% and 2.8% in the PCV13 group for 22F and 33F. For 22F IgG GMC is above the threshold of 0.35 µg/mL, while it is just below, 0.31 µg/mL, for 33F.<br><br>The results of OPA GMTs are consistent with the results as observed for IgG GMCs. |

## Table 24 Summary of Efficacy for trial V114-029

| **Title: A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)** | | | |
|---|---|---|---|
| Study identifier | Protocol Number: P029V114<br>IND: 14115<br>EudraCT: 2018-004109-21 | | |
| Design | A randomized, active-controlled, parallel-group, multi-site, double-blind study of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days [inclusive]).<br>Participants also received the following pediatric vaccines: RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M M-R™II, VARIVAX™, and HIBERIX™.. | | |
| | Duration of main phase:<br><br><br>Duration of Run-in phase:<br>Duration of Extension phase: | | First Participant First Visit: 13-JUN-2019<br>Last Participant Last Visit: 24-MAY-2021<br>Approximately 23 months<br>not applicable<br>not applicable |
| Hypothesis | Non-inferiority, superiority | | |
| Treatments groups | V114 | | Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively).<br>860 participants randomized<br>858 participants vaccinated (99.8%)<br>758 participants completed the study (88.1%) |
| | PCV13 | | Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively).<br>860 participants randomized<br>856 participants vaccinated (99.5%)<br>734 participants completed the study (85.3%) |
| Endpoints and definitions | Primary endpoints | Immuno-genicity | • Serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days following the primary series (dose 3, PPS) and 30 days following the toddler dose (PTD). |

| | | | |
|---|---|---|---|
| | Secondary endpoints | <label> | • Antibody responses to:<br>  • diphtheria toxoid<br>  • tetanus toxoid<br>  • pertussis toxin<br>  • pertussis filamentous hemagglutinin<br>  • pertussis pertactin<br>  • *Haemophilus influenzae* type b polyribosylribitol phosphate<br>  • Anti-Hepatitis B surface antigen<br>  • poliovirus serotypes 1, 2, and 3<br>at 30 days PPS of V114 or PCV13.<br>• Antibody responses to hepatitis A antigen at 30 days PTD4 of V114 or PCV13.<br>• Antibody responses to measles, mumps, and rubella virus at 30 days PTD of V114 or PCV13.<br>• Antibody responses to varicella zoster virus at 30 days PTD of V114 or PCV13.<br>• Antibody responses to PRP at 30 days PTD of V114 or PCV13.<br>• Serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PPS. |
| Database lock | 8-JUN-2021 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | PP population: all randomized participants without deviations from the protocol that could have substantially affected the results of the immunogenicity endpoints.<br>Timepoints: 30 days PPS and 30 days PTD. |
| Results | • V114 met noninferiority criteria for the 13 shared serotypes and 2 unique serotypes as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35 µg/mL (response rates) for each serotype at 30 days PPS (unique serotypes were compared to the lowest response rate of the shared serotypes).<br>• V114 met noninferiority criteria for 12 of the 13 shared serotypes (narrowly missing on serotype 6A) as assessed by serotype-specific IgG GMCs at 30 days PPS.<br>• V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with the IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in PCV13, excluding serotype 3) at 30 days PPS.<br>• V114 met noninferiority criteria for the 13 shared serotypes as assessed by serotype-specific IgG GMCs at 30 days PTD.<br>• V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in PCV13, excluding serotype 3) at 30 days PTD. |
| Notes | Thirty days PPS, serotype 6A missed the non-inferiority margin as the GMC ratio was 0.52 (0.48, 0.58). The IgG GMC for serotype 6A in the V114 group was 1.55 and 2.95 in the PCV13 group, which is well above the surrogate of protection of ⩾0.35 µg/mL. At both 30 days PPS and 30 days PTD the IgG GMC was well above the threshold of 0.35 µg/mL for all serotypes in both treatment arms, indicating a substantial immune response that is likely to confer protection. |
| **Analysis description** | **Secondary analysis** |
| Analysis population and time point description | PP population: all randomized participants without deviations from the protocol that could have substantially affected the results of the immunogenicity endpoints.<br>Timepoints: 30 Days PPS and 30 days PTD. |
| Results | • Immune responses to Pentacel™ administered concomitantly with V114 met noninferiority criteria at 30 days PTD.<br>• Immune response to VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ administered concomitantly with V114 met noninferiority criteria at 30 days PPS.<br>• V114 met superiority criteria for the 2 unique V114 serotypes, as assessed by serotype-specific response rates and IgG GMCs at 30 days PPS and PTD.<br>• V114 met superiority criteria for serotype 3 as assessed by serotype-specific response rates and IgG GMCs at 30 days PPS and PTD.<br>• V114 elicited functional antibodies (OPA) generally comparable to PCV13 for the 13 shared serotypes, and higher than PCV13 for the 2 unique serotypes, as assessed by serotype-specific OPA responses at 30 days PPS |

| | |
|---|---|
| Notes | All responses for the concomitant vaccines showed a within 5 percentage points difference between the treatment arms.<br>The clinical relevance of meeting the superiority criteria for both the 2 unique serotypes and serotype 3 is unknown.<br>The results of the functional OPA antibodies are consistent with the results as observed for IgG GMCs. At 30 days PPS, the OPA titers of the 13 shared serotypes were generally comparable between the 2 treatment arms. |

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

### *Healthy Infants Receiving a 3- or 4-dose Regimen of PCV*

A side-by-side display of immunogenicity responses obtained during studies V114-025, V114-029, V114-008 and V114-027, conducted in healthy infants approximately 2 months of age, is presented below. A more detailed description of Study V114-008 and V114-027 is presented in the section supportive studies.

Although the proportions of participants by race and ethnicity varied across the studies due to the countries where these studies were conducted, the demographic characteristics were generally comparable between intervention groups in each study, see Table 25. Across the studies, the median age at enrolment was 8.0 or 9.0 weeks. Approximately half of the participants were female; the majority (≥55%) of participants were White across the studies and >20% of participants were Asian in V114-029 and V114-027. The majority (>74%) of participants were of non-Hispanic or Latino ethnicity.

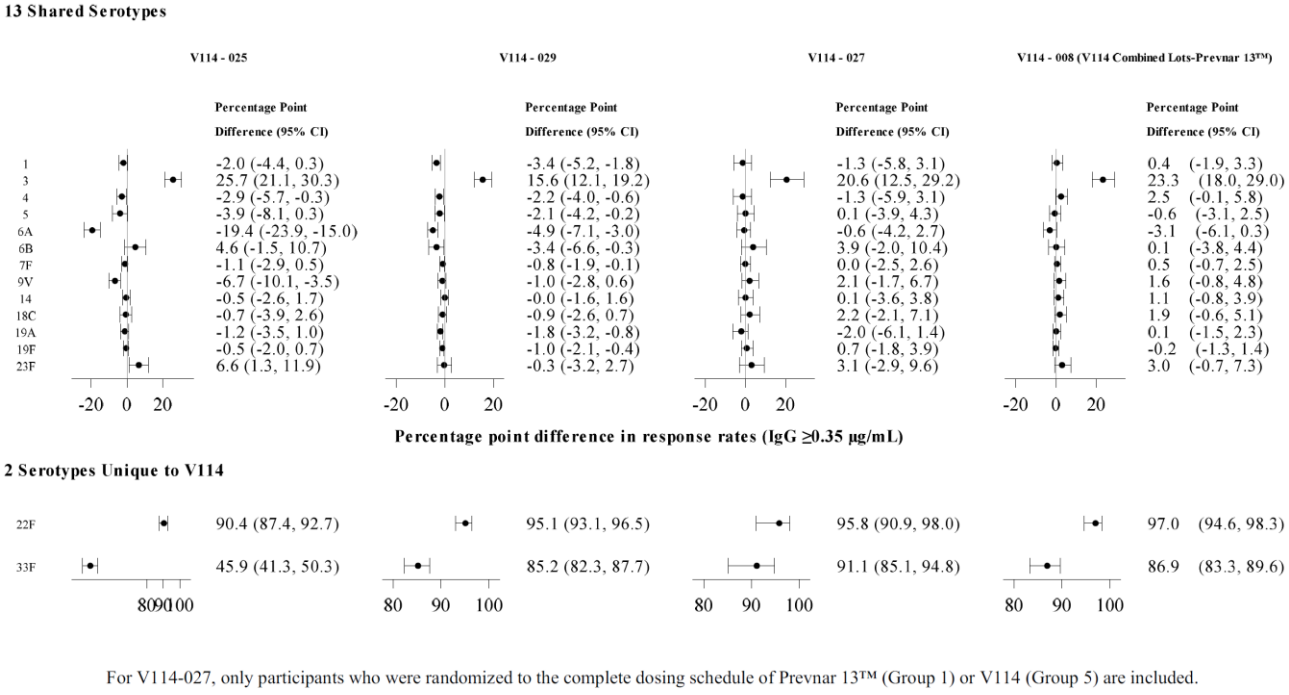
**Table 25 Participant Characteristics (All Vaccinated Participants) (V114-025, V114-029, V114-027, V114-008)**

| | **V114-025** | | | | **V114-029** | | | | **V114-027** | | | | **V114-008** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **V114** | | **PCV13** | | **V114** | | **PCV13** | | **V114** | | **PCV13** | | **V114 Combined Lots** | | **PCV13** | |
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Participants in population | 588 | | 591 | | 858 | | 856 | | 179 | | 179 | | 697 | | 347 | |
| **Sex** | | | | | | | | | | | | | | | | |
| Male | 305 | (51.9) | 306 | (51.8) | 461 | (53.7) | 429 | (50.1) | 92 | (51.4) | 103 | (57.5) | 349 | (50.1) | 174 | (50.1) |
| Female | 283 | (48.1) | 285 | (48.2) | 397 | (46.3) | 427 | (49.9) | 87 | (48.6) | 76 | (42.5) | 348 | (49.9) | 173 | (49.9) |
| **Age (Weeks)** | | | | | | | | | | | | | | | | |
| 6 | 77 | (13.1) | 60 | (10.2) | 75 | (8.7) | 80 | (9.3) | 11 | (6.1) | 6 | (3.4) | 19 | (2.7) | 16 | (4.6) |
| 7 | 80 | (13.6) | 82 | (13.9) | 100 | (11.7) | 98 | (11.4) | 18 | (10.1) | 24 | (13.4) | 46 | (6.6) | 23 | (6.6) |
| 8 | 161 | (27.4) | 152 | (25.7) | 276 | (32.2) | 252 | (29.4) | 51 | (28.5) | 62 | (34.6) | 247 | (35.4) | 118 | (34.0) |
| 9 | 151 | (25.7) | 162 | (27.4) | 281 | (32.8) | 289 | (33.8) | 54 | (30.2) | 58 | (32.4) | 245 | (35.2) | 114 | (32.9) |
| 10 | 53 | (9.0) | 75 | (12.7) | 90 | (10.5) | 96 | (11.2) | 26 | (14.5) | 18 | (10.1) | 75 | (10.8) | 41 | (11.8) |
| 11 | 43 | (7.3) | 39 | (6.6) | 28 | (3.3) | 32 | (3.7) | 14 | (7.8) | 9 | (5.0) | 44 | (6.3) | 22 | (6.3) |
| 12 | 23 | (3.9) | 21 | (3.6) | 8 | (0.9) | 9 | (1.1) | 5 | (2.8) | 2 | (1.1) | 21 | (3.0) | 13 | (3.7) |
| Mean | 8.4 | | 8.5 | | 8.4 | | 8.4 | | 8.7 | | 8.5 | | 8.8 | | 8.7 | |
| SD | 1.5 | | 1.5 | | 1.2 | | 1.3 | | 1.4 | | 1.2 | | 1.2 | | 1.3 | |
| Median | 8.0 | | 9.0 | | 8.0 | | 8.0 | | 9.0 | | 8.0 | | 9.0 | | 9.0 | |
| Range | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | | 6 to 12 | |
| **Race** | | | | | | | | | | | | | | | | |
| American Indian Or Alaska Native | 4 | (0.7) | 5 | (0.8) | 6 | (0.7) | 13 | (1.5) | 0 | (0.0) | 1 | (0.6) | 4 | (0.6) | 2 | (0.6) |
| Asian | 4 | (0.7) | 5 | (0.8) | 223 | (26.0) | 226 | (26.4) | 38 | (21.2) | 36 | (20.1) | 4 | (0.6) | 3 | (0.9) |
| Black Or African American | 4 | (0.7) | 3 | (0.5) | 52 | (6.1) | 53 | (6.2) | 9 | (5.0) | 8 | (4.5) | 58 | (8.3) | 33 | (9.5) |
| Multiple | 5 | (0.9) | 7 | (1.2) | 98 | (11.4) | 80 | (9.3) | 28 | (15.6) | 19 | (10.6) | 43 | (6.2) | 22 | (6.3) |
| Native Hawaiian Or Other Pacific Islander | 0 | (0.0) | 0 | (0.0) | 6 | (0.7) | 4 | (0.5) | 1 | (0.6) | 0 | (0.0) | 5 | (0.7) | 1 | (0.3) |
| White | 571 | (97.1) | 571 | (96.6) | 472 | (55.0) | 480 | (56.1) | 103 | (57.5) | 115 | (64.2) | 582 | (83.5) | 286 | (82.4) |
| Missing | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) | 0 | (0.0) |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ethnicity** | | | | | | | | | | | | | | | | | | | | |
| Hispanic Or Latino | 66 | (11.2) | 65 | (11.0) | 206 | (24.0) | 203 | (23.7) | 43 | (24.0) | 33 | (18.4) | 84 | (12.1) | 51 | (14.7) | | | | |
| Not Hispanic Or Latino | 522 | (88.8) | 524 | (88.7) | 639 | (74.5) | 643 | (75.1) | 136 | (76.0) | 146 | (81.6) | 610 | (87.5) | 293 | (84.4) | | | | |
| Not Reported | 0 | (0.0) | 1 | (0.2) | 11 | (1.3) | 5 | (0.6) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.6) | | | | |
| Unknown | 0 | (0.0) | 1 | (0.2) | 2 | (0.2) | 5 | (0.6) | 0 | (0.0) | 0 | (0.0) | 3 | (0.4) | 1 | (0.3) | | | | |
| For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included. SD=standard deviation. | | | | | | | | | | | | | | | | | | | | |

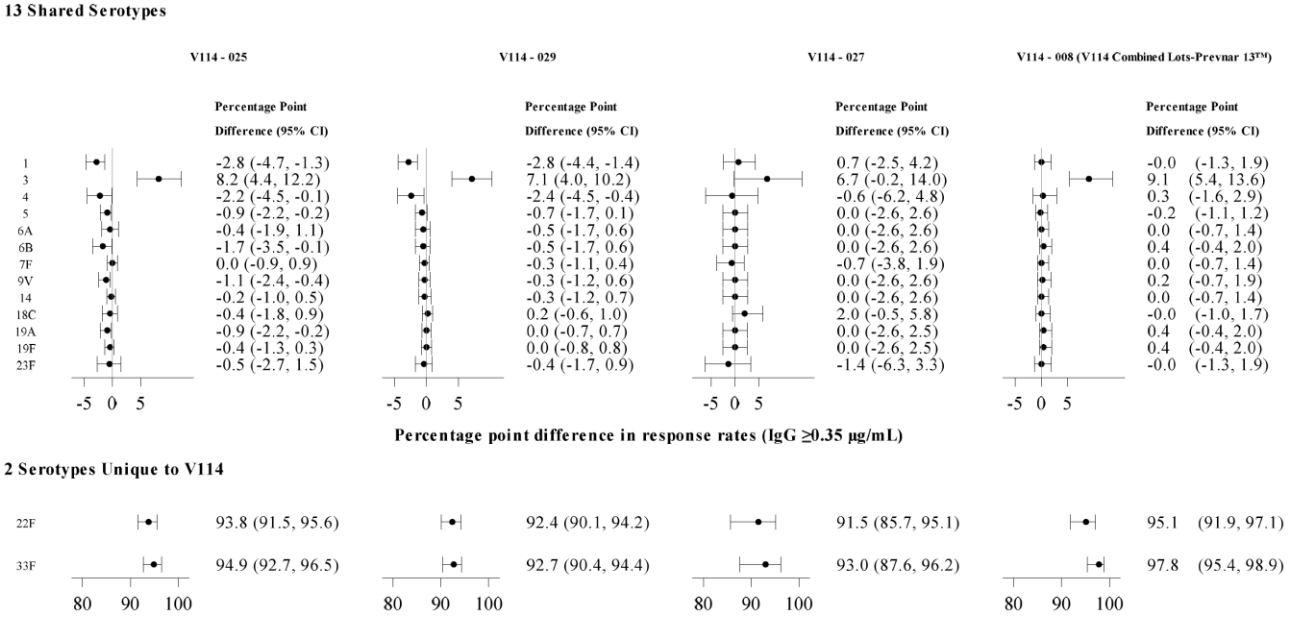
Across the 4 studies, serotype-specific IgG response rates at 30 days PPS varied between serotypes, with the lowest responses observed in study V114-025, where the majority of participants received 2 doses of PCV in the primary series.

The differences in response rates between the V114 and PCV13 groups at 30 days PPS and 30 days PTD were generally consistent across studies in participants receiving a 3- or 4-dose regimen of PCV, see Figure 15 and Figure 16.




For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

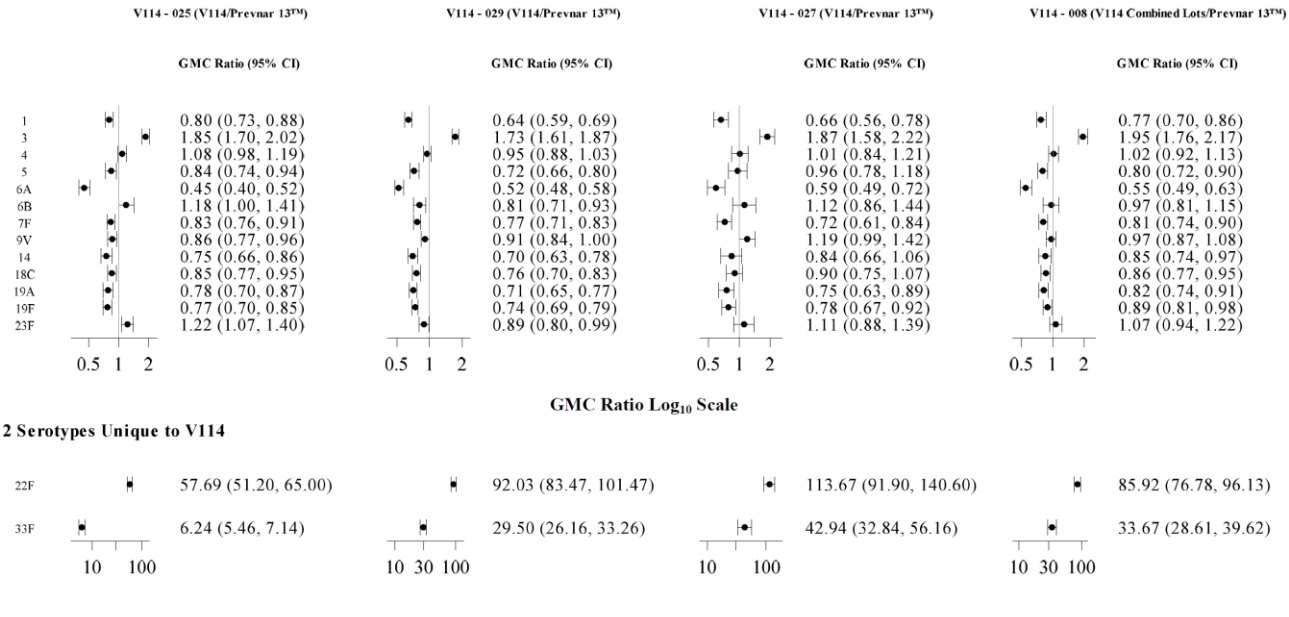
**Figure 15 Forest Plot of IgG Antibody % Difference in Response Rates (IgG ≥0.35 µg/mL) at 30 Days Post Primary Series (PP) – V114-025, V114-029, V114-027 and V114-008**




For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

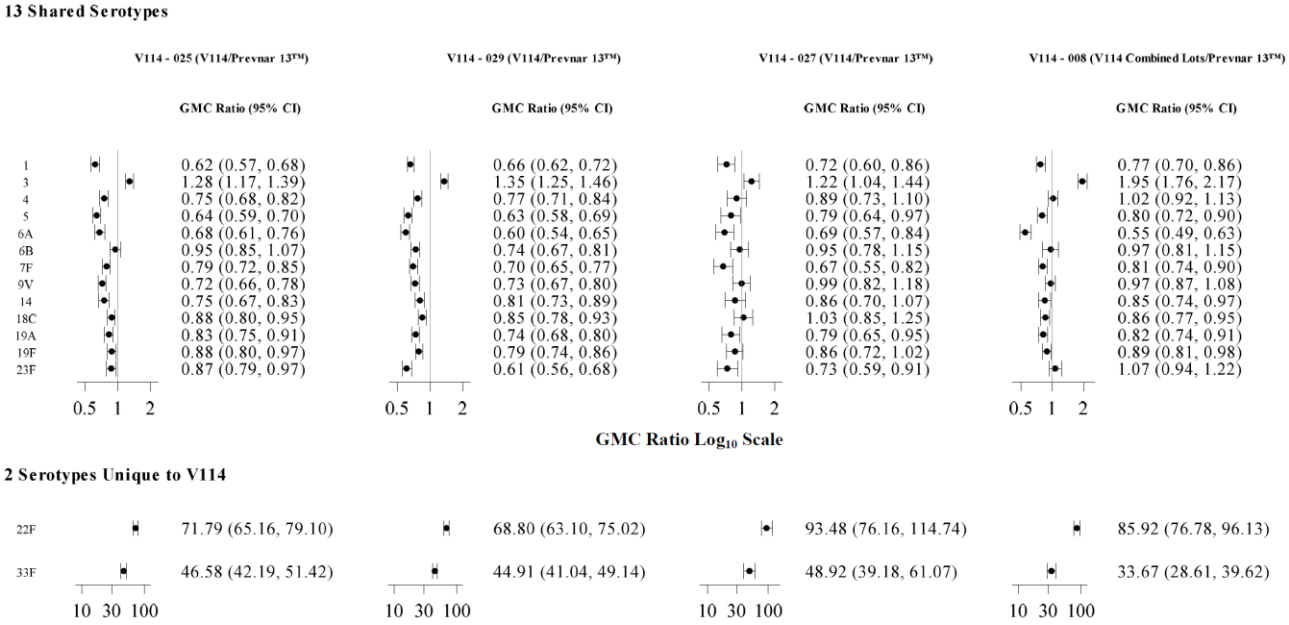
**Figure 16 Forest Plot of IgG Antibody % Difference in Response Rates (IgG ≥0.35 µg/mL) at 30 Days Post Toddler Dose (PP) – V114-025, V114-029, V114-027 and V114-008**

Across the 4 studies, V114 elicited serotype-specific immune responses to all 15 serotypes included in the vaccine when administered as a 3-dose or 4-dose series, as assessed by IgG GMCs at 30 days PPS, pretoddler dose, and at 30 days PTD, see Figure 16 and Figure 17. Serotype-specific IgG GMC ratios (V114/PCV13) at 30 days PPS and 30 days PTD were generally consistent in healthy infants receiving 3 or 4 doses of PCV.




For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

**Figure 17 Forest plot of IgG GMC Ratio at 30 Days Post Primary Series (PP) – V114-025, V114-029, V114-027 and V114-008**




For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

**Figure 18 Forest plot of IgG GMC Ratio at 30 Days Post Toddler Dose (PP) – V114-025, V114-029, V114-027 and V114-008**

***CHMP's comment***

Data from healthy infants was compared across 4 clinical studies: V114-025, V114-029, V114-027 and V114-008.

The design of the 4 studies was similar, except for the number of doses given. All studies were randomized, double-blind, PCV13 controlled, multicenter studies. The studies all enrolled healthy infants approximately 2 months of age. During study V114-025 3 doses (2 in the primary series and 1 toddler dose) of PCV were administered compared to 4 doses (3 in the primary series and 1 toddler dose) in the rest of the studies.

A consistent immune response was observed across studies, as the forest plots all showed a similar pattern for all studies for both IgG response rate and GMC ratio. The results of studies V114-027 and V114-008 were consistent with the results of pivotal studies V114-025 and V114-029. V114 generated an immune response to all 15 serotypes included in the vaccine. At 30 days PTD, the IgG response rate for all serotypes was ≥92% in the V114 group in all studies.

The lowest immune response is seen in study V114-025. At 30 days PPS, the IgG response rate of the 13 shared serotypes ranged from 57.3% to 98.9% in study V114-025 compared to 88.6% to 99.0% in study V114-029, 95.2% to 100.0% in study V114-027 and 91.4% to 99.5% in study V114-008. As at 30 days PPS, GMC ratios were comparable across the 4 studies. This indicates that while V114 generated the lowest immune response in study V114-025, the same holds true for PCV13.

It has been noted that the number of subjects using paracetamol concomitantly is much higher in both pivotal studies compared to the other studies (025: ~48%, 029: ~67%, 027: ~6%, 008: no use of paracetamol). Although the use of paracetamol was overall balanced between groups in all respective studies, further discussion was requested based on post marketing findings with PCV13 indicating that the prophylactic use of antipyretics (ibuprofen and paracetamol) reduced the immune response especially after the primary series. The presented results of subgroup analyses based on concomitant antipyretic use (yes/no) are similar for both vaccines, indicating a similar effect for both vaccines. The

potential influence of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response, as observed in the postmarketing of PCV13, can consequently not be ruled out and respective wording in the SmPC is required.

Overall, these results indicate that V114 induces a slightly lower immune response compared to PCV13 for the majority of the shared serotypes, as evidenced by the GMC ratio that is below 1. However, the immune response is high enough to ensure that the threshold of 0.35 µg/mL is achieved by most participants.

***Preterm Infants***

Four Phase 3 clinical studies (V114-025, V114-027, V114-029, and V114-031) included in the V114 paediatric submission package evaluated the safety, tolerability, and immunogenicity of V114 in healthy infants 6 to 12 weeks of age, including preterm infants (<37 weeks gestational age at birth), see Table 26.

**Table 26 Preterm infants enrolled in the 4 studies V114-025, V114-027, V114-029, and V114-031**

| Population | Study Number | V114 | PCV13 |
|---|---|---|---|
| Healthy infants receiving PCV per recommended immunization regimens starting at ~2 months of age | V114-025 | 32 | 36 |
| | V114-027[a] | 64 | 74 |
| | V114-029 | 74 | 76 |
| | V114-031 | 51 | 48 |
| Overall population | Total: | 221 | 234 |

Participants were counted once for each column according to the intervention they actually received.
[a] A total number of 47 participants in Study V114-027 in groups 2, 3 and 4 received both V114 and PCV13 per study design and were included in both intervention groups.
PCV=Pneumococcal Conjugate Vaccine (V114 or PCV13).

The integrated population included 354 preterm infants who received at least 1 dose of PCV. The majority (>89%) completed the study they were enrolled in, see Table 27.

**Table 27 Number of Participants Who Received ⩾ 1 Dose of PCV (Preterm Infants) - (V114-025, V114-027, V114-029, V114-031)**

| | **V114** | | **PCV13** | | **Total** | |
|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Participants in population | 174 | | 180 | | 354 | |
| **Vaccinated with PCV** | | | | | | |
| Dose 1 of primary series | 174 | (100.0) | 180 | (100.0) | 354 | (100.0) |
| Dose 2 of primary series | 172 | (98.9) | 174 | (96.7) | 346 | (97.7) |
| Dose 3 of primary series | 168 | (96.6) | 172 | (95.6) | 340 | (96.0) |
| Toddler dose | 164 | (94.3) | 162 | (90.0) | 326 | (92.1) |
| **Trial disposition** | | | | | | |
| Completed | 160 | (92.0) | 161 | (89.4) | 321 | (90.7) |
| Discontinued | 14 | (8.0) | 19 | (10.6) | 33 | (9.3) |
| Lost to follow-up | 8 | (4.6) | 4 | (2.2) | 12 | (3.4) |
| Physician decision | 3 | (1.7) | 3 | (1.7) | 6 | (1.7) |
| Withdrawal by Parent/Guardian | 3 | (1.7) | 12 | (6.7) | 15 | (4.2) |

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.
PCV=pneumococcal conjugate vaccine (V114 or PCV13).

The demographic characteristics of the preterm infants included in the integrated population is presented in Table 28. In the integrated population, the median age at enrolment was 8.0 or 9.0

weeks. The median gestational age was 36 weeks. Slighlty more male participants were enrolled (≥62%); the majority (≥69%) of participants were White and. The majority (>82%) of participants were of non-Hispanic or Latino ethnicity.

**Table 28 Participant Characteristics (All Vaccinated Participants) (Preterm Infants) - (V114-025, V114-027, V114-029, V114-031)**

| | V114 | | Prevnar 13™ | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 174 | | 180 | | 354 | |
| **Sex** | | | | | | |
| Male | 113 | (64.9) | 113 | (62.8) | 226 | (63.8) |
| Female | 61 | (35.1) | 67 | (37.2) | 128 | (36.2) |
| **Age (Weeks)** | | | | | | |
| 6 | 20 | (11.5) | 18 | (10.0) | 38 | (10.7) |
| 7 | 17 | (9.8) | 18 | (10.0) | 35 | (9.9) |
| 8 | 53 | (30.5) | 52 | (28.9) | 105 | (29.7) |
| 9 | 41 | (23.6) | 47 | (26.1) | 88 | (24.9) |
| 10 | 24 | (13.8) | 29 | (16.1) | 53 | (15.0) |
| 11 | 14 | (8.0) | 9 | (5.0) | 23 | (6.5) |
| 12 | 5 | (2.9) | 7 | (3.9) | 12 | (3.4) |
| Mean | 8.5 | | 8.6 | | 8.6 | |
| SD | 1.5 | | 1.5 | | 1.5 | |
| Median | 8.0 | | 9.0 | | 8.0 | |
| Range | 6 to 12 | | 6 to 12 | | 6 to 12 | |
| **Gestational Age (Weeks)** | | | | | | |
| <29 | 2 | (1.1) | 0 | (0.0) | 2 | (0.6) |
| ≥29 to <32 | 3 | (1.7) | 2 | (1.1) | 5 | (1.4) |
| ≥32 to <37 | 169 | (97.1) | 178 | (98.9) | 347 | (98.0) |
| Mean | 35.4 | | 35.5 | | 35.4 | |
| SD | 1.5 | | 1.2 | | 1.4 | |
| Median | 35.9 | | 36.0 | | 36.0 | |
| Range | 27 to 37 | | 31 to 37 | | 27 to 37 | |
| **Race** | | | | | | |
| American Indian Or Alaska Native | 2 | (1.1) | 3 | (1.7) | 5 | (1.4) |
| Asian | 22 | (12.6) | 23 | (12.8) | 45 | (12.7) |
| Black Or African American | 9 | (5.2) | 11 | (6.1) | 20 | (5.6) |
| Multiple | 20 | (11.5) | 17 | (9.4) | 37 | (10.5) |
| American Indian Or Alaska Native, Black Or African American | 1 | (0.6) | 0 | (0.0) | 1 | (0.3) |
| American Indian Or Alaska Native, Black Or African American, White | 2 | (1.1) | 1 | (0.6) | 3 | (0.8) |
| American Indian Or Alaska Native, White | 1 | (0.6) | 1 | (0.6) | 2 | (0.6) |
| Black Or African American, White | 14 | (8.0) | 12 | (6.7) | 26 | (7.3) |
| White, Asian | 2 | (1.1) | 3 | (1.7) | 5 | (1.4) |
| Native Hawaiian Or Other Pacific Islander | 1 | (0.6) | 1 | (0.6) | 2 | (0.6) |
| White | 120 | (69.0) | 125 | (69.4) | 245 | (69.2) |
| **Ethnicity** | | | | | | |
| Hispanic Or Latino | 29 | (16.7) | 23 | (12.8) | 52 | (14.7) |
| Not Hispanic Or Latino | 144 | (82.8) | 157 | (87.2) | 301 | (85.0) |
| Not Reported | 1 | (0.6) | 0 | (0.0) | 1 | (0.3) |
| **Region** | | | | | | |
| Europe | 61 | (35.1) | 61 | (33.9) | 122 | (34.5) |
| Ex-Europe | 113 | (64.9) | 119 | (66.1) | 232 | (65.5) |

For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

SD=standard deviation.

The majority (>85%) of preterm infants in the V114 group achieved the IgG threshold value of ≥0.35 µg/mL at 30 days PPS and nearly all (>96%) achieved IgG ≥0.35 µg/mL at 30 days PTD for each of the 15 serotypes contained in the vaccine:

- Serotype-specific IgG response rates at 30 days PPS and 30 days PTD were generally comparable between the V114 and PCV13 intervention groups for the 13 shared serotypes and higher in the V114 group for the 2 serotypes unique to V114 (22F and 33F), see Table 29.
- Serotype-specific IgG response rates at 30 days PPS and 30 days PTD in the FAS population were consistent with those observed for the PP population.

**Table 29 Summary of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Post Primary Series and Post Toddler Dose (PP) (Preterm Infants) - (V114-025, V114-027, V114-029, V114-031)**

| Serotype | | V114 (N=174) | | PCV13 (N=180) | |
|---|---|---|---|---|---|
| | | % (m/n) | 95% CI[a] | % (m/n) | 95% CI[a] |
| *13 Shared Serotypes* | | | | | |
| 1 | 30 days PPS | 96.9% (124/128) | (92.2, 99.1) | 98.5% (131/133) | (94.7, 99.8) |
| | 30 days PTD | 98.5% (129/131) | (94.6, 99.8) | 99.3% (141/142) | (96.1, 100.0) |
| 3 | 30 days PPS | 96.1% (123/128) | (91.1, 98.7) | 81.8% (108/132) | (74.2, 88.0) |
| | 30 days PTD | 96.9% (127/131) | (92.4, 99.2) | 85.9% (122/142) | (79.1, 91.2) |
| 4 | 30 days PPS | 97.7% (125/128) | (93.3, 99.5) | 97.7% (128/131) | (93.5, 99.5) |
| | 30 days PTD | 96.9% (127/131) | (92.4, 99.2) | 97.9% (139/142) | (94.0, 99.6) |
| 5 | 30 days PPS | 95.3% (122/128) | (90.1, 98.3) | 94.7% (125/132) | (89.4, 97.8) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 6A | 30 days PPS | 95.3% (122/128) | (90.1, 98.3) | 98.5% (129/131) | (94.6, 99.8) |
| | 30 days PTD | 99.2% (130/131) | (95.8, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 6B | 30 days PPS | 85.2% (109/128) | (77.8, 90.8) | 90.8% (119/131) | (84.5, 95.2) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 98.6% (140/142) | (95.0, 99.8) |
| 7F | 30 days PPS | 99.2% (127/128) | (95.7, 100.0) | 100% (133/133) | (97.3, 100.0) |
| | 30 days PTD | 99.2% (130/131) | (95.8, 100.0) | 100% (142/142) | (97.4, 100.0) |
| 9V | 30 days PPS | 97.7% (125/128) | (93.3, 99.5) | 96.2% (128/133) | (91.4, 98.8) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 14 | 30 days PPS | 100% (128/128) | (97.2, 100.0) | 98.5% (130/132) | (94.6, 99.8) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 18C | 30 days PPS | 97.7% (125/128) | (93.3, 99.5) | 98.5% (131/133) | (94.7, 99.8) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 19A | 30 days PPS | 96.1% (123/128) | (91.1, 98.7) | 99.2% (132/133) | (95.9, 100.0) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 19F | 30 days PPS | 99.2% (127/128) | (95.7, 100.0) | 100% (133/133) | (97.3, 100.0) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) |
| 23F | 30 days PPS | 91.4% (117/128) | (85.1, 95.6) | 93.2% (124/133) | (87.5, 96.9) |
| | 30 days PTD | 99.2% (130/131) | (95.8, 100.0) | 98.6% (140/142) | (95.0, 99.8) |
| *2 Serotypes Unique to V114* | | | | | |
| 22F | 30 days PPS | 96.1% (123/128) | (91.1, 98.7) | 3.8% (5/131) | (1.3, 8.7) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 7.9% (11/140) | (4.0, 13.6) |
| 33F | 30 days PPS | 85.2% (109/128) | (77.8, 90.8) | 3.0% (4/133) | (0.8, 7.5) |
| | 30 days PTD | 100% (131/131) | (97.2, 100.0) | 6.5% (9/138) | (3.0, 12.0) |

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis;
m=Number of participants with the indicated response.
Note: Per protocol, for studies V114-027, V114-029, V114-031, dose 3 was administered at ~6 months of age and for study V114-025 dose 3 was administered at ~4 months of age.
For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.
CI=confidence interval; IgG=immunoglobulin G.

In preterm infants, V114 elicited serotype-specific immune responses to all 15 serotypes included in the vaccine when administered as a 4-dose series, as assessed by IgG GMCs at 30 days PPS, pretoddler dose, and at 30 days PTD:

- Serotype-specific IgG GMCs and the distribution of serotype-specific IgG concentrations (as displayed by the RCDCs, see Figure 19 and Figure 20) for each time point were generally comparable between the V114 and PCV13 intervention groups for the 13 shared serotypes and higher for serotypes 22F and 33F in V114 recipients.
- Serotype-specific IgG GMCs for each time point in the FAS population were consistent with those observed for the PP population.
- The immune responses observed to all 15 serotypes in the subset of preterm infants were consistent with those observed in the overall healthy infant population (including preterm and term infants) receiving 3 or 4 doses of V114.

In preterm infants, V114 induced an immune memory response following the primary series as supported by the following pattern of vaccine-induced immune responses:

- Serotype-specific IgG GMCs decreased from 30 days PPS to pretoddler dose, and subsequently increased at 30 days PTD to levels higher than those measured at 30 days PPS for most of the 15 serotypes in the V114 group, see Table 30.
- The pattern of serotype-specific immune responses over time were generally comparable between the V114 and PCV13 intervention groups for the 13 shared serotypes.

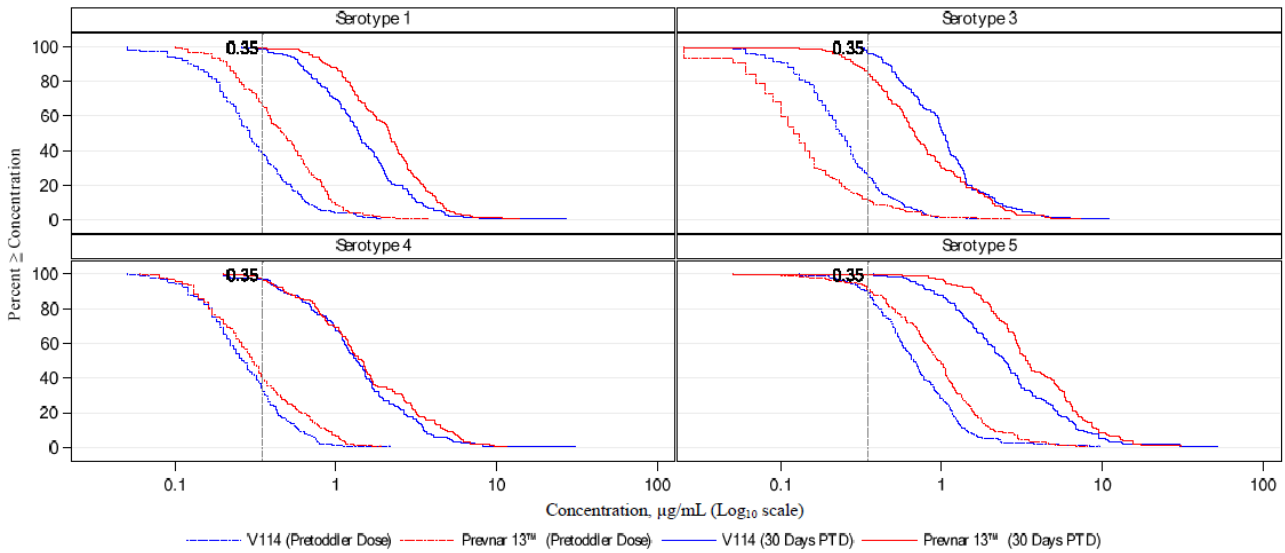



**Figure 19 RCDCs of IgG Concentrations Pretoddler Dose and 30 Days PTD serotype 1, 3, 4, and 5 (PP) Preterm infants – V114-025, V114-027, V114-029 and V114-031**

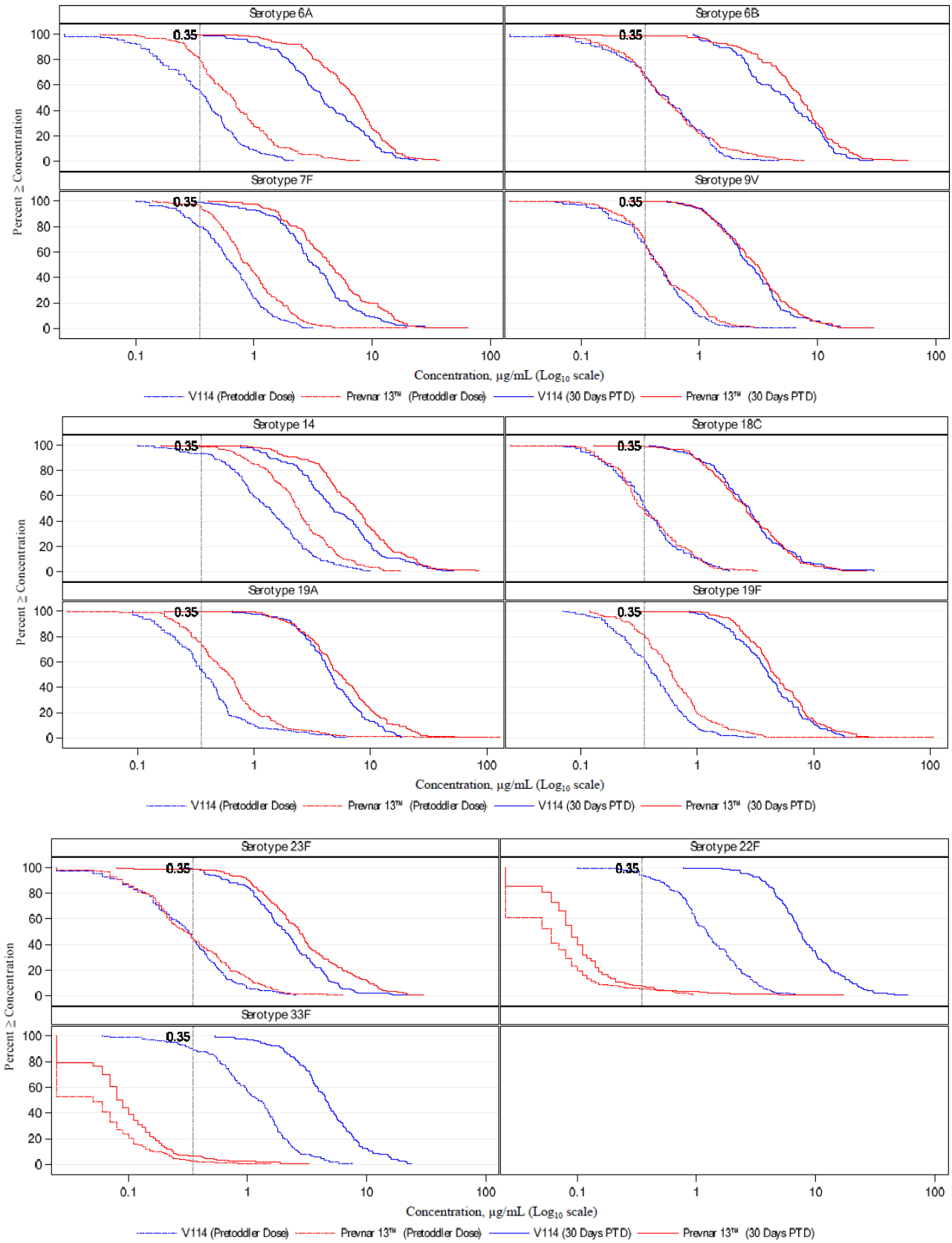



**Figure 20 RCDCs of IgG Concentrations Pretoddler Dose and 30 Days PTD serotype 6A, 6B, 7F, 9V, 14, 18C, 19A and 19F 23F, 22F and 33F (PP) Preterm infants – V114-025, V114-027, V114-029 and V114-031**

### Table 30 Summary of IgG GMCs (PP) (Preterm Infants) - (V114-025, V114-027, V114-029, V114-031)

| Serotype | Timepoint | V114 (N=174) | | | PCV13 (N=180) | | |
|---|---|---|---|---|---|---|---|
| | | n | Response | 95% CI[a] | n | Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | |
| 1 | 30 Days PPS | 128 | 1.28 | (1.14, 1.45) | 133 | 1.67 | (1.49, 1.88) |
| | Pretoddler Dose | 146 | 0.29 | (0.26, 0.33) | 152 | 0.46 | (0.42, 0.51) |
| | 30 Days PTD | 131 | 1.41 | (1.25, 1.60) | 142 | 2.03 | (1.83, 2.26) |
| 3 | 30 Days PPS | 128 | 1.09 | (0.96, 1.23) | 132 | 0.65 | (0.57, 0.74) |
| | Pretoddler Dose | 146 | 0.24 | (0.21, 0.26) | 152 | 0.13 | (0.12, 0.15) |
| | 30 Days PTD | 131 | 1.02 | (0.91, 1.14) | 142 | 0.73 | (0.64, 0.84) |
| 4 | 30 Days PPS | 128 | 1.39 | (1.21, 1.59) | 131 | 1.50 | (1.31, 1.72) |
| | Pretoddler Dose | 146 | 0.27 | (0.24, 0.30) | 152 | 0.32 | (0.28, 0.35) |
| | 30 Days PTD | 131 | 1.37 | (1.19, 1.57) | 142 | 1.51 | (1.31, 1.73) |
| 5 | 30 Days PPS | 128 | 1.52 | (1.29, 1.80) | 132 | 1.66 | (1.41, 1.96) |
| | Pretoddler Dose | 146 | 0.70 | (0.63, 0.78) | 152 | 0.91 | (0.80, 1.03) |
| | 30 Days PTD | 131 | 2.55 | (2.20, 2.96) | 142 | 3.68 | (3.21, 4.21) |
| 6A | 30 Days PPS | 128 | 1.42 | (1.19, 1.70) | 131 | 2.76 | (2.37, 3.20) |
| | Pretoddler Dose | 146 | 0.34 | (0.29, 0.39) | 152 | 0.66 | (0.58, 0.76) |
| | 30 Days PTD | 131 | 3.87 | (3.32, 4.51) | 142 | 6.28 | (5.52, 7.14) |
| 6B | 30 Days PPS | 128 | 1.29 | (1.02, 1.63) | 131 | 1.92 | (1.55, 2.38) |
| | Pretoddler Dose | 146 | 0.48 | (0.41, 0.56) | 152 | 0.53 | (0.46, 0.62) |
| | 30 Days PTD | 131 | 4.92 | (4.25, 5.68) | 142 | 6.24 | (5.34, 7.28) |
| 7F | 30 Days PPS | 128 | 2.29 | (2.01, 2.59) | 133 | 2.76 | (2.46, 3.09) |
| | Pretoddler Dose | 146 | 0.63 | (0.56, 0.70) | 152 | 0.93 | (0.83, 1.04) |
| | 30 Days PTD | 131 | 3.28 | (2.84, 3.79) | 142 | 4.53 | (3.94, 5.22) |
| 9V | 30 Days PPS | 128 | 1.81 | (1.58, 2.08) | 133 | 1.70 | (1.48, 1.95) |
| | Pretoddler Dose | 146 | 0.43 | (0.38, 0.49) | 152 | 0.48 | (0.43, 0.54) |
| | 30 Days PTD | 131 | 2.74 | (2.44, 3.09) | 142 | 2.91 | (2.57, 3.29) |
| 14 | 30 Days PPS | 128 | 5.06 | (4.38, 5.83) | 132 | 7.19 | (6.11, 8.46) |
| | Pretoddler Dose | 146 | 1.29 | (1.12, 1.49) | 152 | 2.35 | (2.07, 2.65) |
| | 30 Days PTD | 131 | 5.12 | (4.37, 6.00) | 142 | 7.24 | (6.23, 8.43) |
| 18C | 30 Days PPS | 128 | 1.60 | (1.41, 1.82) | 133 | 1.89 | (1.65, 2.16) |
| | Pretoddler Dose | 146 | 0.37 | (0.32, 0.41) | 152 | 0.37 | (0.33, 0.42) |
| | 30 Days PTD | 131 | 2.76 | (2.40, 3.19) | 142 | 2.64 | (2.30, 3.04) |
| 19A | 30 Days PPS | 128 | 1.73 | (1.51, 1.97) | 133 | 2.67 | (2.31, 3.09) |
| | Pretoddler Dose | 146 | 0.39 | (0.34, 0.45) | 152 | 0.62 | (0.53, 0.72) |
| | 30 Days PTD | 131 | 4.68 | (4.17, 5.24) | 142 | 5.67 | (4.92, 6.53) |
| 19F | 30 Days PPS | 128 | 2.20 | (1.95, 2.48) | 133 | 2.99 | (2.67, 3.34) |
| | Pretoddler Dose | 146 | 0.41 | (0.37, 0.46) | 152 | 0.64 | (0.56, 0.73) |
| | 30 Days PTD | 131 | 4.12 | (3.65, 4.65) | 142 | 4.89 | (4.34, 5.50) |
| 23F | 30 Days PPS | 128 | 1.27 | (1.07, 1.51) | 133 | 1.29 | (1.09, 1.53) |
| | Pretoddler Dose | 146 | 0.28 | (0.24, 0.33) | 152 | 0.32 | (0.27, 0.37) |
| | 30 Days PTD | 131 | 2.05 | (1.78, 2.36) | 142 | 2.84 | (2.42, 3.33) |
| 2 Serotypes Unique to V114 | | | | | | | |
| 22F | 30 Days PPS | 128 | 4.07 | (3.39, 4.88) | 131 | 0.05 | (0.04, 0.06) |
| | Pretoddler Dose | 146 | 1.23 | (1.09, 1.39) | 152 | 0.06 | (0.05, 0.07) |
| | 30 Days PTD | 131 | 7.88 | (6.98, 8.90) | 140 | 0.10 | (0.08, 0.12) |
| 33F | 30 Days PPS | 128 | 1.53 | (1.18, 1.99) | 133 | 0.05 | (0.04, 0.06) |
| | Pretoddler Dose | 146 | 1.08 | (0.94, 1.24) | 152 | 0.05 | (0.05, 0.06) |
| | 30 Days PTD | 131 | 4.54 | (4.01, 5.13) | 138 | 0.09 | (0.08, 0.10) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, for studies V114-027, V114-029, V114-031, dose 3 was administered at ~6 months of age, and dose 4 was administered at ~12 to 15 months of age and for study V114-025 dose 3 was administered at ~4 months of age, and dose 4 was administered at ~11 to 15 months of age.
For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPS=post primary series; PTD=post toddler dose.

In preterm infants, V114 elicited functional antibodies with opsonophagocytic activity for all 15 serotypes included in the vaccine when administered as a 4-dose series, as assessed by OPA GMTs at 30 days PPS, pretoddler dose, and at 30 days PTD, consistent with those observed for serotype-specific IgG responses. The pattern of functional immune responses over time, as assessed by

serotype-specific OPA responses, was consistent with those observed for serotype-specific IgG responses.

### Table 31 Summary of OPA GMTs (PP) pre-term infants – V114-025, V114-029 and V114-031

| Pneumococcal Serotype | Timepoint | V114 (N=157) | | | PCV13 (N=160) | | |
|---|---|---|---|---|---|---|---|
| | | n | Observed Response | 95% CI[a] | n | Observed Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | |
| 1 | 30 Days PPS | 61 | 42.41 | (27.81, 64.67) | 55 | 68.58 | (45.95, 102.35) |
| | Pretoddler Dose | 53 | 8.59 | (6.28, 11.75) | 42 | 11.75 | (7.70, 17.92) |
| | 30 Days PTD | 46 | 152.40 | (96.22, 241.38) | 43 | 235.39 | (161.78, 342.48) |
| 3 | 30 Days PPS | 60 | 234.16 | (181.11, 302.75) | 54 | 186.89 | (153.33, 227.79) |
| | Pretoddler Dose | 52 | 76.99 | (57.06, 103.89) | 42 | 44.86 | (31.39, 64.11) |
| | 30 Days PTD | 45 | 352.54 | (271.33, 458.07) | 43 | 404.42 | (317.06, 515.85) |
| 4 | 30 Days PPS | 61 | 1347.44 | (1035.29, 1753.70) | 54 | 1644.14 | (1268.51, 2130.99) |
| | Pretoddler Dose | 51 | 193.67 | (126.25, 297.09) | 42 | 240.26 | (141.53, 407.86) |
| | 30 Days PTD | 45 | 3100.54 | (2033.09, 4728.46) | 43 | 4593.28 | (3236.41, 6519.02) |
| 5 | 30 Days PPS | 62 | 381.06 | (267.71, 542.41) | 55 | 411.97 | (297.15, 571.14) |
| | Pretoddler Dose | 53 | 77.55 | (51.67, 116.38) | 43 | 86.48 | (56.28, 132.89) |
| | 30 Days PTD | 46 | 934.46 | (581.95, 1500.49) | 43 | 1197.98 | (826.95, 1735.48) |
| 6A | 30 Days PPS | 60 | 2447.10 | (1781.13, 3362.08) | 53 | 3806.30 | (2925.10, 4952.96) |
| | Pretoddler Dose | 53 | 497.17 | (363.04, 680.85) | 42 | 689.65 | (462.41, 1028.57) |
| | 30 Days PTD | 45 | 5028.17 | (3472.39, 7281.02) | 39 | 11221.59 | (7596.36, 16576.89) |
| 6B | 30 Days PPS | 59 | 1550.20 | (1080.45, 2224.16) | 53 | 2598.13 | (1826.96, 3694.81) |
| | Pretoddler Dose | 52 | 331.47 | (212.66, 516.64) | 43 | 324.37 | (184.95, 568.87) |
| | 30 Days PTD | 44 | 4401.03 | (3152.50, 6144.04) | 41 | 6908.16 | (4101.98, 11634.08) |
| 7F | 30 Days PPS | 61 | 5105.41 | (3681.53, 7079.99) | 54 | 7693.49 | (6059.70, 9767.79) |
| | Pretoddler Dose | 53 | 1695.39 | (1156.49, 2485.42) | 43 | 3467.15 | (2654.26, 4529.00) |
| | 30 Days PTD | 45 | 10540.58 | (7302.06, 15215.42) | 42 | 18932.96 | (13863.46, 25856.25) |
| 9V | 30 Days PPS | 59 | 1006.81 | (752.29, 1347.43) | 53 | 1216.64 | (900.10, 1644.50) |
| | Pretoddler Dose | 52 | 283.06 | (211.23, 379.33) | 42 | 333.31 | (231.88, 479.10) |
| | 30 Days PTD | 45 | 2113.85 | (1652.06, 2704.74) | 42 | 4185.28 | (2736.31, 6401.54) |
| 14 | 30 Days PPS | 60 | 2129.95 | (1524.28, 2976.27) | 53 | 2457.64 | (1655.40, 3648.67) |
| | Pretoddler Dose | 53 | 600.26 | (398.14, 904.97) | 43 | 810.92 | (524.22, 1254.42) |
| | 30 Days PTD | 45 | 3158.06 | (2036.19, 4898.02) | 43 | 3092.47 | (2160.81, 4425.82) |
| 18C | 30 Days PPS | 60 | 1306.48 | (977.18, 1746.76) | 53 | 1475.85 | (1157.93, 1881.06) |
| | Pretoddler Dose | 53 | 258.42 | (190.33, 350.87) | 42 | 280.81 | (186.59, 422.59) |
| | 30 Days PTD | 45 | 2854.52 | (1922.69, 4237.96) | 42 | 3553.24 | (2714.39, 4651.32) |
| 19A | 30 Days PPS | 62 | 1010.71 | (743.74, 1373.51) | 54 | 2213.16 | (1762.91, 2778.42) |
| | Pretoddler Dose | 53 | 207.75 | (135.29, 319.00) | 42 | 469.07 | (282.73, 778.21) |
| | 30 Days PTD | 46 | 3331.76 | (2317.10, 4790.74) | 43 | 8416.33 | (5956.36, 11892.26) |
| 19F | 30 Days PPS | 61 | 772.29 | (595.32, 1001.87) | 54 | 1121.05 | (913.32, 1376.03) |
| | Pretoddler Dose | 52 | 141.91 | (107.40, 187.50) | 43 | 205.20 | (142.70, 295.07) |
| | 30 Days PTD | 45 | 1862.07 | (1313.66, 2639.42) | 41 | 2524.07 | (1850.54, 3442.73) |
| 23F | 30 Days PPS | 61 | 2385.57 | (1725.91, 3297.36) | 53 | 5394.34 | (3632.78, 8010.11) |
| | Pretoddler Dose | 53 | 451.00 | (276.14, 736.59) | 40 | 1319.76 | (758.00, 2297.85) |
| | 30 Days PTD | 45 | 3910.38 | (2425.54, 6304.20) | 42 | 19350.59 | (12317.91, 30398.44) |
| 2 Serotypes Unique to V114 | | | | | | | |
| 22F | 30 Days PPS | 60 | 2248.48 | (1821.83, 2775.05) | 54 | 9.74 | (7.21, 13.17) |
| | Pretoddler Dose | 51 | 496.52 | (325.40, 757.63) | 42 | 15.01 | (9.05, 24.89) |
| | 30 Days PTD | 45 | 3490.32 | (2507.03, 4859.27) | 37 | 11.72 | (7.64, 17.97) |
| 33F | 30 Days PPS | 59 | 6645.19 | (3948.17, 11184.57) | 54 | 131.87 | (66.03, 263.33) |
| | Pretoddler Dose | 53 | 5201.85 | (4007.94, 6751.43) | 42 | 1348.57 | (902.16, 2015.86) |
| | 30 Days PTD | 45 | 13811.27 | (9926.52, 19216.31) | 43 | 1383.00 | (868.75, 2201.65) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, for studies V114-029, V114-031, dose 3 was administered at ~6 months of age, and dose 4 was administered at ~12 to 15 months of age and for study V114-025 dose 3 was administered at ~4 months of age, and dose 4 was administered at ~11 to 15 months of age.
OPA responses were not collected for V114-027.
CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPS=post primary series; PTD=post toddler dose.

***CHMP's comment***

Data from pre-term infants was integrated across 4 Phase 3 clinical studies: V114-025, V114-029, V114-027 and V114-031.

The design of the 4 studies was similar as they were all randomized, double-blind, PCV13 controlled, multicenter studies. Preterm infants in all 4 studies received 4 doses of PCV, with the primary series consisting of 3 single doses followed by a toddler dose. However, during study V114-025 PCV was administered at ~2, 3, 4, 11 to 15 months of age, while for all other studies administration of PCV was performed at ~2, 4, 6, 12 to 15 months of age.

The number of participants that completed the studies was comparable between the intervention groups.

Both 30 days PPS and 30 days PTD, the vast majority of participants achieved the threshold value of 0.35 µg/mL for all serotypes in both treatment arms. Comparable to the total population, the IgG GMCs generated by administration of V114 were consistently lower for 12 of the 13 shared serotypes compared to the IgG GMCs generated by PCV13. As the starting level of IgG was lower in the V114 group, pre-toddler dose 5 out of 13 shared serotypes fell below the threshold level compared to 3 out of 13 serotypes in the PCV13 group. The clinical impact of this observation is unknown. After the toddler dose, a substantial immune response was generated in both treatment arms for all serotypes, as for all serotypes the IgG GMCs increased to the level after the primary series or even above that. This pattern is comparable to the total population, indicating that a comparable immune response is generated in the pre-term infants. However, the lower immune response could impact persistence of protection.

The RCDC curves showed a similar pattern between the 2 treatment arms both pre-toddler dose and 30 days PTD.

OPA GMTs showed that V114 was immunogenic. The OPA GMTs generated by V114 were slightly lower compared to PCV13 for the shared serotypes, while they were higher in the V114 group for the 2 additional serotypes. Overall, the OPA responses were comparable to the IgG responses, although the higher serotype 3 response induced by V114 in IgG GMCs was not reflected in OPA GMTs.

Overall, the immune responses in the pre-term infants were largely comparable to the immune response seen in the total healthy infant population. As in the total infant population, the IgG GMCs generated with V114 were lower compared to the IgG GMCs generated by PCV13 for 12 out of 13 shared serotypes, and higher for serotype 3, 22F and 33F. Of note, for both vaccines the response rates and IgG GMCs were generally higher in preterm infants compared to full term infants.

## Clinical studies in special populations

### *Sickle Cell Disease*

**Study Design**: Study V114-023 was a multicenter, randomized, active-controlled, parallel-group, double-blind study to evaluate the safety, tolerability, and immunogenicity of V114 in children 5 to 17 years of age (inclusive) with sickle cell disease.

**Treatment**: Eligible participants were randomly assigned in a 2:1 ratio to receive a single dose of either V114 or PCV13.

**Study Participants**: Eligible participants were healthy males or females between the ages of 5 and 17 years (inclusive) with a documented diagnosis of sickle cell disease and without a prior history of

invasive pneumococcal disease or prior administration of any pneumococcal vaccine within 3 years of study entry. In total 104 participants were enrolled/randomized.

In the V114 group, 70 participants were randomized, 69 (98.6%) were vaccinated with V114, 65 (92.9%) completed the study, and 5 (7.1%) discontinued from the study. In the PCV13 and all participants completed the study.

Demographics and baseline characteristics, including age, gender, race, and ethnicity, were presented descriptively. Demographic characteristics were generally comparable in both groups. The median age of participants was 11 years (range: 5 to 17 years). The majority of participants were male, Black or African American, and of Hispanic or Latino ethnicity. Reported medical history conditions were as expected for a paediatric SCD population and generally comparable in both groups. The 5 most frequently reported medical history conditions (by preferred term) were sickle cell anaemia with crisis (33%), transfusion (25.2%), pneumonia (16.5%), asthma (16.2%), and acute chest syndrome (10.7%).

**Objectives**: The objectives of this study were to descriptively (1) evaluate the serotype-specific IgG GMCs at 30 days postvaccination for each vaccination group, (2) evaluate the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) for each vaccination group, and (3) evaluate serotype-specific Geometric Mean Fold Rises (GMFRs) from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for each vaccination group.

**Results:**

V114 was immunogenic in children 5 to 17 years of age with SCD as assessed by serotype-specific IgG GMCs at 30 days postvaccination for all 15 serotypes contained in the vaccine, including the 13 serotypes in common with PCV13 and the 2 serotypes unique to V114 (22F and 33F). Serotype-specific IgG GMCs were generally comparable between recipients of V114 and PCV13 for the 13 shared serotypes between the 2 vaccines and higher in recipients of V114 than PCV13 for serotypes 22F and 33F.

Increases in serotype-specific IgG GMCs between Day 1 and Day 30 were observed in both V114 and PCV13 recipients for the 13 shared serotypes. The distribution of immune responses at 30 days postvaccination was generally comparable between the intervention groups for the 13 shared serotypes and higher for 22F and 33F in V114 recipients, see Table 32.

### Table 32 Summary of IgG GMCS at day 30 (PP) – V114-023

| Serotype | Endpoint | Timepoint | V114 (N = 69) | | | PCV13 (N = 34) | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Observed Response | 95% CI[a] | n | Observed Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | |
| 1 | GMC | Day 1 | 68 | 0.35 | (0.26, 0.45) | 32 | 0.44 | (0.26, 0.73) |
| | | Day 30 | 66 | 2.12 | (1.63, 2.75) | 32 | 2.76 | (1.95, 3.91) |
| | GMFR | Day 1 to Day 30 | 66 | 6.2 | (4.6, 8.5) | 30 | 6.0 | (3.7, 9.9) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 62.1% (41/66) | (49.3, 73.8) | 30 | 60.0% (18/30) | (40.6, 77.3) |
| 3 | GMC | Day 1 | 68 | 0.21 | (0.14, 0.30) | 32 | 0.21 | (0.14, 0.32) |
| | | Day 30 | 66 | 1.09 | (0.87, 1.38) | 31 | 1.07 | (0.70, 1.65) |
| | GMFR | Day 1 to Day 30 | 66 | 4.8 | (3.5, 6.6) | 29 | 4.1 | (2.6, 6.7) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 53.0% (35/66) | (40.3, 65.4) | 29 | 48.3% (14/29) | (29.4, 67.5) |
| 4 | GMC | Day 1 | 68 | 0.26 | (0.21, 0.33) | 32 | 0.28 | (0.19, 0.41) |
| | | Day 30 | 66 | 1.58 | (1.18, 2.10) | 31 | 2.90 | (2.00, 4.20) |
| | GMFR | Day 1 to Day 30 | 66 | 6.0 | (4.3, 8.3) | 29 | 9.3 | (5.4, 16.2) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 56.1% (37/66) | (43.3, 68.3) | 29 | 72.4% (21/29) | (52.8, 87.3) |
| 5 | GMC | Day 1 | 68 | 0.86 | (0.68, 1.08) | 32 | 0.98 | (0.71, 1.35) |
| | | Day 30 | 66 | 4.44 | (3.19, 6.17) | 31 | 6.56 | (4.09, 10.52) |
| | GMFR | Day 1 to Day 30 | 66 | 5.3 | (3.8, 7.4) | 29 | 6.4 | (3.8, 10.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 53.0% (35/66) | (40.3, 65.4) | 29 | 58.6% (17/29) | (38.9, 76.5) |
| 6A | GMC | Day 1 | 68 | 0.43 | (0.31, 0.58) | 32 | 0.35 | (0.23, 0.53) |
| | | Day 30 | 66 | 23.29 | (17.22, 31.52) | 31 | 15.97 | (8.82, 28.91) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | GMFR | Day 1 to Day 30 | 66 | 54.7 | (37.9, 78.9) | 29 | 40.6 | (22.9, 71.9) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 93.9% (62/66) | (85.2, 98.3) | 29 | 93.1% (27/29) | (77.2, 99.2) |
| 6B | GMC | Day 1 | 68 | 1.01 | (0.72, 1.42) | 32 | 0.79 | (0.50, 1.25) |
| | | Day 30 | 66 | 38.38 | (28.53, 51.64) | 31 | 22.94 | (13.60, 38.71) |
| | GMFR | Day 1 to Day 30 | 66 | 37.2 | (25.8, 53.6) | 29 | 25.0 | (13.8, 45.3) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 93.9% (62/66) | (85.2, 98.3) | 29 | 89.7% (26/29) | (72.6, 97.8) |
| 7F | GMC | Day 1 | 68 | 0.51 | (0.38, 0.67) | 32 | 0.47 | (0.30, 0.74) |
| | | Day 30 | 66 | 5.81 | (4.42, 7.64) | 32 | 4.65 | (3.06, 7.06) |
| | GMFR | Day 1 to Day 30 | 66 | 11.6 | (8.3, 16.0) | 30 | 9.8 | (6.3, 15.3) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 74.2% (49/66) | (62.0, 84.2) | 30 | 83.3% (25/30) | (65.3, 94.4) |
| 9V | GMC | Day 1 | 68 | 0.60 | (0.45, 0.78) | 32 | 0.58 | (0.38, 0.87) |
| | | Day 30 | 66 | 4.46 | (3.44, 5.78) | 32 | 5.36 | (3.45, 8.33) |
| | GMFR | Day 1 to Day 30 | 66 | 7.4 | (5.3, 10.3) | 30 | 8.1 | (4.9, 13.2) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 62.1% (41/66) | (49.3, 73.8) | 30 | 60.0% (18/30) | (40.6, 77.3) |
| 14 | GMC | Day 1 | 67 | 1.51 | (1.04, 2.21) | 32 | 2.59 | (1.66, 4.02) |
| | | Day 30 | 66 | 16.03 | (11.23, 22.90) | 31 | 20.53 | (12.39, 34.03) |
| | GMFR | Day 1 to Day 30 | 65 | 10.8 | (6.8, 17.2) | 29 | 7.2 | (3.5, 14.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 65 | 63.1% (41/65) | (50.2, 74.7) | 29 | 55.2% (16/29) | (35.7, 73.6) |
| 18C | GMC | Day 1 | 68 | 0.56 | (0.43, 0.72) | 32 | 0.56 | (0.37, 0.84) |
| | | Day 30 | 66 | 6.11 | (4.47, 8.35) | 32 | 4.20 | (2.66, 6.62) |
| | GMFR | Day 1 to Day 30 | 66 | 10.8 | (7.7, 15.1) | 30 | 7.6 | (4.5, 12.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 71.2% (47/66) | (58.7, 81.7) | 30 | 60.0% (18/30) | (40.6, 77.3) |
| 19A | GMC | Day 1 | 68 | 2.44 | (1.87, 3.17) | 32 | 2.66 | (1.73, 4.08) |
| | | Day 30 | 66 | 19.86 | (14.77, 26.70) | 32 | 21.65 | (14.45, 32.44) |
| | GMFR | Day 1 to Day 30 | 66 | 8.2 | (5.4, 12.4) | 30 | 8.6 | (5.0, 14.9) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 57.6% (38/66) | (44.8, 69.7) | 30 | 63.3% (19/30) | (43.9, 80.1) |
| 19F | GMC | Day 1 | 68 | 1.70 | (1.29, 2.24) | 32 | 1.73 | (1.14, 2.64) |
| | | Day 30 | 66 | 13.88 | (9.96, 19.35) | 32 | 12.80 | (9.10, 18.01) |
| | GMFR | Day 1 to Day 30 | 66 | 8.3 | (5.6, 12.3) | 30 | 7.6 | (4.5, 12.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 65.2% (43/66) | (52.4, 76.5) | 30 | 66.7% (20/30) | (47.2, 82.7) |
| 23F | GMC | Day 1 | 68 | 0.56 | (0.42, 0.74) | 32 | 0.48 | (0.33, 0.70) |
| | | Day 30 | 63 | 5.38 | (3.88, 7.46) | 31 | 6.88 | (4.01, 11.83) |
| | GMFR | Day 1 to Day 30 | 63 | 9.3 | (6.1, 14.2) | 29 | 13.1 | (7.4, 23.4) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 63 | 69.8% (44/63) | (57.0, 80.8) | 29 | 72.4% (21/29) | (52.8, 87.3) |
| 2 Serotypes Unique to V114 | | | | | | | | |
| 22F | GMC | Day 1 | 68 | 0.48 | (0.35, 0.66) | 32 | 0.41 | (0.27, 0.64) |
| | | Day 30 | 66 | 7.30 | (5.68, 9.36) | 30 | 0.49 | (0.33, 0.73) |
| | GMFR | Day 1 to Day 30 | 66 | 15.0 | (10.1, 22.1) | 28 | 1.1 | (0.9, 1.3) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 78.8% (52/66) | (67.0, 87.9) | 28 | 0.0% (0/28) | (0.0, 12.3) |
| 33F | GMC | Day 1 | 68 | 0.49 | (0.37, 0.64) | 32 | 0.66 | (0.40, 1.09) |
| | | Day 30 | 66 | 4.46 | (3.38, 5.87) | 32 | 0.97 | (0.62, 1.51) |
| | GMFR | Day 1 to Day 30 | 66 | 9.0 | (6.7, 12.1) | 30 | 1.3 | (1.0, 1.7) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 66 | 75.8% (50/66) | (63.6, 85.5) | 30 | 6.7% (2/30) | (0.8, 22.1) |

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis. Note: Per protocol, Day 1 is prevaccination with PCV and Day 30 is 30 days following vaccination with PCV.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); GMFR=geometric mean fold-rise; IgG=immunoglobulin G; PCV=pneumococcal conjugate vaccine (V114 or PCV13).

As observed with IgG GMCs, V114 was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 15 serotypes contained in the vaccine, including the 13 serotypes shared with PCV13 and the 2 unique serotypes (22F and 33F) contained in V114. Serotype-specific OPA GMTs were generally comparable between recipients of V114 and PCV13 for the 13 shared serotypes between the 2 vaccines and higher in recipients of V114 than PCV13 for serotypes 22F and 33F.

Increases in serotype-specific OPA GMTs between Day 1 and Day 30 were observed in both V114 and PCV13 recipients for the 13 shared serotypes. The distribution of immune responses at 30 days postvaccination was generally comparable between the intervention groups for the 13 shared serotypes and higher for 22F and 33F in V114 recipients, consistent with the results observed for serotype-specific OPA GMTs.

***CHMP's comment***

Study V114-023 was a descriptive study to evaluate the safety, tolerability and immunogenicity of a single dose of V114 in children 5 to 17 years of age with sickle cell disease. In total 104 participants were enrolled.

Based on the Summary of Clinical Efficacy, the study was designed to support a recommendation for V114 in children with SCD who are either PCV-naïve or who have received a lower valent PCV, including Prevenar 13. However, one of the exclusion criteria was that participants had received <3 doses of PCV, suggesting that there were no pneumococcal-vaccine naïve participants included in the study. Therefore, the MAH was asked to clarify whether any pneumococcal-vaccine naïve participants were included in the study and whether the study arms were balanced concerning prior pneumococcal vaccines. Unfortunately, the pneumococcal vaccination history was not adequately collected in this trial. Consequently, no conclusion can be drawn based on pneumococcal vaccination history.

The percentages of participants aged 5 to 9 were lower in the V114 group while the percentage of participants aged 10 to 14 were higher compared to the PCV13 group, indicating a skew in age of the participants between the 2 treatment groups. The fact that the mean age of participants in both groups was 10.8 years of age with a standard deviation of 3.5 years in the V114 group and 3.3 in the PCV13 group the difference is not considered to have relevant impact on the results. Slight differences in race were also observed, which are probably due to small numbers.

Both V114 and PCV13 were immunogenic in children with sickle cell disease. The immune responses generated by V114 and PCV13 were generally comparable. In the V114 group, the proportion of patients that achieved a ≥4-fold rise in IgG GMC 30 days postvaccination ranged from 53.0% to 93.9% for all 15 serotypes. In the PCV13 group the proportion of patients that achieved a ≥4-fold rise in IgG GMC 30 days postvaccination ranged from 48.3% to 93.1% for all 13 serotypes included in the vaccine. No substantial increase in 22F and 33F IgG GMCs were seen in the PCV13 group, as expected.

After the single administration of PCV, the IgG GMCs generated were well above the threshold of 0.35 µg/mL, indicating that the response generated was substantial and clinically relevant.

The response as measured by OPA GMTs was generally comparable to the response as measured by IgG GMCs.

Overall, the immune response to either V114 or PCV13 was generally comparable in the sickle cell disease patients as measured by IgG GMCs and OPA GMTs.

Interestingly the responses to serotype 6A and 6B appeared to be higher in the V114 group compared to the PCV13 group, while the response to serotype 3 was comparable. This might be due to small numbers or to prior vaccination, which is difficult to assess due to pooling of patients with different prior PCV vaccinations history.

***HIV-1 infected subjects***

**Study Design**: Study V114-030 was a multicenter, randomized, double-blind, active comparator controlled, parallel-group study to evaluate the safety, tolerability, and immunogenicity of V114 in children 6 to 17 years of age (inclusive) living with HIV (CD4+ T-cell count ≥200 cells/µL and a plasma HIV ribonucleic acid [RNA] value <50,000 copies/mL tested at screening).

**Treatment**: Participants in Study V114-030 were randomized in a 1:1 ratio to receive a single dose of V114 or PCV13 on Day 1, followed by a single dose of PPV23 at Week 8. Randomization was stratified by CD4+ T-cell count as follows:

- Stratum 1: CD4+ T-cell count ≥200 to <500 cells/μL.
- Stratum 2: CD4+ T-cell count ≥500 cells/μL.

**Study Participants**: The study population consisted of males or females between the ages of 6 to 17 years (inclusive) living with HIV (CD4+ T-cell count ≥200 cells/μL and a plasma HIV RNA value <50,000 copies/mL tested at screening) without a prior history of invasive pneumococcal disease and were (1) pneumococcal conjugate vaccine (PCV) naïve, previously vaccinated with a <13-valent PCV, partially vaccinated with PCV13, or had a history of previous PCV13 vaccination ≥3 years before Day 1; and (2) pneumococcal polysaccharide (PnPs) vaccine naïve or had a history of 1 previous PnPs vaccination ≥5 years before Day 1.

In the V114 group, 203 participants were randomized and vaccinated with V114 and PPV23. All participants completed the study. In the PCV13 group, 204 participants were randomized and vaccinated with PCV13, 202 (99.0%) were vaccinated with PPV23, 201 (98.5%) completed the study, and 3 (1.5%) discontinued from the study.

Demographics and baseline characteristics, including age, gender, race, ethnicity, and CD4+ T-cell count, were presented descriptively. The median age was 13 years, ranging from 6 to 17 year. The majority of participants were male (52.1%) and not Hispanic or Latino (99.3%). Demographic and baseline characteristics were generally comparable for vaccinated participants across intervention groups. In total, 34 (8.4%) participants with CD4+ T-cell count ≥200 to <500 cells/μL, and 373 (91.6%) participants with CD4+ T-cell count ≥500 cells/μL were included. The vast majority of participants received antiretroviral therapy (ART) prior to study entry (99%). In addition, 377 (92.6%) of participants were PCV naïve and 406 (99.8%) were PPV23 naïve.

**Objectives**: The objectives of this study were (1) to evaluate the serotype-specific IgG GMCs at Day 30 postvaccination with either V114 or PCV13 in each vaccination group, (2) to evaluate the serotype-specific OPA GMTs at Day 30 postvaccination with either V114 or PCV13 in each vaccination group, (3) to evaluate the serotype-specific OPA GMTs and IgG GMCs at day 30 postvaccination with PPV23 (Week 12) by each vaccination group.

**Results:**

V114 was immunogenic for all 15 serotypes contained in the vaccine in children 6 to 17 years of age living with HIV.

Overall, serotype-specific IgG GMCs at 30 days postvaccination with PCV were generally comparable in both intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 (22F and 33F) in the V114 group compared with the PCV13 group, see Table 33.

### Table 33 Summary of IgG antibody responses (PP) – V114-030

| Serotype | Endpoint | Timepoint | V114 (N=203) | | | PCV13 (N=204) | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Observed Response | 95% CI[a] | n | Observed Response | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | |
| 1 | GMC | Day 1 | 202 | 0.15 | (0.13, 0.17) | 204 | 0.15 | (0.13, 0.17) |
| | | Day 30 | 194 | 2.17 | (1.89, 2.48) | 196 | 3.26 | (2.82, 3.77) |
| | GMFR | Day 1 to Day 30 | 193 | 13.9 | (12.1, 15.9) | 196 | 20.8 | (17.9, 24.2) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 88.6% (171/193) | (83.3, 92.7) | 196 | 91.3% (179/196) | (86.5, 94.9) |
| 3 | GMC | Day 1 | 202 | 0.24 | (0.19, 0.29) | 204 | 0.20 | (0.16, 0.24) |
| | | Day 30 | 194 | 1.05 | (0.93, 1.19) | 196 | 0.84 | (0.73, 0.97) |
| | GMFR | Day 1 to Day 30 | 193 | 3.9 | (3.4, 4.6) | 196 | 3.9 | (3.4, 4.5) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 45.6% (88/193) | (38.4, 52.9) | 196 | 45.9% (90/196) | (38.8, 53.2) |
| 4 | GMC | Day 1 | 202 | 0.16 | (0.14, 0.19) | 204 | 0.16 | (0.14, 0.19) |
| | | Day 30 | 194 | 2.59 | (2.23, 3.00) | 196 | 4.27 | (3.57, 5.11) |
| | GMFR | Day 1 to Day 30 | 193 | 15.1 | (12.6, 18.1) | 196 | 25.1 | (20.9, 30.2) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 81.9% (158/193) | (75.7, 87.0) | 196 | 90.3% (177/196) | (85.3, 94.1) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 | GMC | Day 1 | 202 | 0.71 | (0.65, 0.78) | 204 | 0.69 | (0.63, 0.76) |
| | | Day 30 | 194 | 2.94 | (2.44, 3.54) | 196 | 2.78 | (2.30, 3.37) |
| | GMFR | Day 1 to Day 30 | 193 | 4.1 | (3.5, 4.9) | 196 | 4.0 | (3.4, 4.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 41.5% (80/193) | (34.4, 48.7) | 196 | 36.2% (71/196) | (29.5, 43.4) |
| 6A | GMC | Day 1 | 202 | 0.24 | (0.20, 0.30) | 204 | 0.25 | (0.20, 0.31) |
| | | Day 30 | 194 | 7.98 | (6.30, 10.11) | 196 | 7.56 | (6.06, 9.45) |
| | GMFR | Day 1 to Day 30 | 193 | 30.8 | (25.0, 37.9) | 196 | 27.4 | (22.2, 33.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 91.7% (177/193) | (86.9, 95.2) | 196 | 87.8% (172/196) | (82.3, 92.0) |
| 6B | GMC | Day 1 | 202 | 0.34 | (0.28, 0.41) | 204 | 0.31 | (0.26, 0.38) |
| | | Day 30 | 194 | 11.44 | (9.07, 14.43) | 196 | 6.92 | (5.45, 8.79) |
| | GMFR | Day 1 to Day 30 | 193 | 32.7 | (26.5, 40.2) | 196 | 21.0 | (17.1, 25.8) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 91.7% (177/193) | (86.9, 95.2) | 196 | 84.2% (165/196) | (78.3, 89.0) |
| 7F | GMC | Day 1 | 202 | 0.21 | (0.18, 0.25) | 204 | 0.21 | (0.18, 0.25) |
| | | Day 30 | 194 | 4.84 | (4.10, 5.71) | 196 | 5.00 | (4.29, 5.83) |
| | GMFR | Day 1 to Day 30 | 193 | 21.4 | (18.1, 25.2) | 196 | 22.2 | (18.8, 26.2) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 90.2% (174/193) | (85.1, 94.0) | 196 | 91.8% (180/196) | (87.1, 95.3) |
| 9V | GMC | Day 1 | 202 | 0.26 | (0.22, 0.31) | 204 | 0.25 | (0.21, 0.29) |
| | | Day 30 | 194 | 4.15 | (3.56, 4.85) | 196 | 4.78 | (4.03, 5.66) |
| | GMFR | Day 1 to Day 30 | 193 | 15.3 | (13.0, 18.0) | 196 | 18.3 | (15.4, 21.6) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 87.0% (168/193) | (81.5, 91.4) | 196 | 89.3% (175/196) | (84.1, 93.2) |
| 14 | GMC | Day 1 | 202 | 0.85 | (0.69, 1.05) | 204 | 0.88 | (0.71, 1.10) |
| | | Day 30 | 194 | 20.38 | (16.39, 25.35) | 196 | 18.29 | (14.43, 23.17) |
| | GMFR | Day 1 to Day 30 | 193 | 23.9 | (18.7, 30.4) | 196 | 20.9 | (16.7, 26.3) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 81.9% (158/193) | (75.7, 87.0) | 196 | 83.7% (164/196) | (77.7, 88.6) |
| 18C | GMC | Day 1 | 202 | 0.31 | (0.26, 0.37) | 204 | 0.27 | (0.23, 0.33) |
| | | Day 30 | 194 | 5.18 | (4.32, 6.20) | 196 | 5.15 | (4.29, 6.18) |
| | GMFR | Day 1 to Day 30 | 193 | 15.5 | (12.7, 18.9) | 196 | 17.2 | (14.0, 21.0) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 80.3% (155/193) | (74.0, 85.7) | 196 | 81.1% (159/196) | (74.9, 86.3) |
| 19A | GMC | Day 1 | 202 | 1.83 | (1.57, 2.14) | 204 | 1.59 | (1.36, 1.85) |
| | | Day 30 | 194 | 14.20 | (11.81, 17.07) | 196 | 14.78 | (12.45, 17.54) |
| | GMFR | Day 1 to Day 30 | 193 | 7.8 | (6.6, 9.2) | 196 | 9.0 | (7.6, 10.6) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 69.4% (134/193) | (62.4, 75.8) | 196 | 73.5% (144/196) | (66.7, 79.5) |
| 19F | GMC | Day 1 | 202 | 0.91 | (0.75, 1.09) | 204 | 0.80 | (0.67, 0.95) |
| | | Day 30 | 194 | 9.76 | (8.03, 11.85) | 196 | 8.61 | (7.28, 10.18) |
| | GMFR | Day 1 to Day 30 | 193 | 10.6 | (8.8, 12.9) | 196 | 10.4 | (8.7, 12.5) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 73.6% (142/193) | (66.8, 79.6) | 196 | 71.4% (140/196) | (64.6, 77.6) |
| 23F | GMC | Day 1 | 202 | 0.31 | (0.26, 0.37) | 203 | 0.30 | (0.25, 0.36) |
| | | Day 30 | 194 | 6.71 | (5.42, 8.31) | 196 | 6.35 | (5.14, 7.85) |
| | GMFR | Day 1 to Day 30 | 193 | 20.0 | (16.1, 24.8) | 195 | 20.3 | (16.5, 24.9) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 83.9% (162/193) | (78.0, 88.8) | 195 | 83.6% (163/195) | (77.6, 88.5) |
| 2 Serotypes Unique to V114 | | | | | | | | |
| 22F | GMC | Day 1 | 202 | 0.18 | (0.15, 0.21) | 204 | 0.18 | (0.15, 0.22) |
| | | Day 30 | 194 | 9.28 | (7.76, 11.09) | 193 | 0.24 | (0.20, 0.29) |
| | GMFR | Day 1 to Day 30 | 193 | 49.1 | (38.6, 62.5) | 193 | 1.2 | (1.1, 1.4) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 90.7% (175/193) | (85.7, 94.4) | 193 | 1.6% (3/193) | (0.3, 4.5) |
| 33F | GMC | Day 1 | 202 | 0.24 | (0.21, 0.28) | 204 | 0.23 | (0.20, 0.26) |
| | | Day 30 | 194 | 4.53 | (3.80, 5.39) | 196 | 0.29 | (0.25, 0.33) |
| | GMFR | Day 1 to Day 30 | 193 | 17.9 | (15.1, 21.3) | 196 | 1.2 | (1.2, 1.3) |
| | % ≥ 4-fold rise | Day 1 to Day 30 | 193 | 89.6% (173/193) | (84.4, 93.6) | 196 | 2.0% (4/196) | (0.6, 5.1) |

[a] For the continuous endpoints, the within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis. Note: Per protocol, Day 1 is prevaccination with PCV, and Day 30 is 30 days following vaccination with PCV.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); GMFR=geometric mean fold-rise; IgG=immunoglobulin G; PCV=pneumococcal conjugate vaccine (V114 or PCV13).

V114 was immunogenic for all 15 serotypes contained in the vaccine, as assessed by OPA GMTs at 30 days postvaccination. Serotype-specific OPA GMTs at 30 days postvaccination with PCV were generally comparable in both intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 (22F and 33F) in the V114 group compared with the PCV13 group.

In the V114 group, PPV23 was immunogenic for all 15 serotypes contained in V114, as assessed by IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12), see Table 34. Serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12) were generally comparable in both intervention groups for the 15 serotypes in V114.

### Table 34 IgG GMCs at Week 12 (post PPV23) (PP) – V114-03

| Pneumococcal Serotype | V114 (N=203) n | Response | 95% CI[a] | PCV13 (N=204) n | Response | 95% CI[a] |
|---|---|---|---|---|---|---|
| 13 Shared Serotypes | | | | | | |
| 1 | 192 | 2.58 | (2.31, 2.88) | 183 | 3.33 | (2.95, 3.75) |
| 3 | 192 | 1.10 | (0.97, 1.24) | 183 | 1.08 | (0.94, 1.24) |
| 4 | 192 | 2.36 | (2.08, 2.69) | 182 | 3.61 | (3.09, 4.23) |
| 5 | 192 | 3.01 | (2.58, 3.52) | 183 | 3.24 | (2.75, 3.82) |
| 6A | 192 | 4.67 | (3.74, 5.84) | 183 | 4.91 | (3.94, 6.11) |
| 6B | 192 | 7.12 | (5.75, 8.81) | 183 | 4.96 | (3.96, 6.22) |
| 7F | 192 | 4.10 | (3.55, 4.72) | 183 | 4.27 | (3.71, 4.92) |
| 9V | 192 | 3.69 | (3.20, 4.25) | 183 | 4.52 | (3.89, 5.24) |
| 14 | 192 | 18.88 | (15.43, 23.09) | 183 | 19.89 | (16.00, 24.72) |
| 18C | 192 | 3.75 | (3.18, 4.43) | 183 | 4.11 | (3.48, 4.85) |
| 19A | 192 | 11.23 | (9.48, 13.31) | 183 | 12.19 | (10.38, 14.32) |
| 19F | 192 | 8.56 | (7.26, 10.08) | 183 | 7.98 | (6.83, 9.33) |
| 23F | 192 | 4.40 | (3.63, 5.34) | 183 | 4.83 | (3.96, 5.88) |
| 2 Serotypes Unique to V114 | | | | | | |
| 22F | 192 | 8.18 | (7.10, 9.42) | 183 | 10.32 | (8.67, 12.29) |
| 33F | 192 | 3.76 | (3.23, 4.38) | 183 | 6.18 | (5.23, 7.30) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t- distribution.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis. Note: Per protocol, Week 12 is 30 days following vaccination with PPV23.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPV23=pneumococcal polysaccharide vaccine (PNEUMOVAX™23).

***CHMP's comment***

Study V114-030 was an active-comparator controlled, double blind study in HIV-1 infected children. Patients either received V114 or PCV13 followed 8 weeks later by PPV23. The vast majority of participants included in the study received antiretroviral therapy and had a CD4+ T-cell count ≥500 cells/µL. This indicates that the participants still had a functioning immune system.

Both V114 and PCV13 were immunogenic. The immune response generated by V114 and PCV13 were generally comparable and at 30 days after vaccination the IgG GMCs achieved for all serotypes were above the threshold value of 0.35 µg/mL in both treatment arms. In the V114 group, the proportion of patients that achieved a ≥4-fold rise in IgG GMCs 30 days postvaccination ranged from 41.5% to 91.7% for all 15 serotypes. In the PCV13 group, the proportion of patients that achieved a ≥4-fold rise in IgG GMC 30 days postvaccination ranged from 36.2% to 91.8% for all 13 serotypes. The results for OPA GMTs were comparable to the results achieved with IgG GMCs.

Both V114 and PCV13 were immunogenic in both CD4+ T-cell count subgroups (≥200 to <500 cells/µL, ≥500 cells/µL) as assessed by IgG GMCs 30 days postvaccination. The response in the subgroup with CD4+ T-cell counts ≥200 to <500 cells/µL were overall slightly lower compared to the total population.

Overall, the immune response to either V114 or PCV13 was generally comparable in the HIV infected participants as measured by IgG GMCs and OPA GMTs for the 13 shared serotypes and higher in the V114 group for the 2 unique serotypes. Similar results were observed when looking at the OPA GMTs.

Following vaccination with PPV23 IgG GMCs at Week 12 were generally comparable with those observed at 30 days postvaccination with either V114 or PCV13. As there is no prevaccination measurement prior to vaccination with PPV23, the only way to judge whether an immune response was elicited is by looking at 22F and 33F in the PCV13 group. An increase in OPA GMT titres was seen

for 22F and 33F in the PCV13 group compared to Day 30, indicating that PPV23 was immunogenic in HIV-1 infected participants.

## Supportive studies

### Study V114-024

**Study Design**: Study V114-024 was a multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity catch-up vaccination regimens of V114 in healthy infants, children, and adolescents.

**Treatment**: Participants in Study V114-024 were randomized in a 1:1 ratio to receive 1 to 3 doses of either V114 or PCV13 IM depending on age of enrollment. The intervention groups were as follows:

- 7 to 11 months of age (PCV-naïve): 3 doses IM, with Dose 1 at randomization, Dose 2 at 4 to 8 weeks after Dose 1 and Dose 3 at 8 to 12 weeks after Dose 2 and ≥12 months of age.
- 12 to 23 months of age (PCV naïve): 2 doses IM, with Dose 1 at randomization, and Dose 2 at 8 to 12 weeks after Dose 1.
- 2 to 17 years of age (PCV naïve or PCV experienced): Single dose IM administered at randomization and at least 8 weeks after previous dose of PCV for participants who were PCV-experienced.

**Study Participants**: The study population will consist of healthy individuals from 7 months to 17 years of age (inclusive). Participants <2 years of age were to be PCV-naïve. Participants 2 to 17 years of age were to be PCV-naïve or to have previously received a partial regimen of licensed PCV (PCV7, PCV10, or PCV13) or a full regimen of PCV7 or PCV10. In total 606 subjects were enrolled.

In the V114 group, 303 participants were randomized and received at least 1 dose of V114, 302 (99.7%) completed the study, and 1 (0.3%) discontinued the study. In the PCV13 group, 303 participants were randomized and received at least 1 dose of PCV13, 303 (100.0%) completed the study.

Demographic characteristics, including age, gender, race, and ethnicity, were presented descriptively. Demographic characteristics were generally comparable for vaccinated participants across intervention groups. No inferential statistics were planned.

**Objectives**: The objectives of this study were (1) to evaluate the serotype-specific IgG GMCs at 30 days following the last dose for each vaccination group, and (2) to evaluate serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following the last dose for each vaccination group.

**Results:**

Catch-up vaccination with V114 elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days following the last dose of study intervention, for all 15 serotypes contained in the vaccine. Serotype-specific IgG GMCs at 30 days following the last dose of study intervention were generally comparable between the intervention groups for the 13 shared serotypes, see Table 35. IgG GMCs for the 2 serotypes unique to V114 (serotypes 22F and 33F) at 30 days following the last dose of study intervention were higher in the V114 group than in the PCV13 group.

### Table 35 Summary of IgG GMCs at Day 30 (PP) - V114-024

| Serotype | Participants 7 to 11 Months of Age | | | | Participants 12 to 23 Months of Age | | | | Participants 2 to 17 Years of Age | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V114 (N = 64) | | PCV13 (N = 64) | | V114 (N = 62) | | PCV13 (N = 64) | | V114 (N = 177) | | PCV13 (N = 175) | |
| | n | GMC 95% CI[a] | n | GMC 95% CI[a] | n | GMC 95% CI[a] | n | GMC 95% CI[a] | n | GMC 95% CI[a] | n | GMC 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | | | | | |
| 1 | 60 | 2.47 (2.09, 2.92) | 59 | 3.66 (2.98, 4.50) | 56 | 3.83 (3.07, 4.77) | 60 | 4.20 (3.30, 5.34) | 162 | 3.00 (2.60, 3.46) | 162 | 3.99 (3.48, 4.58) |
| 3 | 60 | 2.65 (2.30, 3.05) | 59 | 1.71 (1.40, 2.08) | 56 | 2.96 (2.44, 3.58) | 60 | 1.68 (1.29, 2.20) | 162 | 1.37 (1.19, 1.58) | 162 | 1.03 (0.88, 1.21) |
| 4 | 60 | 2.21 (1.82, 2.68) | 59 | 3.85 (3.12, 4.76) | 56 | 3.46 (2.67, 4.50) | 60 | 4.89 (3.76, 6.36) | 162 | 2.53 (2.17, 2.96) | 162 | 5.22 (4.52, 6.03) |
| 5 | 60 | 3.82 (3.14, 4.63) | 59 | 4.56 (3.58, 5.80) | 56 | 3.39 (2.65, 4.34) | 60 | 3.12 (2.52, 3.88) | 162 | 3.43 (2.89, 4.07) | 162 | 4.24 (3.46, 5.20) |
| 6A | 60 | 2.23 (1.71, 2.91) | 59 | 4.30 (3.28, 5.65) | 56 | 2.05 (1.30, 3.23) | 60 | 3.73 (2.64, 5.29) | 162 | 9.03 (7.07, 11.53) | 162 | 8.81 (6.96, 11.14) |
| 6B | 60 | 3.03 (2.41, 3.82) | 59 | 4.17 (3.25, 5.36) | 56 | 2.69 (1.70, 4.25) | 60 | 2.87 (1.92, 4.30) | 162 | 13.55 (10.52, 17.46) | 161 | 10.51 (8.01, 13.78) |
| 7F | 60 | 5.16 (4.27, 6.23) | 59 | 6.42 (5.25, 7.85) | 56 | 4.80 (3.63, 6.34) | 60 | 5.42 (4.30, 6.82) | 162 | 4.03 (3.46, 4.70) | 162 | 4.63 (3.92, 5.46) |
| 9V | 60 | 2.61 (2.09, 3.26) | 59 | 3.59 (2.86, 4.51) | 56 | 2.48 (1.97, 3.11) | 60 | 2.89 (2.21, 3.78) | 162 | 3.60 (3.06, 4.24) | 162 | 4.35 (3.65, 5.20) |
| 14 | 60 | 9.62 (7.94, 11.67) | 59 | 13.07 (10.40, 16.42) | 56 | 8.23 (6.19, 10.94) | 60 | 8.30 (6.56, 10.51) | 162 | 9.21 (7.11, 11.92) | 162 | 8.04 (6.24, 10.36) |
| 18C | 60 | 3.45 (2.80, 4.24) | 59 | 3.50 (2.75, 4.45) | 56 | 5.09 (3.98, 6.52) | 60 | 3.68 (2.85, 4.75) | 162 | 7.16 (6.03, 8.52) | 162 | 4.46 (3.76, 5.30) |
| 19A | 60 | 4.59 (3.95, 5.33) | 59 | 5.81 (4.92, 6.85) | 56 | 6.74 (5.29, 8.60) | 60 | 5.87 (4.85, 7.11) | 162 | 10.99 (9.12, 13.26) | 162 | 14.90 (12.23, 18.16) |
| 19F | 60 | 3.49 (2.94, 4.15) | 59 | 4.83 (4.03, 5.79) | 56 | 5.90 (4.69, 7.43) | 60 | 5.92 (4.93, 7.11) | 162 | 8.95 (7.45, 10.76) | 162 | 12.28 (10.07, 14.97) |
| 23F | 60 | 2.62 (2.02, 3.39) | 59 | 2.79 (2.10, 3.69) | 56 | 2.85 (1.99, 4.07) | 60 | 2.18 (1.54, 3.07) | 162 | 5.36 (4.41, 6.50) | 162 | 5.12 (4.12, 6.37) |
| 2 Serotypes Unique to V114 | | | | | | | | | | | | |
| 22F | 60 | 9.04 (7.48, 10.93) | 58 | 0.14 (0.10, 0.19) | 56 | 15.90 (12.16, 20.78) | 60 | 0.12 (0.09, 0.16) | 162 | 14.99 (12.73, 17.66) | 159 | 0.31 (0.24, 0.38) |
| 33F | 60 | 3.37 (2.78, 4.10) | 59 | 0.13 (0.10, 0.16) | 56 | 5.17 (3.96, 6.74) | 60 | 0.15 (0.12, 0.19) | 162 | 4.89 (4.12, 5.80) | 160 | 0.27 (0.22, 0.32) |

a The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, participants 2 to 17 years of age received 1 dose of PCV at Day 1. Day 30 is 30 days following vaccination with PCV.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PCV=pneumococcal conjugate vaccine (V114 or PCV13).

A majority (>83.0%) of participants in the V114 group achieved the IgG threshold value of ≥0.35 µg/mL at 30 days following the last dose of study intervention for each of the 15 serotypes contained in the vaccine. Serotype-specific IgG response rates at 30 days following the last dose of study intervention were generally comparable between the intervention groups for the 13 shared serotypes. IgG response rates for the 2 serotypes unique to V114 (serotypes 22F and 33F) at 30 days following the last dose of study intervention were higher in the V114 group than in the PCV13 group.

***CHMP's comment***

Study V114-024 investigated the immunogenicity of catch-up vaccination with V114 in children aged 7 to 11 months, 12 to 23 months and 2 to 17 years of age. The different catch-up schedules were documented in an appreciable number of children (n=303; 62-177/group).

The 3 catch-up vaccination schedules evaluated were: (1) 3 doses for children aged 7 to 11 months, with the first 2 doses given 4 to 8 weeks apart, followed by a booster dose 2 dose at least 8 to 12 weeks after Dose 2 and by at least 12 months of age, (2) 2 doses for children age 12 to 23 months of age given at 8 to 12 weeks apart and (3) 1 dose for children 2 to 17 years of age given at least 8 weeks after any previous dose of PCV for participants who were PCV experienced. These are the schedules currently proposed in the SmPC and are similar to the recommended schedules for PCV13 in the 3 age groups.

A potential benefit of an additional vaccination with V114 in children previously fully vaccinated with PCV7 or PCV10 is difficult to assess, as stratification based on the history of prior PCV vaccination status was binary (yes/no), and participants with varied history of PCV vaccination (PCV7, PCV10 or PCV13) and different status (partially or fully vaccinated) were pooled together. This binary stratification is considered suboptimal, since theoretically more fully vaccinated participants or more participants who received higher-valent PCV could have ended up in the V114 arm thereby skewing the data. Unfortunately, this could not be assessed, since respective data was not collected.

The results showed that the proportion of subjects achieving IgG antibody level >0.35 µg/ml after vaccination with V114 was high (83.9% to 100%) for all serotypes and for all 3 age groups. This was comparable to the response rate seen in the PCV13 groups, which ranged from 87.7% to 100% for all serotypes included in the vaccine.

As seen in the pivotal studies, the IgG GMCs were slightly lower in the V114 group compared to the PCV13 group for the majority of the shared serotypes for all 3 age groups. However, in both the V114 and PCV13 groups the IgG GMCs were well above the threshold level of 0.35 µg/ml for all 15 serotypes included in V114 and the 13 serotypes in PCV13.

Overall, the data suggest that the catch-up schedules induce an immune response that is substantial and sufficient to ensure protection against IPD. The response after vaccination with V114 although slightly lower is similar to the response seen after vaccination with PCV13.

**Study V114-027**

**Study Design**: Study V114-027 was a multicenter, randomized, active-controlled, double-blind interchangeability study to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age.

**Treatment**: Participants in Study V114-024 were randomized in a 1:1:1:1:1 ratio to 1 of 5 intervention groups, see Table 36.

**Table 36 V114/PCV13 dosing schedule**

| Intervention Group Name | Dose 1 (Visit 1, ~2 months of age) ≥42 days of age to ≤90 days of age | Dose 2 (Visit 2, ~4 months of age) 4 months of age to 1 day prior to 5 months of age | Dose 3 (Visit 3, ~6 months of age) 6 months of age to 1 day prior to 7 months of age | Dose 4 (Visit 5, ~12 to 15 months of age) 12 months of age to 1 day prior to 16 months of age |
|---|---|---|---|---|
| Group 1 | PCV13 | PCV13 | PCV13 | PCV13 |
| Group 2 | PCV13 | PCV13 | PCV13 | V114 |
| Group 3 | PCV13 | PCV13 | V114 | V114 |
| Group 4 | PCV13 | V114 | V114 | V114 |
| Group 5 | V114 | V114 | V114 | V114 |

Infants also received other licensed paediatric vaccines administered concomitantly with the PCV, including RECOMBIVAX HB™ and RotaTeq™.

**Study Participants**: The study population will consist of healthy male or female infants approximately 2 months of age (42 to 90 days, inclusive) without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. In total 900 subjects were enrolled.

In group 1, 179 participants were randomized and received at least 1 dose of PCV, 164 (91.6%) completed the study, and 15 (8.4%) discontinued the study. In group 2, 181 participants were randomized and received at least 1 dose of PCV, 167 (92.3%) completed the study, and 14 (7.7%) discontinued the study. In group 3, 180 participants were randomized, 178 (98.9%) received at least

1 dose of PCV, 147 (81.7%) completed the study, and 33 (18.3%) discontinued the study. In group 4, 180 participants were randomized, 179 (99.4%) received at least 1 dose of PCV, 160 (88.9%) completed the study, and 20 (11.1%) discontinued the study. In group 5, 180 participants were randomized, 179 (99.4%) received at least 1 dose of PCV, 167 (92.8%) completed the study, and 13 (7.2%) discontinued the study.

Demographic characteristics, including age, gender, race, and ethnicity, were presented descriptively. Demographic and baseline characteristics were generally comparable across intervention groups.

The median age of participants at the time of consent was 9.0 weeks (range: 6 to 12 weeks). The majority of participants were male, white, and of non-Hispanic or Latino ethnicity. Approximately 10% of participants were preterm infants (gestational age < 37 weeks). Most participants (97.8%) received a hepatitis B vaccination before study enrolment.

**Objectives**: The objectives of this study were (1) to evaluate the serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered mixed dosing schedules of PCV13/V114 (Groups 2, 3, and 4) compared with participants administered a complete dosing schedule of PCV13(Group 1), (2) to compare the proportion of participants with anti-hepatitis B surface antigen (HBsAg) concentration ≥10 mIU/mL at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RECOMBIVAX HB™ versus participants administered a complete primary infant series dosing schedule of PCV13 (Groups 1 and 2) concomitantly with RECOMBIVAX HB™, (3) to compare the anti-rotavirus Immunoglobulin A (IgA) GMT at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RotaTeq™ versus participants administered a complete primary infant series dosing schedule of PCV13 (Groups 1 and 2) concomitantly with RotaTeq™, (4) to evaluate the serotype-specific IgG GMCs and the serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following Dose 3 separately for each vaccination group (Groups 1, 2, 3, 4, and 5), and (5) to evaluate the serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered a complete dosing schedule of V114 (Group 5) compared with participants administered a complete dosing schedule of PCV13 (Group 1).

**Results:**

Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered mixed regimens and for participants administered a complete dosing regimen of PCV13, see Table 37.

### Table 37 Summary of IgG GMCs for the 13 shared serotypes 30 days post dose 4 (PP) – V114-027

| Serotype | Group 1 (N = 179) | | Group 2 (N = 181) | | Group 3 (N = 178) | | Group 4 (N = 179) | | Group 5 (N = 179) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Response 95% CI[a] | n | Response 95% CI[a] | n | Response 95% CI[a] | n | Response 95% CI[a] | n | Response 95% CI[a] |
| 1 | 147 | 2.02 (1.78, 2.30) | 151 | 1.69 (1.48, 1.93) | 128 | 1.89 (1.63, 2.18) | 139 | 1.68 (1.48, 1.91) | 147 | 1.46 (1.30, 1.63) |
| 3 | 148 | 0.72 (0.64, 0.82) | 151 | 0.77 (0.68, 0.87) | 128 | 0.68 (0.61, 0.77) | 139 | 0.73 (0.66, 0.82) | 147 | 0.89 (0.79, 0.99) |
| 4 | 146 | 1.51 (1.30, 1.76) | 151 | 1.33 (1.14, 1.56) | 128 | 1.27 (1.10, 1.46) | 139 | 1.23 (1.08, 1.41) | 147 | 1.35 (1.17, 1.57) |
| 5 | 147 | 3.66 (3.18, 4.20) | 151 | 3.39 (2.91, 3.94) | 128 | 3.82 (3.23, 4.51) | 138 | 2.90 (2.50, 3.38) | 147 | 2.90 (2.50, 3.35) |
| 6A | 146 | 6.42 (5.56, 7.42) | 151 | 7.16 (6.30, 8.15) | 128 | 7.16 (6.17, 8.30) | 139 | 5.17 (4.43, 6.03) | 147 | 4.43 (3.86, 5.09) |
| 6B | 146 | 6.15 (5.36, 7.07) | 151 | 7.58 (6.61, 8.68) | 128 | 6.64 (5.73, 7.69) | 139 | 6.62 (5.75, 7.62) | 147 | 5.83 (5.09, 6.68) |
| 7F | 146 | 5.10 (4.43, 5.88) | 151 | 5.69 (4.93, 6.56) | 128 | 5.06 (4.33, 5.92) | 139 | 3.98 (3.47, 4.57) | 147 | 3.43 (3.02, 3.91) |
| 9V | 147 | 2.93 (2.56, 3.34) | 151 | 2.76 (2.41, 3.16) | 128 | 2.57 (2.22, 2.97) | 139 | 2.46 (2.19, 2.78) | 147 | 2.89 (2.56, 3.26) |
| 14 | 146 | 7.62 (6.55, 8.86) | 151 | 10.59 (9.01, 12.44) | 128 | 10.91 (9.29, 12.81) | 139 | 7.87 (6.77, 9.16) | 147 | 6.57 (5.73, 7.55) |
| 18C | 147 | 2.57 (2.21, 2.99) | 151 | 3.88 (3.38, 4.45) | 128 | 3.70 (3.20, 4.29) | 139 | 2.76 (2.42, 3.15) | 147 | 2.65 (2.34, 3.01) |
| 19A | 148 | 5.92 (5.15, 6.80) | 151 | 5.52 (4.88, 6.25) | 128 | 5.20 (4.42, 6.12) | 139 | 4.95 (4.27, 5.73) | 147 | 4.66 (4.15, 5.24) |
| 19F | 148 | 4.78 (4.22, 5.42) | 151 | 4.88 (4.33, 5.51) | 128 | 5.02 (4.40, 5.73) | 139 | 4.60 (4.00, 5.28) | 147 | 4.10 (3.66, 4.59) |
| 23F | 146 | 2.89 (2.42, 3.44) | 150 | 2.72 (2.33, 3.18) | 127 | 2.29 (1.93, 2.70) | 138 | 2.22 (1.92, 2.56) | 146 | 2.11 (1.81, 2.46) |

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Note: Per protocol, dose 4 was administered at ~12 to 15 months of age.
Group 1: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → Prevnar 13™
Group 2: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → V114
Group 3: Prevnar 13™ → Prevnar 13™ → V114 → V114
Group 4: Prevnar 13™ → V114 → V114 → V114
Group 5: V114 → V114 → V114 → V114
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Responses to RECOMBIVAX HB™ administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in proportions of participants with anti-HBsAg concentration ≥10 mIU/mL [Group 5 minus (Group 1 + Group 2)] was greater than -10 percentage points. Responses to RotaTeq™ administered concomitantly with V114 met noninferiority criteria as assessed by anti-rotavirus IgA GMTs at 30 days PD3. The lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [Group 5/(Group 1 + Group 2)] was greater than 0.50.

Serotype-specific immune responses at 30 days post primary series (post dose 3) for the 13 shared serotypes were generally comparable across intervention groups as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35 µg/mL (response rates) and IgG GMCs. Serotype-specific immune responses for serotype 22F were higher after 1 dose of V114 in the infant series (Group 3); similar responses were observed in Groups 4 and 5 which received additional V114 doses in the infant series as assessed by response rates and IgG GMCs. Serotype-specific immune responses for serotype 33F were higher after 1 dose of V114 in the infant series (Group 3) and increased incrementally with additional V114 primary series doses administered (Groups 4 and 5) as assessed by response rates and IgG GMCs.

### Table 38 Summary of the Proportions of Participants With IgG ≥0.35 µg/mL at 30 Days Postdose 3 (PP) – V114-027

| Serotype | Group 1 (N = 179) | | Group 2 (N = 181) | | Group 3 (N = 178) | | Group 4 (N = 179) | | Group 5 (N = 179) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | % (m/n) | 95% CI[a] | % (m/n) | 95% CI[a] | % (m/n) | 95% CI[a] | % (m/n) | 95% CI[a] | % (m/n) | 95% CI[a] |
| 13 Shared Serotypes | | | | | | | | | | |
| 1 | 97.9% (139/142) | (94.0, 99.6) | 100% (142/142) | (97.4, 100.0) | 99.2% (128/129) | (95.8, 100.0) | 97.8% (135/138) | (93.8, 99.5) | 96.6% (143/148) | (92.3, 98.9) |
| 3 | 73.2% (104/142) | (65.2, 80.3) | 73.9% (105/142) | (65.9, 80.9) | 79.1% (102/129) | (71.0, 85.7) | 81.9% (113/138) | (74.4, 87.9) | 93.9% (138/147) | (88.7, 97.2) |
| 4 | 97.9% (138/141) | (93.9, 99.6) | 98.6% (137/139) | (94.9, 99.8) | 93.0% (119/128) | (87.1, 96.7) | 94.2% (129/137) | (88.8, 97.4) | 96.6% (142/147) | (92.2, 98.9) |
| 5 | 97.9% (138/141) | (93.9, 99.6) | 99.3% (140/141) | (96.1, 100.0) | 97.7% (125/128) | (93.3, 99.5) | 97.1% (134/138) | (92.7, 99.2) | 98.0% (145/148) | (94.2, 99.6) |
| 6A | 99.3% (139/140) | (96.1, 100.0) | 99.3% (139/140) | (96.1, 100.0) | 99.2% (127/128) | (95.7, 100.0) | 97.1% (134/138) | (92.7, 99.2) | 98.6% (146/148) | (95.2, 99.8) |
| 6B | 91.3% (126/138) | (85.3, 95.4) | 94.3% (132/140) | (89.1, 97.5) | 96.1% (122/127) | (91.1, 98.7) | 95.7% (132/138) | (90.8, 98.4) | 95.2% (140/147) | (90.4, 98.1) |
| 7F | 100% (142/142) | (97.4, 100.0) | 100% (142/142) | (97.4, 100.0) | 100% (129/129) | (97.2, 100.0) | 100% (138/138) | (97.4, 100.0) | 100% (148/148) | (97.5, 100.0) |
| 9V | 96.5% (138/143) | (92.0, 98.9) | 96.5% (137/142) | (92.0, 98.8) | 96.1% (123/128) | (91.1, 98.7) | 95.7% (132/138) | (90.8, 98.4) | 98.6% (146/148) | (95.2, 99.8) |
| 14 | 98.6% (140/142) | (95.0, 99.8) | 98.6% (140/142) | (95.0, 99.8) | 96.9% (124/128) | (92.2, 99.1) | 100% (138/138) | (97.4, 100.0) | 98.6% (146/148) | (95.2, 99.8) |
| 18C | 95.8% (136/142) | (91.0, 98.4) | 100% (142/142) | (97.4, 100.0) | 99.2% (128/129) | (95.8, 100.0) | 97.8% (135/138) | (93.8, 99.5) | 98.0% (145/148) | (94.2, 99.6) |
| 19A | 99.3% (142/143) | (96.2, 100.0) | 100% (142/142) | (97.4, 100.0) | 98.4% (127/129) | (94.5, 99.8) | 97.1% (134/138) | (92.7, 99.2) | 97.3% (144/148) | (93.2, 99.3) |
| 19F | 99.3% (142/143) | (96.2, 100.0) | 99.3% (141/142) | (96.1, 100.0) | 99.2% (127/128) | (95.7, 100.0) | 100% (138/138) | (97.4, 100.0) | 100% (148/148) | (97.5, 100.0) |
| 23F | 91.4% (128/140) | (85.5, 95.5) | 97.9% (137/140) | (93.9, 99.6) | 90.6% (116/128) | (84.2, 95.1) | 92.6% (125/135) | (86.8, 96.4) | 94.6% (139/147) | (89.6, 97.6) |
| 2 Serotypes Unique to V114 | | | | | | | | | | |
| 22F | 2.9% (4/138) | (0.8, 7.3) | 1.4% (2/140) | (0.2, 5.1) | 93.8% (120/128) | (88.1, 97.3) | 99.3% (136/137) | (96.0, 100.0) | 98.6% (146/148) | (95.2, 99.8) |
| 33F | 2.1% (3/141) | (0.4, 6.1) | 2.2% (3/139) | (0.4, 6.2) | 39.4% (50/127) | (30.8, 48.4) | 75.9% (104/137) | (67.9, 82.8) | 93.2% (138/148) | (87.9, 96.7) |

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.
N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of partic ipants with the indicated response. Note: Per protocol, dose 3 was administered at ~6 months of age.
Group 1: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → Prevnar 13™
Group 2: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → V114
Group 3: Prevnar 13™ → Prevnar 13™ → V114 → V114
Group 4: Prevnar 13™ → V114 → V114 → V114
Group 5: V114 → V114 → V114 → V114
CI=confidence interval; IgG=immunoglobulin G.

***CHMP's comment***

Study V114-027 investigated the interchangeability of both PCV13 and V114 in infants aged approximately 2 months of age. The study treatment consisted of 4 doses, 3 primary series and 1 toddler dose. In total 5 groups were investigated with group 1 receiving PCV13 for all doses and group 5 V114 for all doses. The remaining groups received progressively less PCV13 doses. The different switch schedules were investigated in an appreciable number of children (179-181/group).

At 30 days PTD, the GMC ratio of the mixed groups vs PCV13 (Group 4,3,2/1) varied between 0.77 and 1.51 for the 13 shared serotypes in all groups. This indicates that the mixed dosing regimen generated an immune response that is comparable to the 4-dose PCV13 regimen. Interestingly, in group 5 receiving only V114 the IgG GMC at 30 days PTD for serotype 3 is lower compared to 30 days PPS, which is also observed in study V114-029.

During the primary series, groups 1 and 2 only received PCV13, group 5 only V114, while groups 3 and 4 received both PCV13 and V114. At 30 days post primary series, the vast majority of participants achieved the threshold of 0.35 µg/mL. The response rate was largely comparable between the groups, except for serotype 3 and the 2 unique serotypes. The response rate to serotypes 3 and 33F increased progressively with additional V114 primary doses administered. In addition, for serotype 33F IgG GMCs

seem to increase substantially in groups 3, 4 and 5 from 30 days PPS to 30 days PTD and are similar in these three groups, indicating that at least one primary dose of V114 and the respective booster dose of V114 are required for a protective effect for serotype 33F. For serotype 22F, 1 dose of V114 was enough to increase the response rate from 1.4%-2.9% in groups 1 and 2 to 93.8% in group 3. After a second or third vaccination, the response rate did not increase substantially.

These results indicate that switching between the vaccines is possible and does not substantially impact the immune response for the 13 shared serotypes. The majority of subjects acquired antibody levels above the threshold of 0.35 µg/mL in all arms at both 30 days PPS and PTD for the 13 shared serotypes. A clinical benefit concerning serotypes 3, 22F and 33F was not established for all scenarios. Respective wording in the SmPC is required.

**Study V114-008**

**Study Design**: Study V114-008 was a multicenter, randomized, double-blind study to evaluate the safety, tolerability, and immunogenicity of 2 different lots of V114 in healthy infants. PCV13 served as the active control.

**Treatment**: Participants in Study V114-008 were randomized in a 1:1:1 ratio to receive 4 doses of either 1 of 2 lots of V114 or PCV13 IM. PCV was administered at 2, 4, 6 and 12 to 15 months of age.

**Study Participants**: The study population will consist of healthy male or female infants approximately 2 months of age (42 to 90 days, inclusive) without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. In total 1051 subjects were enrolled.

In the Lot 1 V114 group, 351 participants were randomized, 350 (99.7%) received at least 1 vaccination, 308 (87.7%) completed the study, and 43 (12.3%) discontinued the study. In the Lot 2 V114 group, 350 participants were randomized, 347 (99.1%) received at least 1 vaccination, 305 (87.1%) completed the study, and 45 (12.9%) discontinued the study. In the PCV13 group, 350 participants were randomized, 347 (99.1%) received at least 1 vaccination, 308 (88.0%) completed the study, and 42 (12.0%) discontinued the study.

Demographic characteristics, including age, gender, race, and ethnicity, were presented descriptively. Demographic characteristics were generally comparable for vaccinated participants across intervention groups. No inferential statistics were planned. Overall, the median age was 9.0 weeks (range: 6 to 12 weeks), 528 (50.2%) were male, the majority was white (83.3%) and of non-Hispanic or Latino (86.3%) ethnicity.

**Objectives**: The objectives of this study were (1) to demonstrate that V114 (either V114 Lot 1 or V114 Lot 2) is noninferior to PCV13 for the 13 shared serotypes, based on response rate (the proportion of subjects meeting serotype-specific IgG reference level of ≥0.35 µg/mL) at 1 month PPS, (2) to evaluate the serotype-specific IgG GMCs of V114 Lot 1, V114 Lot 2, and PCV13, and the IgG GMC ratios between each of the 2 V114 lots and PCV13 for all 15 serotypes included in V114 at 1 month PPS and (2) to evaluate the serotype-specific IgG GMCs of V114 Lot 1, V114 Lot 2, and PCV13, and the IgG GMC ratios between each for the 2 V114 lots and PCV13 for all 15 serotypes included in V114 at predose 4 and 1 month PTD.

**Results:**

Both V114 Lot 1 and V114 Lot 2 were noninferior to PCV13 for each of the 13 shared serotypes as assessed by IgG response rates (proportion of participants meeting serotype-specific IgG ≥0.35 µg/mL) at 1 month PPS. The lower bound of the 2-sided 95% CI for the between-treatment difference in the proportion of participants meeting serotype-specific IgG ≥0.35 µg/mL at 1 month PPS was

greater than -15 percentage points for all 13 shared serotypes. IgG response rates at 1 month PD3 were generally comparable between both V114 Lot 1 and V114 Lot 2 and PCV13.

IgG GMCs and GMC ratios at 1 month PPS were generally comparable, with the exception of a few serotypes, between both V114 Lot 1 and V114 Lot 2 and PCV13. Reverse cumulative distribution curves show that IgG concentrations at 1 month PPS were generally comparable for the 13 shared serotypes across the 3 vaccination groups, and IgG concentrations were higher in the V114 groups compared with the PCV13 group for the 2 serotypes unique to V114.

For the 13 shared serotypes, IgG GMCs at predose 4 and 1 month PTD varied by serotype but were generally comparable across the V114 Lot 1, V114 Lot 2, and PCV13 groups.

***CHMP's comment***

Considering that consistency between lots was in fact not tested, this is regarded as a Phase 2 study. Lot-to-lot consistency studies are not routinely required based on the guideline on clinical evaluation of vaccines. The additional data on the immune response in healthy children aged approximately 2 months is appreciated.

The 2 lots of V114 elicited a consistent response in the participants as measured by IgG GMCs at 30 days PPS and PTD, indicating that the response to V114 is robust.

Both V114 and PCV13 are able to elicit an immune response in healthy infants. For both interventions, the vast majority of participants achieved the threshold of 0.35 µg/mL both PPS and PTD. At 30 days PPS, the GMC ratio for lot 1 and 2 are comparable and range from 0.54 to 1.98 for the 13 shared serotypes for Lot 1 and 0.57 to 1.93 for Lot 2. At 30 days PTD, the IgG GMC ratio is narrower, and ranges from 0.67 to 1.44 for Lot 1 and from 0.71 to 1.48 for Lot 2. The IgG GMCs for the 2 unique serotypes are higher in the V114 groups compared to the PCV13 group at both timepoints, as expected.

These results are in line with the results of the pivotal studies.

## 2.4.2. Discussion on clinical efficacy

The MAH applied for an extension of indication for Vaxneuvance (V114). The indication applied for is "*active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in infants, children, and adolescents from 6 weeks through 17 years of age (prior to 18th birthday)*".

Currently two vaccines are licensed for this indication in children in the EU: Prevenar13 (PCV13) and Synflorix (only for children up to 5 years of age). V114 is a 15-valent pneumococcal conjugated vaccine (PCV) containing the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in the licensed vaccine PCV13, plus 2 additional serotypes (22F and 33F), not included in either PCV13 or Synflorix.

This submission is based on the inference of V114 effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of noninferior immune responses to the 13 shared serotypes in PCV13. The immunobridging approach is in accordance with EMA guidance (EMEA/CHMP/VWP/164653/2005) and scientific advice (EMEA/H/SA/1492/1/FU/1/2017/III).

A surrogate of protection, IgG of 0.35 µg/mL, has been established for invasive pneumococcal disease (IPD) in children, which can be used to infer protection against IPD. However, it needs to be taken into consideration that for pneumonia and acute otitis media (AOM) no correlate or surrogate of protection exists. PCV13 has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed. However, no exact vaccine efficacy estimate was determined, nor the immune response required to achieve protection. Therefore, the strategy of non-inferiority testing for V114 to PCV13 introduces the possibility of biocreep for the shared serotypes, considering that the immune response required to induce a protective effect is unknown. CHMP recommended during scientific advice that the Company should conduct post-marketing studies to evaluate vaccine effectiveness against AOM and pneumonia (EMEA/H/SA/1492/1/2010/PED/III). An AOM vaccine-efficacy clinical trial is currently ongoing, which will evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal AOM. In addition, PSURs, including information on breakthrough disease/vaccine failure, serotype distribution and incidence of IPD will provide an indication on efficacy against the new serotypes included in the vaccine, as frequency of IPD caused by these serotypes is expected to decline after V114 uptake. In addition this might also provide insight into impact of the lower titres on immune persistence as frequency of IPD is reported per age category.

The submission consists of a total of 7 phase 3 studies (V114-023, V114-024, V114-025, V114-027, V114-029, V114-030, and V114-031) and 1 phase 2 study (V114-008). Studies V114-025 (3-dose regimen) and V114-029 (4-dose regimen) are considered pivotal as they provide the main evidence for immunogenicity and safety in the target population.

## Design and conduct of clinical studies

All 8 clinical studies included in the application were randomized, double-blind, active comparator PCV13-controlled, multicentre studies. This study design is adequate. In all studies, the vaccination regimen, was identical to the posology for PCV13 and the posology in the updated SmPC of V114. In addition, V114 and PCV13 were administered concomitantly with vaccines administered in the frame of routine child vaccination programs as offered in some European countries during several studies, which is appreciated. This is in line with the scientific advice given. The studies were conducted globally, allowing evaluation of the results in different populations.

The serological assays used to determine immunogenicity were validated and shown to be fit for purpose. In addition, the PnECL assay was bridged to the WHO ELISA, confirming a link between the immune responses generated by V114 vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevnar.

In both pivotal studies the population enrolled consisted of healthy infants 6 to 12 weeks of age, which adequately reflects the target population for vaccination with V114.

Based on the study objectives for both pivotal studies, the immune response induced by V114 can be adequately compared to the immune response induced by PCV13, as proportion of participants achieving titer of 0.35µg/mL, IgG GMCs and OPA GMTs will be determined at different time points and compared between the 2 groups.

Primary analyses to conclude on non-inferiority were performed on the PP population, with supportive analyses based on the FAS. The analysis sets and the statistical analysis of the primary and secondary endpoints are generally considered adequate. However, the analyses were not stratified by centre/region. The applicant justified the choice to refrain from stratifying by centre, taking into account the sample size, the fact that geographical differences in immune responses following infant vaccination with PCVs vary with serotype, the objectivity of immunogenicity endpoints and the standardization of safety assessment across study sites. Although the argumentation cannot be fully

understood, post-hoc sensitivity analyses adjusted for region (Europe versus ex-Europe) indicated that region had limited impact on immunogenicity results. Multiplicity was adequately controlled for the primary objectives but was not strictly controlled for the secondary objectives.

## Immunogenicity data

Both V114 and PCV13 were immunogenic in all studies and subgroups tested. Generally, the immune response to V114 was numerically lower compared to PCV13 as assessed by IgG GMCs for the 13 shared serotypes and higher for the 2 unique serotypes. When comparing IgG GMCs generated by V114 to PCV13, the GMC ratio fell below 1 for the majority of the shared serotypes. However, the response rate, defined as the proportion of participants achieving ≥0.35 µg/mL, was largely comparable and indicated that the majority of participants in both treatment groups achieved the threshold of 0.35 µg/mL. A consistent immune response was observed across studies, with the lowest response rate being observed for serotype 6B and the highest for serotype 19F for the shared serotypes. The response rates in these serotypes were comparable between the V114 and PCV13 group. A higher response rate was observed for the 2 unique serotypes in the V114 group compared to the PCV13 group, as expected. The response to serotype 6A was consistently lower in the V114 group compared to the PCV13 group, leading to not meeting non-inferiority criteria in both the pivotal studies at 30 days post primary series (PPS).

Study V114-029 formally failed to achieve one of the predefined primary endpoints (non-inferiority of IgG GMCs at 30 days PPS for all shared serotypes), therefore the study was considered failed and no further statistical testing of secondary endpoints is justified. Secondary endpoints should be descriptive. Considering the fact that the percentage of participants achieving the IgG threshold value of ≥0.35 µg/mL was 93.7% in the V114 compared to 98.6% in the PCV13 group at 30 days PPS and no difference between the groups could be observed at 30 days PTD in response rate, the clinical impact of the reduced response is likely limited.

In all studies, the antibody concentration decreased over time as IgG GMCs immediately prior to the toddler dose were lower compared to 30 days PPS in both treatment arms. The toddler dose increased IgG GMCs to levels comparable to or higher than PPS. This indicates that immune memory is induced.

When looking at the reverse cumulative distribution curves (RCDCs) of the 13 shared serotypes, all serotypes showed a similar pattern for the V114 group and the PCV13 group, although the curves for V114 generally fell below the curve for PCV13. Visually, the curves are comparable, indicating that the groups respond comparably. The data indicate that IgG concentrations decline at a similar rate after vaccination with V114 and PCV13 and consequently also the response rates. Given that the initial concentrations were lower with V114, it could be assumed that the protective effect of V114 might wane earlier compared to PCV13. Since no data after a longer period are available, this issue can currently not be answered. PSURs, including information on breakthrough disease/vaccine failure, serotype distribution and incidence of IPD will provide an indication on impact of the lower titres on immune persistence as frequency of IPD is reported per age category.

The results of the functional OPA antibodies were consistent with the results as observed for IgG GMCs, with the OPA GMTs being generally comparable between the 2 treatment groups though slightly lower in the V114 group. Interestingly, no difference in serotype 3 OPA antibodies was seen between V114 and PCV13 30 days post toddler dose (PTD).

It has been noted that the number of subjects using paracetamol concomitantly is much higher in both pivotal studies compared to the other studies (025: ~48%, 029: ~67%, 024: ~25-35%, 027: ~6%, 008: no use of paracetamol). Although the use of paracetamol was overall balanced between groups in all respective studies, further discussion was requested based on post marketing findings with PCV13,

which indicated that the prophylactic use of antipyretics (ibuprofen and paracetamol) reduced the immune response especially after the primary series. The potential influence of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response, as observed in the post-marketing of PCV13, cannot be ruled out given the current data. The presented results of subgroup analyses based on concomitant antipyretic use (yes/no) are similar for both vaccines, indicating a similar effect for both vaccines. Consequently, respective wording in the SmPC is required.

A lower immune response is seen in study V114-025, leading to slightly lower response rates, indicating that the immune reaction induced by the 2-dose primary series is reduced compared to the 3-dose primary series. However, at 30 days PPS and 30 days PTD, GMC ratios were comparable across the 4 studies, indicating that while V114 generated the lowest immune response in study V114-025, the same holds true for PCV13. It is in the remit of the NITAGs to determine the benefit/risk balance of the 2- vs 3-dose primary series, taking into consideration the burden of disease in the respective country and the fact that no increase in occurrence of AEs after subsequent dosing could be observed using the different regimens.

***Subgroup analyses***

Slight differences in immune response could be observed between the subgroups in sex, race and ethnicity; however, no clear trends were observed. The differences observed between subgroups are small and considered not to impact the use of V114 in these subpopulations.

***Concomitant administration of routine childhood vaccines***

The immune response to the concomitantly administered vaccines was comparable between the V114 and PCV13 group, indicating that the generation of the immune response to the concomitantly administered vaccines was not impacted differently by the 2 treatment arms. All responses for the concomitant vaccines showed a within 5 percentage points difference between the treatment arms.

***Interchangeability***

Study V114-027 investigated the interchangeability of both PCV13 and V114 in infants aged approximately 2 months of age. The study treatment consisted of 4 doses, 3 primary series and 1 toddler dose; group 1 received PCV13 for all doses and group 5 V114 for all doses. The remaining groups received progressively less PCV13 doses. The different switch schedules were investigated in an appreciable number of children (179-181/group).

Overall, the results of the study suggest that switching between the vaccines is possible and does not substantially impact the immune response. The majority of subjects acquired antibody levels above the threshold of 0.35 µg/mL in all arms at both 30 days PPS and PTD for the 13 shared serotypes. The response rates were largely comparable between the groups, except for serotype 3 and the 2 unique serotypes. The response rate to serotypes 3 and 33F increased progressively with additional V114 primary doses administered. In addition, for serotype 33F IgG GMCs seem to increase substantially in groups 3, 4 and 5 from 30 days PPS to 30 days PTD and are similar in these three groups, indicating that at least one primary dose of V114 and the respective booster dose of V114 are required for a protective effect for serotype 33F. For serotype 22F, 1 dose of V114 was enough to increase the response rate from 1.4%-2.9% in groups 1 and 2 to 93.8% in group 3 and no further substantial increase was seen after additional doses. At 30 days PTD, the GMC ratio of the mixed groups vs PCV13 (Group 4,3,2/1) varied between 0.77 and 1.51 for the 13 shared serotypes in all groups. This indicates that the mixed dosing regimen generated an immune response that is comparable to the 4-dose PCV13 regimen. A clinical benefit concerning serotypes 3, 22F and 33F was not established for all scenarios. Consequently, respective wording should be included in the SmPC.

***Catch-up vaccination***

Study V114-024 investigated the immunogenicity of catch-up vaccination with V114 in children aged 7 to 11 months, 12 to 23 months and 2 to 17 years of age. The different catch-up schedules were documented in an appreciable number of children (n=303; 62-177/group). The three catch-up vaccination schedules evaluated were identical to the schedules currently proposed in the SmPC and are similar to the recommended schedules for PCV13 in the 3 age groups, with 3 doses for children aged 7 to 11 months, 2 doses for children 12 to 23 months of age and 1 dose for children 2 to 17 years of age.

Overall, the data suggest that the catch-up schedules induce an immune response that is substantial and sufficient to ensure protection against IPD, as the proportion of subjects achieving IgG antibody level ≥0.35 µg/ml after vaccination with V114 was high (83.9% to 100%) for all serotypes and for all 3 age groups. This was comparable to the response rate seen in the PCV13 groups, which ranged from 87.7% to 100% for all serotypes included in the vaccine. Again, the IgG GMCs were slightly lower in the V114 group compared to the PCV13 group for the majority of the shared serotypes for all 3 age groups. However, in both the V114 and PCV13 groups the IgG GMCs were well above the threshold level of 0.35 µg/ml for all 15 serotypes included in V114 and the 13 serotypes in PCV13.

A potential benefit of an additional vaccination with Vaxneuvance in children previously fully vaccinated with PCV7 or PCV10 is difficult to assess, as participants with varying PCV vaccination history (PCV7, PCV10 or PCV13) and vaccination status (partially or fully vaccinated) were pooled. The applied binary stratification based on the history of prior PCV vaccination, would theoretically allow more fully vaccinated participants or more participants who previously received higher-valent PCV in the Vaxneuvance arm thereby skewing the results. Unfortunately, respective data was not collected.

## Immunogenicity in special populations

***Pre-term***

Considering the fact that preterm infants are at increased risk of pneumococcal disease, the immunogenicity of this population was evaluated separately to ensure adequate protection.

Data from pre-term infants was integrated across 4 Phase 3 clinical studies: V114-025, V114-029, V114-027 and V114-031, as the design of the studies was similar. Treatment consisted of 4 doses of PCV, with the primary series consisting of 3 single doses followed by a toddler dose. However, during study V114-025 PCV was administered at ~2, 3, 4, 11 to 15 months of age, while for all other studies administration of PCV was performed at ~2, 4, 6, 12 to 15 months of age.

Both 30 days PPS and 30 days PTD, the vast majority of participants achieved the threshold value of 0.35 µg/mL for all serotypes in both treatment arms. Comparable to the total population, the IgG GMCs generated by administration of V114 were consistently lower for 12 of the 13 shared serotypes (except serotype 3) compared to the IgG GMCs generated by PCV13. The immune response generated for the 2 additional serotypes was higher in the V114 group. The RCDC curves showed a similar pattern between the 2 treatment arms.

The results of the OPA GMTs were comparable to the IgG GMCs and showed that V114 was immunogenic. The OPA GMTs generated by V114 were slightly lower compared to PCV13 for the shared serotypes, while they were higher in the V114 group for the 2 additional serotypes.

Of note, for both vaccines the response rates and IgG GMCs were generally higher in pre term infants compared to full term infants. Due to the low numbers of preterm infants included in the separate

studies, this is not expected to substantially impact the immune response observed for the total population.

***Immunocompromised***

Study V114-023 was a descriptive study to evaluate the safety, tolerability and immunogenicity of a single dose of V114 in children 5 to 17 years of age with sickle cell disease. In total 104 participants were enrolled. Both V114 and PCV13 were immunogenic in children with sickle cell disease. The immune responses generated by a single dose of V114 and PCV13 were generally comparable. The IgG GMCs generated were well above the threshold of 0.35 µg/mL, indicating that the response generated was substantial and clinically relevant. The response as measured by OPA GMTs was generally comparable to the response as measured by IgG GMCs.

Study V114-030 was an active-comparator controlled, double blind study in HIV-1 infected children. Patients either received V114 or PCV13 followed 8 weeks later by PPV23. The vast majority of participants included in the study received antiretroviral therapy and had a CD4+ T-cell count ≥500 cells/µL. This indicates that the participants still had a functioning immune system.

Both V114 and PCV13 were immunogenic. The immune responses induced by V114 and PCV13 were generally comparable and at 30 days after vaccination the IgG GMCs achieved for all serotypes were above the threshold value of 0.35 µg/mL in both treatment arms. The results for OPA GMTs were comparable to the results achieved for IgG GMCs. The response in the subgroup with CD4+ T-cell counts ≥200 to <500 cells/µL was overall slightly lower compared to the total population. Following vaccination with PPV23 IgG GMCs at Week 12 were generally comparable with those observed at 30 days postvaccination with either V114 or PCV13.

### 2.4.3. Conclusions on the clinical efficacy

Overall, V114 was observed to be immunogenic in all studies and subgroups tested and induced an immune response to all 15 serotypes included in the vaccine. Generally, the immune response to V114 was lower compared to PCV13 as assessed by IgG GMCs for the 13 shared serotypes, and higher for the 2 unique serotypes. However, the response rate, defined as the proportion of participants achieving ≥0.35 µg/mL, was largely comparable and indicated that the majority of participants in both groups achieved the threshold of 0.35 µg/mL. Therefore, no concern is raised for the immediate protective effect, but an earlier waning of the achieved protective effect might be possible.

Of note, the surrogate of protection of 0.35 µg/mL only applies to IPD and no surrogate or correlate of protection exist for pneumonia or AOM. As recommended in Scientific Advice, the Company should conduct post-marketing studies to evaluate vaccine effectiveness against AOM and pneumonia. The post-marketing program should also include population-based surveillance of the incidence rates of IPD in several different countries for an appreciable number of years using national surveillance systems, in particular for the new serotypes for which efficacy against IPD is not known, including analysis of break-through cases over time after vaccination to determine waning of the protective effect over time.

## *2.5. Clinical safety*

### Introduction

The discussion of clinical safety is based on available safety data from 8 clinical studies: 1 Phase 2 study (V114-008) and 7 Phase 3 studies (V114-025, -029, -023, -024, -027, -030 and -031).

The 8 studies contributing to the evaluation of safety enrolled a diverse population of over 8300 children across 26 countries. A total of 5366 infants (including 221 preterm infants [<37 weeks gestational age at birth]) and children received at least 1 dose of V114 in these studies, allowing for an evaluation of safety in the paediatric population.

*Safety evaluation methods*

The duration of AE collection, requirements for AE reporting, and methods used for safety evaluation were consistent across all studies in the V114 paediatric program.

All participants were observed for at least 30 minutes after administration of study intervention for any immediate reactions. Postvaccination safety evaluations were reported on an electronic vaccine report card (VRC). The following information was reported daily by the participant or the participant's legally acceptable representative on the VRC:

- Day 1 through Day 7 postvaccination: body temperature (and Day 8 through Day 14 postvaccination if fever was suspected).
- Day 1 through Day 14 postvaccination:
  - Solicited injection-site complaints: redness (erythema), swelling, tenderness (pain), and hard lump (induration)
  - Solicited systemic complaints (using age-appropriate terms for infants and children of different ages):
    - For participants <3 years of age: irritability, drowsiness (somnolence), appetite lost (decreased appetite), and hives or welts (urticaria)
    - For participants ≥3 years of age: muscle pain (myalgia), joint pain (arthralgia), headache, tiredness (fatigue), and hives or welts (urticaria)
  - Other unsolicited injection-site or systemic complaints
  - Use/receipt of concomitant medications and vaccinations
- Intensity or size of the complaints: injection-site erythema, injection-site induration, and injection-site swelling were graded by size; all other complaints were graded by intensity.

For complaints reported on the VRC, the investigator reviewed the data with the participant or participant's legally acceptable representative and reported events meeting the protocol-specified AE definition in the clinical database. Investigators also assessed the causal relationship to the study vaccine, intensity, and seriousness of each identified AE using the protocol-specified criteria.

In all 8 studies, all AEs were collected from the day of each vaccination through 14 days postvaccination.

In the 7 Phase 3 studies, SAEs were collected through 6 months after the last dose of V114 or PCV13. In the Phase 2 study, V114-008, SAEs were collected through 30 days after the last dose of V114 or PCV13.

In studies with more than 1 vaccination timepoint (V114-008, V114-024, V114-025, V114-027, V114-029, V114-030, and V114-031), discontinuation from study intervention due to AEs was evaluated.

*Safety evaluation populations*

Safety analyses were performed in the APaT population, defined as all randomized participants who received at least 1 dose of study intervention.

To evaluate the safety of V114 when administered as a complete 3- or 4-dose regimen, safety data from the 4 Phase 3 studies (V114-025, V114-027 [Groups 1 and 5 only], V114-029, and V114-031) were integrated based on similarities in study design, population, and dosing strategy (either V114 or PCV13 administered as a 2-dose or 3-dose primary series during the first 4 to 6 months of life followed by a toddler dose at 11 to 15 months of age). Participants who received both V114 and PCV13 either inadvertently or based on study design (including the mixed 4-dose regimens in V114-027 Groups 2, 3, and 4) were not included in the integrated analysis. Results are shown for all infants (regardless of gestational age) and separately for the subset of preterm infants (<37 weeks gestational age at birth) who were enrolled in these studies.

***CHMP's comment***

In general methods to assess the reactogenicity and safety of V114 are appropriate. Reactogenicity was followed for 14 days when concerning solicited injection-site and systemic reactions and for 7 days concerning body temperature, which is considered appropriate (see Guideline on clinical evaluation of vaccines). Subjects were followed for 6 months, which is considered a sufficient period of time to collect relevant adverse events. Only in the Phase 2 Study V114-008, SAEs were collected through 30 days post-vaccination, which is considered short.

The safety section as described below is focussed mainly on the integrated safety population of participants aged approximately 2 months included in Study V114-025, V114-027 (groups 1 and 5 only), V114-029 and V114-031. Where relevant, additional information from the other studies is included.

All participants were observed for at least 30 minutes after administration of study intervention for any immediate reactions. The MAH was asked to present a table including immediate reactions for pooled study data as well as for individual studies. The information was provided and did not give rise to any new safety concerns.

## Patient exposure

Overall, 5366 participants received ≥1 dose of V114 and 3491 participants received ≥1 dose of PCV13 in the 8 studies submitted, see Table 39.

**Table 39 Number of Participants Who Received ≥ 1 Dose of PCV**

| Population | Study Number | V114 | PCV13 |
|---|---|---|---|
| Healthy infants receiving PCV per recommended immunization regimens starting at ~2 months of age | V114-008 | 697 | 347 |
| | V114-025[a] | 588 | 592 |
| | V114-027[b] | 677 | 717 |
| | V114-029[a] | 859 | 856 |
| | V114-031[a] | 1970 | 438 |
| Healthy infants and children receiving a catch-up regimen of PCV | V114-024 | 303 | 303 |
| Special populations | V114-023 | 69 | 34 |
| | V114-030 | 203 | 204 |
| Overall population | Total: | 5366 | 3491 |

Participants were counted once for each column according to the intervention they actually received.
[a] One participant in Study V114-025, 1 participant in Study V114-029 and 5 participants in Study V114-031 inadvertently received both V114 and PCV13 and were included in both intervention groups.
[b] A total number of 498 participants in Study V114-027 in groups 2, 3, and 4 received both V114 and PCV13 per study design and were included in both intervention groups.
Study V114-023 enrolled participants with sickle cell disease; Study V114-030 enrolled participants with HIV. HIV=Human Immunodeficiency Virus; PCV=Pneumococcal Conjugate Vaccine (V114 or PCV13).

Demographic characteristics in the integrated population were generally comparable in both intervention groups. The median age was 9.0 weeks (range: 6 to 12 weeks). Approximately equal proportions of male and female participants were enrolled. The population was diverse with regard to

race, approximately 17% of participants were of Hispanic or Latino ethnicity, and approximately 31% of participants were from Europe. A total of 6.3% of participants were preterm infants (<37 weeks gestational age at birth).

***CHMP's comment***

In total 5366 participants were exposed to V114. The size of the safety database is considered sufficient for the assessment of the safety profile of V114. In addition, the composition of the safety database also appears to be acceptable as it is considered sufficiently representative of the target population (healthy infants approximately 2 months of age).

## Adverse events

*Integrated population*

The proportions of participants with AEs, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs, after each dose in the primary series, after the toddler dose, and after any dose, see Table 40, were generally comparable in both intervention groups.

**Table 40 Analysis of Adverse Event Summary (APaT) following any dose – 4 Phase 3 studies (V114-025, V114-027, V114-029, V114-031)**

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Participants in population | 3,589 | | 2,058 | | |
| With one or more AEs | 3,363 | (93.7) | 1,912 | (92.9) | 0.8 (-0.5, 2.2) |
| injection-site | 2,501 | (69.7) | 1,387 | (67.4) | |
| Systemic | 3,266 | (91.0) | 1,846 | (89.7) | |
| With no adverse event | 226 | (6.3) | 146 | (7.1) | |
| With vaccine-related[b] AEs | 3,209 | (89.4) | 1,793 | (87.1) | 2.3 (0.6, 4.1) |
| injection-site | 2,498 | (69.6) | 1,385 | (67.3) | |
| Systemic | 2,894 | (80.6) | 1,567 | (76.1) | |
| With serious AEs | 358 | (10.0) | 217 | (10.5) | -0.6 (-2.3, 1.1) |
| With serious vaccine-related AEs | 2 | (0.1) | 1 | (0.0) | 0.0 (-0.2, 0.2) |
| Who died | 2 | (0.1) | 2 | (0.1) | -0.0 (-0.3, 0.1) |
| Discontinued vaccine due to an AE | 0 | (0.0) | 0 | (0.0) | 0.0 (-0.2, 0.1) |
| Discontinued vaccine due to a vaccine-related AE | 0 | (0.0) | 0 | (0.0) | |
| Discontinued vaccine due to a SAE | 0 | (0.0) | 0 | (0.0) | |
| Discontinued vaccine due to a vaccine-related SAE | 0 | (0.0) | 0 | (0.0) | |

AE=adverse event; SAE=serious adverse event
[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the integrated statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
CI=confidence interval.
Source Table 5.3.5.3.3-pedspneumo: 9

***CHMP's comment***

In both intervention groups, the vast majority of participants experienced at least 1 AE, with the majority also experiencing a vaccine-related AE.

The percentage of participants experiencing vaccine-related SAEs was low in both treatment groups, <1%.

Common AEs

The most commonly reported AEs with an incidence of ≥1% in either treatment group are presented in Table 41. The proportions of participants with specific AEs by SOC and PT after any dose were generally comparable in both intervention groups.

**Table 41 Analysis of Participants With Adverse Events Incidence ≥ 1% in One or More Vaccination Groups Following Any Dose - (V114-025, V114-027, V114-029, V114-031)**

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Participants in population | 3,589 | | 2,058 | | |
| with one or more adverse events | 3,363 | (93.7) | 1,912 | (92.9) | 0.8 (-0.5, 2.2) |
| with no adverse events | 226 | (6.3) | 146 | (7.1) | -0.8 (-2.2, 0.5) |
| **Eye disorders** | **24** | **(0.7)** | **27** | **(1.3)** | **-0.6 (-1.3, -0.1)** |
| **Gastrointestinal disorders** | **716** | **(19.9)** | **421** | **(20.5)** | **-0.5 (-2.7, 1.6)** |
| Abdominal pain | 27 | (0.8) | 22 | (1.1) | -0.3 (-0.9, 0.2) |
| Constipation | 80 | (2.2) | 44 | (2.1) | 0.1 (-0.7, 0.9) |
| Diarrhoea | 287 | (8.0) | 163 | (7.9) | 0.1 (-1.4, 1.5) |
| Flatulence | 65 | (1.8) | 55 | (2.7) | -0.9 (-1.7, -0.1) |
| Teething | 95 | (2.6) | 57 | (2.8) | -0.1 (-1.1, 0.7) |
| Vomiting | 196 | (5.5) | 101 | (4.9) | 0.6 (-0.7, 1.7) |
| **General disorders and administration site conditions** | **2,844** | **(79.2)** | **1,585** | **(77.0)** | **2.2 (-0.0, 4.5)** |
| Injection site bruising | 66 | (1.8) | 33 | (1.6) | 0.2 (-0.5, 0.9) |
| Injection site erythema[b] | 1,497 | (41.7) | 834 | (40.5) | 1.2 (-1.5, 3.8) |
| Injection site induration[b] | 1,016 | (28.3) | 633 | (30.8) | -2.4 (-4.9, 0.0) |
| Injection site pain[b] | 1,593 | (44.4) | 811 | (39.4) | 5.0 (2.3, 7.6) |
| Injection site swelling[b] | 1,013 | (28.2) | 521 | (25.3) | 2.9 (0.5, 5.3) |
| Injection site urticaria | 33 | (0.9) | 22 | (1.1) | -0.1 (-0.8, 0.4) |
| Pyrexia | 1,354 | (37.7) | 752 | (36.5) | 1.2 (-1.4, 3.8) |
| **Infections and infestations** | **1,035** | **(28.8)** | **565** | **(27.5)** | **1.4 (-1.1, 3.8)** |
| Bronchiolitis | 100 | (2.8) | 56 | (2.7) | 0.1 (-0.9, 0.9) |
| Conjunctivitis | 43 | (1.2) | 27 | (1.3) | -0.1 (-0.8, 0.5) |
| Gastroenteritis | 71 | (2.0) | 37 | (1.8) | 0.2 (-0.6, 0.9) |
| Nasopharyngitis | 233 | (6.5) | 102 | (5.0) | 1.5 (0.3, 2.8) |
| Otitis media | 52 | (1.4) | 28 | (1.4) | 0.1 (-0.6, 0.7) |
| Otitis media acute | 38 | (1.1) | 22 | (1.1) | -0.0 (-0.6, 0.5) |
| Respiratory syncytial virus bronchiolitis | 33 | (0.9) | 26 | (1.3) | -0.3 (-1.0, 0.2) |
| Rhinitis | 77 | (2.1) | 57 | (2.8) | -0.6 (-1.5, 0.2) |
| Upper respiratory tract infection | 215 | (6.0) | 97 | (4.7) | 1.3 (0.0, 2.5) |
| Viral infection | 39 | (1.1) | 18 | (0.9) | 0.2 (-0.4, 0.7) |
| Viral upper respiratory tract infection | 32 | (0.9) | 23 | (1.1) | -0.2 (-0.8, 0.3) |
| **Injury, poisoning and procedural complications** | **48** | **(1.3)** | **29** | **(1.4)** | **-0.1 (-0.8, 0.5)** |
| **Metabolism and nutrition disorders** | **1,378** | **(38.4)** | **729** | **(35.4)** | **3.0 (0.4, 5.6)** |
| Decreased appetite[b] | 1,372 | (38.2) | 726 | (35.3) | 3.0 (0.3, 5.5) |
| **Nervous system disorders** | **1,981** | **(55.2)** | **1,126** | **(54.7)** | **0.5 (-2.2, 3.2)** |
| Somnolence[b] | 1,973 | (55.0) | 1,117 | (54.3) | 0.7 (-2.0, 3.4) |
| **Psychiatric disorders** | **2,682** | **(74.7)** | **1,459** | **(70.9)** | **3.8 (1.4, 6.3)** |
| Insomnia | 50 | (1.4) | 16 | (0.8) | 0.6 (0.0, 1.2) |
| Irritability[b] | 2,675 | (74.5) | 1,458 | (70.8) | 3.7 (1.3, 6.1) |
| **Respiratory, thoracic and mediastinal disorders** | **332** | **(9.3)** | **218** | **(10.6)** | **-1.3 (-3.0, 0.3)** |

| | V114 | | PCV13 | | Difference in % vs PCV13 Estimate (95% CI)[a] |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | |
| Cough | 147 | (4.1) | 100 | (4.9) | -0.8 (-1.9, 0.3) |
| Nasal congestion | 102 | (2.8) | 84 | (4.1) | -1.2 (-2.3, -0.3) |
| Rhinorrhoea | 114 | (3.2) | 68 | (3.3) | -0.1 (-1.1, 0.8) |
| **Skin and subcutaneous tissue disorders** | **476** | **(13.3)** | **263** | **(12.8)** | **0.5 (-1.4, 2.3)** |
| Dermatitis diaper | 50 | (1.4) | 31 | (1.5) | -0.1 (-0.8, 0.5) |
| Rash | 122 | (3.4) | 57 | (2.8) | 0.6 (-0.3, 1.5) |
| Urticaria[b] | 206 | (5.7) | 121 | (5.9) | -0.1 (-1.5, 1.1) |

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method. Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
[b] Injection site erythema, injection site induration, injection site pain, injection site swelling, decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following each dose.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.
Adverse event terms are reported using MedDRA version 24.0.
CI=confidence interval.
Source: Table 5.3.5.3.3-pedspneumo: 20

The most frequently reported (≥5%) AEs after each dose of V114 were the solicited AEs of irritability, somnolence, injection-site pain, injection-site erythema, decreased appetite, injection-site swelling, and injection-site induration and the unsolicited AE of pyrexia.

A rainfall plot of AEs after any dose with an incidence of ≥5% in either treatment groups is presented in Figure 21.

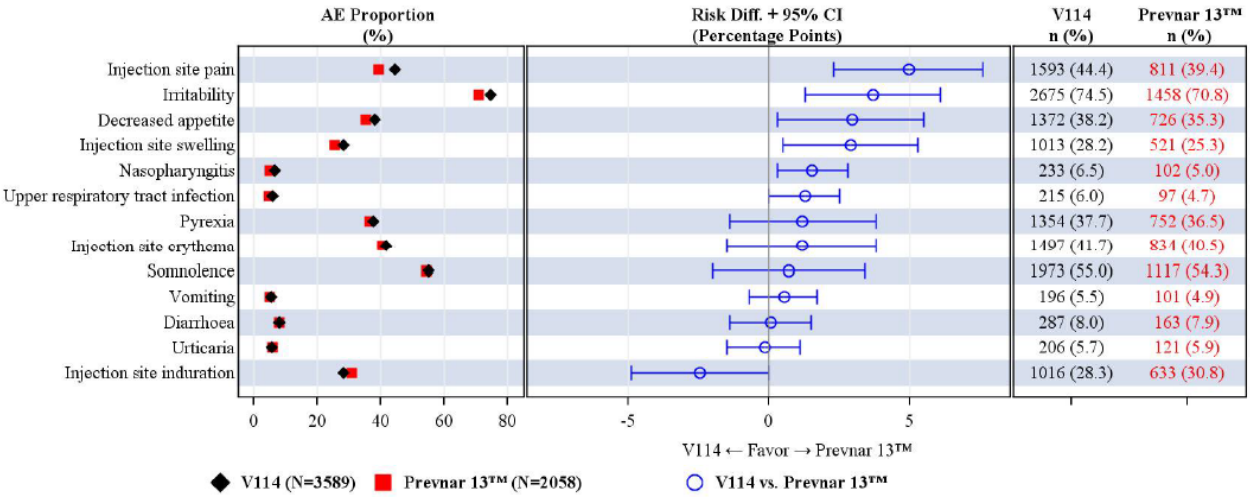



**Figure 21 Rainfall Plot of Adverse Events occurring ≥5% in either treatment group following any dose - (V114-025, V114-027, V114-029, V114-031) (Source: Figure 5.3.5.3.3-pedspneumo: 4)**

The proportions of participants with AEs (solicited and unsolicited) by maximum intensity were generally comparable in both intervention groups. Of the participants with AEs graded by intensity, the majority experienced AEs with a maximum intensity of mild to moderate in both intervention groups, see Table 42.

**Table 42 Adverse Events by Maximum Intensity Following Any Dose - (V114-025, V114-027, V114-029, V114-031)**

| | Intensity Grading | V114 n | (%) | PCV13 n | (%) |
|---|---|---|---|---|---|
| Participants in population | | 3,589 | | 2,058 | |
| **Any adverse events** | | | | | |
| with one or more adverse events graded by intensity | Total | 3,304 | (92.1) | 1,874 | (91.1) |
| | Mild | 734 | (20.5) | 443 | (21.5) |
| | Moderate | 1,871 | (52.1) | 1,055 | (51.3) |
| | Severe | 699 | (19.5) | 376 | (18.3) |
| **Solicited adverse events** | | | | | |
| with one or more solicited adverse events graded by intensity | Total | 3,075 | (85.7) | 1,725 | (83.8) |
| | Mild | 783 | (21.8) | 475 | (23.1) |
| | Moderate | 1,776 | (49.5) | 981 | (47.7) |
| | Severe | 516 | (14.4) | 269 | (13.1) |
| **Solicited injection site adverse events** | | | | | |
| Injection site pain | Total | 1,593 | (44.4) | 811 | (39.4) |
| | Mild | 711 | (19.8) | 403 | (19.6) |
| | Moderate | 758 | (21.1) | 364 | (17.7) |
| | Severe | 124 | (3.5) | 44 | (2.1) |
| **Solicited systemic adverse events** | | | | | |
| Decreased appetite | Total | 1,372 | (38.2) | 726 | (35.3) |
| | Mild | 654 | (18.2) | 338 | (16.4) |
| | Moderate | 624 | (17.4) | 343 | (16.7) |
| | Severe | 94 | (2.6) | 45 | (2.2) |
| Irritability | Total | 2,675 | (74.5) | 1,458 | (70.8) |
| | Mild | 738 | (20.6) | 422 | (20.5) |
| | Moderate | 1,529 | (42.6) | 838 | (40.7) |
| | Severe | 408 | (11.4) | 198 | (9.6) |
| Somnolence | Total | 1,973 | (55.0) | 1,117 | (54.3) |
| | Mild | 896 | (25.0) | 492 | (23.9) |
| | Moderate | 991 | (27.6) | 569 | (27.6) |
| | Severe | 86 | (2.4) | 56 | (2.7) |
| Urticaria | Total | 205 | (5.7) | 121 | (5.9) |
| | Mild | 128 | (3.6) | 75 | (3.6) |
| | Moderate | 67 | (1.9) | 40 | (1.9) |
| | Severe | 10 | (0.3) | 6 | (0.3) |

Every participant is counted a single time for each applicable specific adverse event, and is classified according to the highest non-missing intensity grading.
Injection site pain, decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following each dose. Injection site erythema, injection site induration, and injection site swelling solicited from Day 1 through Day 14 following any dose are not included in this table as these events were graded by size and are displayed in a separate summary.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.
Adverse event terms are reported using MedDRA version 24.0.

The proportions of participants with injection-site erythema, induration, or swelling by maximum size after each dose in the primary series, after the toddler dose, and after any dose were generally comparable in both intervention groups.

Of the participants with solicited injection-site erythema, induration, or swelling following each dose, most had events with a maximum size ≤2 inches (5.1 cm) and the proportions of participants with a maximum size >3 inches (7.6 cm) were low (<1%).

Of the participants with solicited AEs, the majority had events of short duration (≤3 days).

***CHMP's comment***

The majority of participants in both treatment groups experienced at least 1 AE. The distribution of AEs was generally comparable between the 2 groups, as the percentage of participants experiencing the different AEs did not differ more than 10%.

The most frequently reported AEs, reported in >20% of participants, were, next to the unsolicited AE of pyrexia, the solicited AEs: injection site AEs (injection site pain, -erythema, -induration and -swelling) and systemic AEs (irritability, somnolence and decreased appetite). Of note, the solicited systemic AE of urticaria only occurred in 5.7% of participants in the V114 group.

The rainfall plot of the most frequently reported AEs after each dose of V114 showed that the V114 was slightly more reactogenic compared to PCV13, as the majority of AEs occurred slightly more frequently after injection with V114 compared to PCV13.

The majority of AEs experienced were mild to moderate in intensity in both treatment groups.

Overall, the safety profile is comparable between V114 and PCV13.

*Vaccine-related AEs*

The proportions of participants with injection-site AEs (solicited and unsolicited) and vaccine-related systemic AEs (solicited and unsolicited) after each dose in the primary series, after the toddler dose, and after any dose were generally comparable in both intervention groups.

Nearly all injection-site AEs in both intervention groups were considered by the investigator to be vaccine related. The most frequently reported (≥1%) vaccine-related injection-site AEs after each dose of V114 were the solicited injection-site AEs (injection-site pain, injection-site erythema, injection-site swelling, and injection-site induration). Injection-site urticaria and injection-site bruising occurred consistently in >0.1% of participants after each dose of V114.

The most frequently reported (≥1%) vaccine-related systemic AEs after each dose of V114 were the solicited systemic AEs (irritability, somnolence, and decreased appetite) and the unsolicited AE of pyrexia.

## Table 43 Participants With Systemic Adverse Events Related to Study Vaccine (Incidence > 0% in One or More Vaccination Groups) Following Any Dose - V114-025, V114-027, V114-029, V114-031

| | V114 | | PCV13 | |
|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** |
| Participants in population | 3,589 | | 2,058 | |
| with ≥1 systemic AE related to study vaccine | 2,894 | (80.6) | 1,567 | (76.1) |
| with no systemic AEs related to study vaccine | 695 | (19.4) | 491 | (23.9) |
| **Blood and lymphatic system disorders** | **1** | **(0.0)** | **1** | **(0.0)** |
| Lymphadenopathy | 1 | (0.0) | 1 | (0.0) |
| **Ear and labyrinth disorders** | **1** | **(0.0)** | **0** | **(0.0)** |
| Ear pain | 1 | (0.0) | 0 | (0.0) |
| **Eye disorders** | **0** | **(0.0)** | **1** | **(0.0)** |
| Conjunctival hyperaemia | 0 | (0.0) | 1 | (0.0) |
| **Gastrointestinal disorders** | **163** | **(4.5)** | **79** | **(3.8)** |
| Abdominal discomfort | 3 | (0.1) | 1 | (0.0) |
| Abdominal distension | 1 | (0.0) | 1 | (0.0) |
| Abdominal pain | 3 | (0.1) | 1 | (0.0) |
| Abdominal pain upper | 6 | (0.2) | 3 | (0.1) |
| Change of bowel habit | 1 | (0.0) | 0 | (0.0) |
| Constipation | 7 | (0.2) | 5 | (0.2) |
| Diarrhoea | 72 | (2.0) | 36 | (1.7) |
| Dyspepsia | 1 | (0.0) | 1 | (0.0) |
| Dysphagia | 1 | (0.0) | 0 | (0.0) |
| Eructation | 1 | (0.0) | 0 | (0.0) |
| Faeces discoloured | 2 | (0.1) | 0 | (0.0) |
| Faeces soft | 1 | (0.0) | 0 | (0.0) |
| Flatulence | 12 | (0.3) | 7 | (0.3) |
| Frequent bowel movements | 2 | (0.1) | 1 | (0.0) |
| Gastrooesophageal reflux disease | 2 | (0.1) | 0 | (0.0) |
| Infantile colic | 1 | (0.0) | 1 | (0.0) |
| Infantile spitting up | 10 | (0.3) | 2 | (0.1) |
| Mucous stools | 1 | (0.0) | 0 | (0.0) |
| Regurgitation | 5 | (0.1) | 0 | (0.0) |
| Teething | 0 | (0.0) | 3 | (0.1) |
| Vomiting | 61 | (1.7) | 26 | (1.3) |
| Vomiting projectile | 0 | (0.0) | 1 | (0.0) |
| **General disorders and administration site conditions** | **1,087** | **(30.3)** | **586** | **(28.5)** |
| Asthenia | 2 | (0.1) | 0 | (0.0) |
| Chills | 2 | (0.1) | 0 | (0.0) |
| Crying | 19 | (0.5) | 4 | (0.2) |
| Decreased activity | 2 | (0.1) | 0 | (0.0) |
| Discomfort | 2 | (0.1) | 2 | (0.1) |
| Fatigue | 4 | (0.1) | 1 | (0.0) |
| Feeling hot | 2 | (0.1) | 1 | (0.0) |
| Hunger | 0 | (0.0) | 1 | (0.0) |
| Ill-defined disorder | 1 | (0.0) | 0 | (0.0) |
| Malaise | 2 | (0.1) | 1 | (0.0) |
| Pain | 7 | (0.2) | 2 | (0.1) |
| Peripheral swelling | 1 | (0.0) | 0 | (0.0) |
| Pyrexia | 1,069 | (29.8) | 581 | (28.2) |
| Tenderness | 1 | (0.0) | 0 | (0.0) |
| Thirst | 0 | (0.0) | 1 | (0.0) |
| **Infections and infestations** | **23** | **(0.6)** | **6** | **(0.3)** |
| Ear infection | 1 | (0.0) | 0 | (0.0) |
| Gastroenteritis | 1 | (0.0) | 2 | (0.1) |
| Influenza | 2 | (0.1) | 0 | (0.0) |
| Nasopharyngitis | 2 | (0.1) | 0 | (0.0) |
| Otitis media acute | 0 | (0.0) | 1 | (0.0) |
| Respiratory tract infection | 0 | (0.0) | 1 | (0.0) |
| Rhinitis | 6 | (0.2) | 0 | (0.0) |
| Upper respiratory tract infection | 11 | (0.3) | 2 | (0.1) |
| **Injury, poisoning and procedural complications** | **1** | **(0.0)** | **0** | **(0.0)** |
| Contusion | 1 | (0.0) | 0 | (0.0) |
| **Investigations** | **11** | **(0.3)** | **9** | **(0.4)** |
| Body temperature increased | 11 | (0.3) | 9 | (0.4) |
| **Metabolism and nutrition disorders** | **1,070** | **(29.8)** | **540** | **(26.2)** |
| Decreased appetite[a] | 1,068 | (29.8) | 539 | (26.2) |
| Hyperphagia | 1 | (0.0) | 0 | (0.0) |
| Increased appetite | 5 | (0.1) | 2 | (0.1) |

| | V114 | | PCV13 | |
|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** |
| **Musculoskeletal and connective tissue disorders** | **1** | **(0.0)** | **0** | **(0.0)** |
| Myalgia | 1 | (0.0) | 0 | (0.0) |
| **Nervous system disorders** | **1,741** | **(48.5)** | **942** | **(45.8)** |
| Hyperaesthesia | 1 | (0.0) | 0 | (0.0) |
| Hypersomnia | 0 | (0.0) | 1 | (0.0) |
| Lethargy | 2 | (0.1) | 1 | (0.0) |
| Psychomotor hyperactivity | 1 | (0.0) | 0 | (0.0) |
| Somnolence[a] | 1,741 | (48.5) | 941 | (45.7) |
| **Psychiatric disorders** | **2,436** | **(67.9)** | **1,292** | **(62.8)** |
| Apathy | 0 | (0.0) | 1 | (0.0) |
| Emotional poverty | 1 | (0.0) | 0 | (0.0) |
| Initial insomnia | 0 | (0.0) | 3 | (0.1) |
| Insomnia | 25 | (0.7) | 6 | (0.3) |
| Irritability[a] | 2,431 | (67.7) | 1,292 | (62.8) |
| Listless | 1 | (0.0) | 0 | (0.0) |
| Merycism | 1 | (0.0) | 0 | (0.0) |
| Middle insomnia | 1 | (0.0) | 1 | (0.0) |
| Poor quality sleep | 8 | (0.2) | 0 | (0.0) |
| Restlessness | 6 | (0.2) | 1 | (0.0) |
| Sleep disorder | 5 | (0.1) | 2 | (0.1) |
| Tearfulness | 2 | (0.1) | 0 | (0.0) |
| **Renal and urinary disorders** | **1** | **(0.0)** | **0** | **(0.0)** |
| Urine odour abnormal | 1 | (0.0) | 0 | (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **15** | **(0.4)** | **10** | **(0.5)** |
| Cough | 6 | (0.2) | 2 | (0.1) |
| Dysphonia | 1 | (0.0) | 0 | (0.0) |
| Dyspnoea | 1 | (0.0) | 0 | (0.0) |
| Nasal congestion | 4 | (0.1) | 5 | (0.2) |
| Rhinorrhoea | 5 | (0.1) | 4 | (0.2) |
| Sneezing | 1 | (0.0) | 0 | (0.0) |
| **Skin and subcutaneous tissue disorders** | **122** | **(3.4)** | **64** | **(3.1)** |
| Acne | 1 | (0.0) | 0 | (0.0) |
| Acne infantile | 1 | (0.0) | 0 | (0.0) |
| Dermatitis | 1 | (0.0) | 0 | (0.0) |
| Dermatitis allergic | 0 | (0.0) | 1 | (0.0) |
| Dermatitis atopic | 0 | (0.0) | 1 | (0.0) |
| Dermatitis diaper | 1 | (0.0) | 1 | (0.0) |
| Ecchymosis | 0 | (0.0) | 1 | (0.0) |
| Eczema | 2 | (0.1) | 0 | (0.0) |
| Eczema nummular | 1 | (0.0) | 0 | (0.0) |
| Erythema | 8 | (0.2) | 0 | (0.0) |
| Hyperhidrosis | 1 | (0.0) | 1 | (0.0) |
| Macule | 3 | (0.1) | 1 | (0.0) |
| Pain of skin | 1 | (0.0) | 0 | (0.0) |
| Rash | 24 | (0.7) | 5 | (0.2) |
| Rash erythematous | 4 | (0.1) | 0 | (0.0) |
| Rash macular | 3 | (0.1) | 1 | (0.0) |
| Rash maculo-papular | 0 | (0.0) | 3 | (0.1) |
| Rash papular | 2 | (0.1) | 0 | (0.0) |
| Rash vesicular | 3 | (0.1) | 0 | (0.0) |
| Skin disorder | 1 | (0.0) | 0 | (0.0) |
| Skin warm | 0 | (0.0) | 1 | (0.0) |
| Urticaria[a] | 77 | (2.1) | 50 | (2.4) |
| **Vascular disorders** | **2** | **(0.1)** | **0** | **(0.0)** |
| Cyanosis | 1 | (0.0) | 0 | (0.0) |
| Pallor | 1 | (0.0) | 0 | (0.0) |

Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
[a] Decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following each dose.
Relatedness to study vaccine was determined by the investigator.
For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.
Adverse event terms are reported using MedDRA version 24.0.
Source: Table 5.3.5.3.3-pedspneumo: 53

Body temperature increased

The proportions of participants with maximum body temperature measurements based on the Brighton Collaboration cut points were generally comparable in both intervention groups.

Of the participants with a maximum body temperature ≥38.0°C (100.4°F), the majority had a maximum body temperature <39.0° C (102.2°F). The proportion of participants in each intervention group reporting a maximum body temperature ≥40.0°C (104.0°F) was low (<2%) following any dose, see Table 44.

**Table 44 Analysis of Maximum Temperatures by Brighton Collaboration Cut Points Following Any Dose – V114-025, V114-027, V114-029, V114-031**

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Participants in population | 3,589 | | 2,058 | | |
| without temperature data (Day 1 through Day 7)[b] | 3 | (0.1) | 7 | (0.3) | -0.3 (-0.6, -0.0) |
| with temperature data (Day 1 through Day 7) | 3,586 | (99.9) | 2,051 | (99.7) | 0.3 (0.0, 0.6) |
| **Maximum Temperature (Rectal or Rectal Equivalent)** | | | | | |
| < 100.4 °F (38.0 °C) | 890 | (24.8) | 506 | (24.7) | 0.1 (-2.2, 2.5) |
| ≥ 100.4 °F (38.0 °C) and < 101.3 °F (38.5 °C) | 1,391 | (38.8) | 829 | (40.4) | -1.6 (-4.3, 1.0) |
| ≥ 101.3 °F (38.5 °C) and < 102.2 °F (39.0 °C) | 856 | (23.9) | 464 | (22.6) | 1.2 (-1.1, 3.5) |
| ≥ 102.2 °F (39.0 °C) and < 103.1 °F (39.5 °C) | 269 | (7.5) | 164 | (8.0) | -0.5 (-2.0, 0.9) |
| ≥ 103.1 °F (39.5 °C) and < 104.0 °F (40.0 °C) | 122 | (3.4) | 67 | (3.3) | 0.1 (-0.9, 1.1) |
| ≥ 104.0 °F (40.0 °C) and < 104.9 °F (40.5 °C) | 41 | (1.1) | 16 | (0.8) | 0.4 (-0.2, 0.9) |
| ≥ 104.9 °F (40.5 °C) and < 105.8 °F (41.0 °C) | 10 | (0.3) | 1 | (0.0) | 0.2 (-0.0, 0.5) |
| ≥ 105.8 °F (41.0 °C) | 7 | (0.2) | 4 | (0.2) | 0.0 (-0.3, 0.2) |

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method.
[b] Includes participants whose temperature methods were unreported or unable to be converted to rectal equivalent for Day 1 through Day 7 following any dose.
Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data.
Multiple occurrences of maximum temperature are counted only once. Non-rectal temperatures have been converted to rectal equivalent.
For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.
CI=confidence interval.
Source: Table 5.3.5.3.3-pedspneumo: 120

***CHMP's comment***

Overall, the majority of participants experienced vaccine-related AEs in both intervention groups. The proportion of vaccine-related AEs were comparable between the 2 intervention groups for all SOCs and PTs.

The ADR table in section 4.8 of the SmPC should include all vaccine-related AEs, which is currently not the case for infants and children 6 weeks to less than 2 years. The MAH should include, unless otherwise justified, the following related AEs in section 4.8 of the SmPC: vomiting, rash (pooling different terms when possible), injection-site bruising, insomnia and febrile convulsion.

Single cases of possibly related AEs do not provide a clear signal and do not need to be included in section 4.8 of the SmPC.

The proportion of participants with maximum body temperature measurements based on the Brighton Collaboration cut points were comparable between intervention groups. In addition, the proportion of participants with the maximum body temperature ≥40.0°C (104.0°F) was low (<2%) in both intervention groups.

## Serious adverse event/deaths/other significant events

***SAEs***

The proportion of participants with SAEs after each dose was comparable across the V114 and PCV13 intervention groups in each of the 8 studies included in the submission.

**Table 45 Summary of severe adverse events**

| Study | | All SAEs | | Vaccine-related SAE | |
|---|---|---|---|---|---|
| | | **V114** | **PCV13** | **V114** | **PCV13** |
| V114-008 | | 37/697 (5.3%) | 15/347 (4.3%) | 2/697 (0.3%) | 0/347 (0.0%) |
| V114-023 | | 13/69 (18.8%) | 8/34 (23.5%) | 0/69 (0.0%) | 0/34 (0.0%) |
| V114-024 | 7-11 mo of age | 7/64 (10.9%) | 5/64 (7.8%) | 0/64 (0.0%) | 0/64 (0.0%) |
| | 12-23 mo of age | 4/62 (6.5%) | 4/64 (6.3%) | 0/62 (0.0%) | 0/64 (0.0%) |
| | 2-17 yrs of age | 4/177 (2.3%) | 4/175 (2.3%) | 0/177 (0.0%) | 0/175 (0.0%) |
| V114-025 | | 57/587 (9.7%) | 70/591 (11.8%) | 0/587 (0.0%) | 1/591 (0.2%) |
| V114-027[a] | | 21/179 (11.7%) | 21/179 (11.7%) | 0/179 (0.0%) | 0/179 (0.0%) |
| V114-029 | | 88/858 (10.3%) | 81/855 (9.5%) | 0/858 (0.0%) | 0/855 (0.0%) |
| V114-030[b] | | 3/203 (1.5%) | 3/204 (1.5%) | 0/203 (0.0%) | 0/204 (0.0%) |
| V114-031 | | 192/1965 (9.8%) | 45/433 (10.4%) | 2/1965 (0.1%) | 0/433 (0.0%) |

Mo=months; yrs= years

[a] Only including the participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5)

[b] In both treatment groups 1 SAE was observed after PCV vaccination and 2 SAEs were observed following PPV vaccination.

V114-008

The proportions of participants with SAEs occurring within the 30 days following administration of V114 or PCV13 were low and comparable across intervention groups (Table 45). Overall, bronchiolitis (0.6% and 0.3% of participants in the V114 and PCV13 groups, respectively) and gastroenteritis viral (0.4% and 0.6% of participants in the V114 and PCV13 groups, respectively) were the most frequently reported SAEs.

Two subjects both in the V114 group reported a vaccine-related SAE in this study, see Table 45.

- One participant experienced a vaccine-related SAE of febrile convulsion following vaccination 1. On Day 1, the participant received V114 Lot 2 in addition to diphtheria, tetanus, hepatitis B, acellular pertussis, poliovirus, Hib, and rotavirus vaccines. The investigator considered that all the vaccinations received on Day 1 were possibly related to the event of seizure. The participant was discontinued from the study and the event resolved without sequelae.
- One participant experienced a vaccine-related SAE of purpura following vaccination 4. The participant received the fourth dose of V114 Lot 2 on Day 311, and on Day 312 the participant experienced purpura involving the ankles, hands, arms, and ears. The investigator considered that the event of purpura was related to study vaccine, and potentially related to meningococcal C conjugated vaccine, and measles, mumps and rubella vaccine all received on Day 311. Purpura resolved on Day 319 without sequelae

V114-023

The proportion of participants with SAEs was comparable across intervention groups (Table 45). The most frequently reported SAE was sickle cell anaemia with crisis, and no SAEs were considered by the investigator to be vaccine-related (Table 45).

V114-024

The proportion of participants with SAEs was comparable across intervention groups (Table 45). Gastroenteritis was the only SAE reported for >1 participant in a study intervention group (2 participants, 7 to 11 months of age in the V114 group). No SAE was considered to be related to study intervention (Table 45).

V114-025

The proportions of participants with SAEs occurring within the 30 days following administration of V114 or PCV13 were low and comparable across intervention groups (Table 45). Approximately 10% of the participants reported an SAE; overall, bronchiolitis (1.5% and 1.7% of participants in the V114 and PCV13 groups, respectively) and respiratory syncytial virus bronchiolitis (1.4% and 0.8% of participants in the V114 and PCV13 groups, respectively) were the most frequently reported SAEs. No participant discontinued due to an SAE.

One subject in the PCV13 group reported a vaccine-related SAE in this study, see Table 45.

- One participant experienced a vaccine-related SAE of pyrexia following vaccination 1. The participant was afebrile from Day 3 and pyrexia was considered resolved. The investigator considered the event of pyrexia related to the study vaccination.

V114-027

The proportions of participants with SAEs were comparable across intervention groups (Table 45). Bronchiolitis (26 participants) and respiratory syncytial virus bronchiolitis (11 participants) were the most commonly reported SAEs overall.

One participant (Group 3: PCV13, PCV13, V114 and V114) had an SAE (epilepsy) considered to be related to study intervention (following Dose 2, PCV13 and concomitant vaccinations).

- On Day 77 (Day 1 Postvaccination 2), the participant 0091-108486 developed focal to generalized tonic-clonic seizures and was taken to the hospital and treated with IV diazepam and levetiracetam. The seizure stopped after approximately 20 minutes. On Day 124 (Postvaccination 1, Day 48 Postvaccination 2) the result of the gene mutation blood test showed the presence of a likely pathogenic missense sodium voltage-gated channel alpha subunit 1 variant, heterogenous c.1277A>G (p.Tyr426Cys), which was consistent with a diagnosis of severe myoclonic epilepsy in infancy (Dravet syndrome).

V114-029

The proportion of participants with SAEs was comparable across intervention groups (Table 45). Respiratory syncytial virus bronchiolitis (19 [1.1%] participants), gastroenteritis (18 [1.0%] participants), and bronchiolitis (17 [1.0%] participants) were the top 3 most frequently reported SAEs overall. None of the SAEs were assessed by the investigator to be related to study intervention (Table 45).

V114-030

The proportion of participants with SAEs was comparable across intervention groups (Table 45). None of the SAEs were assessed by the investigator to be related to study intervention (Table 45).

V114-031

The proportions of participants with SAEs were generally comparable between intervention groups (Table 45). Approximately 10% of the participants reported an SAE; bronchiolitis (<2%) and pneumonia (<1%) were the most commonly reported SAEs overall.

Two participants (V114 group) reported SAEs (both were events of pyrexia) that were considered by the investigator to be related to study vaccine, had durations of 3 days, and were resolved. Of these, one participant reported a maximum body temperature of 100.4°F (38.0°C, event considered mild in intensity), with onset on the day of vaccination with Dose 1; concomitant vaccines included RotaTeq (rotavirus), Pentaxim (DTaP-IPV-HepB), and HIBERIX (Hib). The other participant reported a maximum body temperature of 102.9°F (39.4°C, event considered moderate in intensity), with onset on the day of vaccination with Dose 3; concomitant vaccines included DTwP-Hib-HB-and OPV.

***CHMP's comment***

Overall, the proportions of participants with SAEs were comparable across intervention groups and the majority of SAEs were in the SOC Infections and Infestations. Very few SAEs were considered related to the vaccine, which is agreed.

In addition, several observations of the assessment of relatedness to the vaccine were not followed with regards to PCV13.

In study V114-027 it is questioned why the SAE of epilepsy was assessed as related to the vaccine, since a gene mutation blood test showed the presence of a likely pathogenic missense sodium voltage-gated channel alpha subunit 1 variant, heterogenous c.1277A>G (p.Tyr426Cys), which was consistent with a diagnosis of severe myoclonic epilepsy in infancy (Dravet syndrome).

During study V114-029 participants 0053-246077 and 0164-245152, both in the PCV13 group, experienced the SAE of pyrexia on Day 24 and Day 10 respectively after treatment 1. As no cause for the fever was determined, the assessment of the investigator that the pyrexia was not related to the vaccine is questioned.

However, considering the fact that it involves PCV13, the issues are not further pursued as it is not considered relevant for the current procedure.

***Deaths***

Five participant deaths were reported in the 8 studies. None of the deaths were considered by the investigator to be related to study vaccine.

Three participants who had received V114 had the following AEs resulting in death: congenital heart disease (V114-029), craniocerebral injury after a car accident (V114-031), and unknown cause of death (V114-008).

Two participants who had received PCV13 had the following AEs resulting in death: head injury and septic shock (V114-029) and cardiorespiratory arrest (sudden unexplained infant death) (V114-031).

***CHMP's comment***

It can be agreed that the number of deaths in the 8 studies is low and comparable between study interventions, as in the V114 group 3 out of 5366 participants (0.06%) died and 2 out of 3491 participants (0.06%) in the PCV13 group.

Narratives of participants who died were reviewed and no indication of a causal relationship to the vaccine could be identified. There is limited information available on 1 death due to unknown cause during study V114-008, therefore causality cannot be formally excluded however is deemed unlikely. One 8-week old female participant from the study V114-008 died on Day 19 post-vaccination. An autopsy was performed, which concluded that the cause and manner of death remained undetermined,

although environmental factors were cited. It mentioned that the risk of sudden death increases when an infant is placed in an unsafe sleep environment, such as an adult bed. Additional information is not available, therefore, no further assessment can be made.

## Laboratory findings

Clinical laboratory evaluations were not conducted for the studies included in this submission.

## Safety in special populations

### *Sex, Race and Ethnicity*

Safety results observed in the integrated population for both male and female subgroups were generally consistent with the overall population (data not shown).

Safety results observed in the integrated population within the race subgroups analysed (Asian, multiple, white) are presented in Table 46. Injection-site AEs, systemic AEs, and vaccine-related AEs were reported for a lower proportion of Asian participants compared with white and multiple race participants in both intervention groups. Higher proportions of participant with SAEs were reported among Asian participants in both intervention groups.

**Table 46 Adverse Event Summary by race – V114-025, V114-027, V114-029 and V114-031**

| | Asian | | | | Multiple | | | | White | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V114 | | PCV13 | | V114 | | PCV13 | | V114 | | PCV13 | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 991 | | 417 | | 285 | | 137 | | 2,108 | | 1,377 | |
| with one or more AEs | 863 | (87.1) | 359 | (86.1) | 270 | (94.7) | 127 | (92.7) | 2,037 | (96.6) | 1,311 | (95.2) |
| injection-site | 508 | (51.3) | 190 | (45.6) | 207 | (72.6) | 93 | (67.9) | 1,629 | (77.3) | 1,013 | (73.6) |
| systemic | 818 | (82.5) | 345 | (82.7) | 265 | (93.0) | 123 | (89.8) | 1,996 | (94.7) | 1,267 | (92.0) |
| with no AE | 128 | (12.9) | 58 | (13.9) | 15 | (5.3) | 10 | (7.3) | 71 | (3.4) | 66 | (4.8) |
| with vaccine-related[a] AEs | 789 | (79.6) | 326 | (78.2) | 259 | (90.9) | 116 | (84.7) | 1,978 | (93.8) | 1,246 | (90.5) |
| injection-site | 507 | (51.2) | 190 | (45.6) | 207 | (72.6) | 93 | (67.9) | 1,627 | (77.2) | 1,011 | (73.4) |
| systemic | 690 | (69.6) | 298 | (71.5) | 212 | (74.4) | 83 | (60.6) | 1,824 | (86.5) | 1,096 | (79.6) |
| with SAEs | 165 | (16.6) | 65 | (15.6) | 28 | (9.8) | 17 | (12.4) | 157 | (7.4) | 129 | (9.4) |
| with vaccine-related SAEs | 1 | (0.1) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) |
| who died | 0 | (0.0) | 1 | (0.2) | 1 | (0.4) | 0 | (0.0) | 1 | (0.0) | 0 | (0.0) |
| discontinued vaccine due to an AE | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued vaccine due to a vaccine-related AE | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued vaccine due to a SAE | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued vaccine due to a vaccine- related SAE | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

AE=adverse event; SAE=serious adverse event
[a] Determined by the investigator to be related to the vaccine.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.

Safety results observed in the integrated population for participants of Hispanic and Latino ethnicity and for participants not of Hispanic and Latino ethnicity were generally consistent with the overall population (data not shown).

***CHMP's comment***

Overall, the safety profile in the subgroups of sex, race and ethnicity were similar to the safety profile in the entire population and no new safety signals are observed.

In the integrated analysis, no clear trends were observed with respect to reactogenicity between males and females in the V114 group. Interestingly, in participants with SCD and HIV, reactogenicity appears to be slightly higher in females compared to males in the V114 group. However, considering the small differences, no impact is expected.

A trend towards higher reactogenicity in White subjects was observed for both intervention groups compared to Asian and multiple race participants. In participants with multiple race, V114 was considered more reactogenic compared to PCV13. However, these results do not give rise to concern.

In the integrated analysis, no clear trends were observed with respect to reactogenicity between the ethnic subgroups.

Upon request the MAH presented the safety results per sex, race and ethnicity for study V114-008. The results were generally in line with the safety profile seen in the integrated safety population.

***Pre-term***

A total of 221 preterm infants (<37 weeks gestational age at birth) received ≥1 dose of V114 and 234 preterm infants received ≥1 dose of PCV13, see Table 47.

**Table 47 Number of preterm infants who received ≥1 dose of PCV**

| Population | Study Number | V114 | PCV13 |
|---|---|---|---|
| Healthy infants receiving PCV per recommended immunization regimens starting at ~2 months of age | V114-025 | 32 | 36 |
| | V114-027[a] | 64 | 74 |
| | V114-029 | 74 | 76 |
| | V114-031 | 51 | 48 |
| Overall population | Total: | 221 | 234 |
| Participants were counted once for each column according to the intervention they actually received.<br>[a] A total number of 47 participants in Study V114-027 in groups 2, 3 and 4 received both V114 and PCV13 per study design and were included in both intervention groups.<br>PCV=Pneumococcal Conjugate Vaccine (V114 or PCV13). | | | |

Demographic characteristics in the preterm population were generally comparable in both intervention groups. The median age was 8.0 weeks (range: 6 to 12 weeks) in the V114 group compared to 9.0 weeks in the PCV13 group (range: 6 to 12 weeks. The proportion of male participants was higher in the both treatment groups compared to females. The population was diverse with regard to race, with the majority being white and not Hispanic or Latino for the majority of participants. Approximately 34% of participants were from Europe.

Adverse events

The proportions of participants with AEs, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs, after each dose in the primary series, after the toddler dose, and after any dose, see Table 48, were generally comparable in both intervention groups.

**Table 48 Analysis of Adverse Event Summary (APaT) following any dose – Pre-term infants (V114-025, V114-027, V114-029, V114-031)**

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Participants in population | 174 | | 180 | | |
| With one or more adverse events | 167 | (96.0) | 171 | (95.0) | 1.0 (-3.7, 5.7) |
| injection-site | 129 | (74.1) | 125 | (69.4) | |
| systemic | 164 | (94.3) | 167 | (92.8) | |
| With no adverse event | 7 | (4.0) | 9 | (5.0) | |
| With vaccine-related[b] adverse events | 160 | (92.0) | 161 | (89.4) | 2.5 (-3.7, 8.8) |
| injection-site | 129 | (74.1) | 124 | (68.9) | |
| systemic | 141 | (81.0) | 144 | (80.0) | |
| With serious adverse events | 26 | (14.9) | 26 | (14.4) | 0.5 (-7.0, 8.0) |
| With serious vaccine-related adverse events | 0 | (0.0) | 0 | (0.0) | 0.0 (-2.1, 2.2) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0.0 (-2.1, 2.2) |
| Discontinued vaccine due to an adverse event | 0 | (0.0) | 0 | (0.0) | 0.0 (-2.1, 2.2) |
| Discontinued vaccine due to a vaccine- related adverse event | 0 | (0.0) | 0 | (0.0) | |
| Discontinued vaccine due to a serious adverse event | 0 | (0.0) | 0 | (0.0) | |
| Discontinued vaccine due to a serious vaccine-related adverse event | 0 | (0.0) | 0 | (0.0) | |

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the integrated statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
CI=confidence interval.
Source: Table 5.3.5.3.3-pedspneumo: 12

Common AEs

The most commonly reported AEs with an incidence of ≥1% in either treatment group are presented in Table 49. The proportions of participants with specific AEs by SOC and PT after any dose were generally comparable in both intervention groups.

## Table 49 Analysis of Participants With Adverse Events Incidence ≥ 1% in One or More Vaccination Groups Following Any Dose – Preterm Infants (V114-025, V114-027, V114-029, V114-031)

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Participants in population | 174 | | 180 | | |
| with one or more adverse events | 167 | (96.0) | 171 | (95.0) | 1.0 (-3.7, 5.7) |
| with no adverse events | 7 | (4.0) | 9 | (5.0) | -1.0 (-5.7, 3.7) |
| **Ear and labyrinth disorders** | **0** | **(0.0)** | **2** | **(1.1)** | **-1.1 (-4.0, 1.1)** |
| **Eye disorders** | **0** | **(0.0)** | **3** | **(1.7)** | **-1.7 (-4.8, 0.5)** |
| Eye discharge | 0 | (0.0) | 3 | (1.7) | -1.7 (-4.8, 0.5) |
| **Gastrointestinal disorders** | **42** | **(24.1)** | **47** | **(26.1)** | **-2.0 (-11.0, 7.1)** |
| Abnormal faeces | 2 | (1.1) | 0 | (0.0) | 1.1 (-1.0, 4.1) |
| Constipation | 4 | (2.3) | 9 | (5.0) | -2.7 (-7.2, 1.4) |
| Diarrhoea | 15 | (8.6) | 22 | (12.2) | -3.6 (-10.2, 2.9) |
| Flatulence | 1 | (0.6) | 6 | (3.3) | -2.8 (-6.6, 0.2) |
| Frequent bowel movements | 0 | (0.0) | 2 | (1.1) | -1.1 (-4.0, 1.1) |
| Gastrooesophageal reflux disease | 5 | (2.9) | 1 | (0.6) | 2.3 (-0.5, 6.1) |
| Infantile colic | 4 | (2.3) | 1 | (0.6) | 1.7 (-1.0, 5.3) |
| Infantile spitting up | 2 | (1.1) | 1 | (0.6) | 0.6 (-2.0, 3.6) |
| Regurgitation | 3 | (1.7) | 1 | (0.6) | 1.2 (-1.5, 4.5) |
| Teething | 2 | (1.1) | 2 | (1.1) | 0.0 (-2.9, 3.1) |
| Vomiting | 13 | (7.5) | 10 | (5.6) | 1.9 (-3.4, 7.5) |
| **General disorders and administration site conditions** | **145** | **(83.3)** | **147** | **(81.7)** | **1.7 (-6.4, 9.7)** |
| Crying | 2 | (1.1) | 1 | (0.6) | 0.6 (-2.0, 3.6) |
| Injection site bruising | 1 | (0.6) | 3 | (1.7) | -1.1 (-4.3, 1.7) |
| Injection site erythema[b] | 76 | (43.7) | 71 | (39.4) | 4.2 (-6.0, 14.4) |
| Injection site induration[b] | 44 | (25.3) | 53 | (29.4) | -4.2 (-13.4, 5.2) |
| Injection site pain[b] | 87 | (50.0) | 90 | (50.0) | 0.0 (-10.4, 10.4) |
| Injection site swelling[b] | 48 | (27.6) | 50 | (27.8) | -0.2 (-9.5, 9.2) |
| Injection site urticaria | 1 | (0.6) | 4 | (2.2) | -1.6 (-5.1, 1.2) |
| Injection site warmth | 2 | (1.1) | 1 | (0.6) | 0.6 (-2.0, 3.6) |
| Pyrexia | 65 | (37.4) | 85 | (47.2) | -9.9 (-20.0, 0.4) |
| **Infections and infestations** | **55** | **(31.6)** | **50** | **(27.8)** | **3.8 (-5.7, 13.3)** |
| Bronchiolitis | 13 | (7.5) | 11 | (6.1) | 1.4 (-4.1, 7.0) |
| Bronchitis | 0 | (0.0) | 2 | (1.1) | -1.1 (-4.0, 1.1) |
| Conjunctivitis | 2 | (1.1) | 2 | (1.1) | 0.0 (-2.9, 3.1) |
| Conjunctivitis bacterial | 2 | (1.1) | 0 | (0.0) | 1.1 (-1.0, 4.1) |
| Croup infectious | 0 | (0.0) | 2 | (1.1) | -1.1 (-4.0, 1.1) |
| Ear infection | 3 | (1.7) | 0 | (0.0) | 1.7 (-0.4, 5.0) |
| Exanthema subitum | 2 | (1.1) | 1 | (0.6) | 0.6 (-2.0, 3.6) |
| Gastroenteritis | 2 | (1.1) | 1 | (0.6) | 0.6 (-2.0, 3.6) |
| Nasopharyngitis | 10 | (5.7) | 4 | (2.2) | 3.5 (-0.6, 8.3) |
| Otitis media | 2 | (1.1) | 6 | (3.3) | -2.2 (-6.1, 1.2) |
| Otitis media acute | 4 | (2.3) | 2 | (1.1) | 1.2 (-1.9, 4.8) |
| Pneumonia | 6 | (3.4) | 0 | (0.0) | 3.4 (1.3, 7.3) |
| RSV bronchiolitis | 2 | (1.1) | 4 | (2.2) | -1.1 (-4.6, 2.1) |
| RSV infection | 3 | (1.7) | 3 | (1.7) | 0.1 (-3.3, 3.5) |
| Rhinitis | 4 | (2.3) | 6 | (3.3) | -1.0 (-5.1, 2.8) |
| Upper respiratory tract infection | 15 | (8.6) | 11 | (6.1) | 2.5 (-3.1, 8.3) |
| Viral upper respiratory tract infection | 1 | (0.6) | 2 | (1.1) | -0.5 (-3.5, 2.2) |
| **Injury, poisoning and procedural complications** | **3** | **(1.7)** | **3** | **(1.7)** | **0.1 (-3.3, 3.5)** |
| **Investigations** | **0** | **(0.0)** | **3** | **(1.7)** | **-1.7 (-4.8, 0.5)** |
| Body temperature increased | 0 | (0.0) | 3 | (1.7) | -1.7 (-4.8, 0.5) |
| **Metabolism and nutrition disorders** | **67** | **(38.5)** | **69** | **(38.3)** | **0.2 (-9.9, 10.3)** |
| Decreased appetite[b] | 66 | (37.9) | 69 | (38.3) | -0.4 (-10.5, 9.7) |
| **Nervous system disorders** | **110** | **(63.2)** | **106** | **(58.9)** | **4.3 (-5.8, 14.4)** |
| Febrile convulsion | 2 | (1.1) | 0 | (0.0) | 1.1 (-1.0, 4.1) |
| Somnolence[b] | 110 | (63.2) | 104 | (57.8) | 5.4 (-4.8, 15.5) |
| **Psychiatric disorders** | **135** | **(77.6)** | **133** | **(73.9)** | **3.7 (-5.3, 12.6)** |
| Insomnia | 1 | (0.6) | 2 | (1.1) | -0.5 (-3.5, 2.2) |
| Irritability[b] | 135 | (77.6) | 133 | (73.9) | 3.7 (-5.3, 12.6) |
| **Respiratory, thoracic and mediastinal disorders** | **22** | **(12.6)** | **28** | **(15.6)** | **-2.9 (-10.3, 4.5)** |
| Bronchial hyperreactivity | 2 | (1.1) | 0 | (0.0) | 1.1 (-1.0, 4.1) |
| Bronchospasm | 0 | (0.0) | 2 | (1.1) | -1.1 (-4.0, 1.1) |
| Cough | 8 | (4.6) | 18 | (10.0) | -5.4 (-11.2, 0.0) |

| | V114 | | PCV13 | | Difference in % vs PCV13 |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | Estimate (95% CI)[a] |
| Nasal congestion | 6 | (3.4) | 11 | (6.1) | -2.7 (-7.6, 2.0) |
| Rhinorrhoea | 5 | (2.9) | 5 | (2.8) | 0.1 (-3.8, 4.1) |
| Sneezing | 3 | (1.7) | 0 | (0.0) | 1.7 (-0.4, 5.0) |
| **Skin and subcutaneous tissue disorders** | **22** | **(12.6)** | **16** | **(8.9)** | **3.8 (-2.8, 10.5)** |
| Dermatitis diaper | 1 | (0.6) | 3 | (1.7) | -1.1 (-4.3, 1.7) |
| Eczema | 0 | (0.0) | 2 | (1.1) | -1.1 (-4.0, 1.1) |
| Erythema | 3 | (1.7) | 2 | (1.1) | 0.6 (-2.4, 4.0) |
| Miliaria | 2 | (1.1) | 0 | (0.0) | 1.1 (-1.0, 4.1) |
| Rash | 5 | (2.9) | 3 | (1.7) | 1.2 (-2.3, 5.1) |
| Urticaria[b] | 8 | (4.6) | 6 | (3.3) | 1.3 (-3.1, 5.9) |

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method. Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Reported adverse events include nonserious adverse events that occurred within 14 days of any dose and serious adverse events that occurred after dose 1 through completion of study participation.
[b] Injection site erythema, injection site induration, injection site pain, injection site swelling, decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following each dose.
For V114-027, only participants who were randomized to the complete dosing schedule of Prevnar 13™ (Group 1) or V114 (Group 5) are included.
Adverse event terms are reported using MedDRA version 24.0.
CI=confidence interval; RSV= respiratory syncytial virus

A rainfall plot of AEs after any dose with an incidence of ≥5% in either treatment groups is presented in Figure 22.

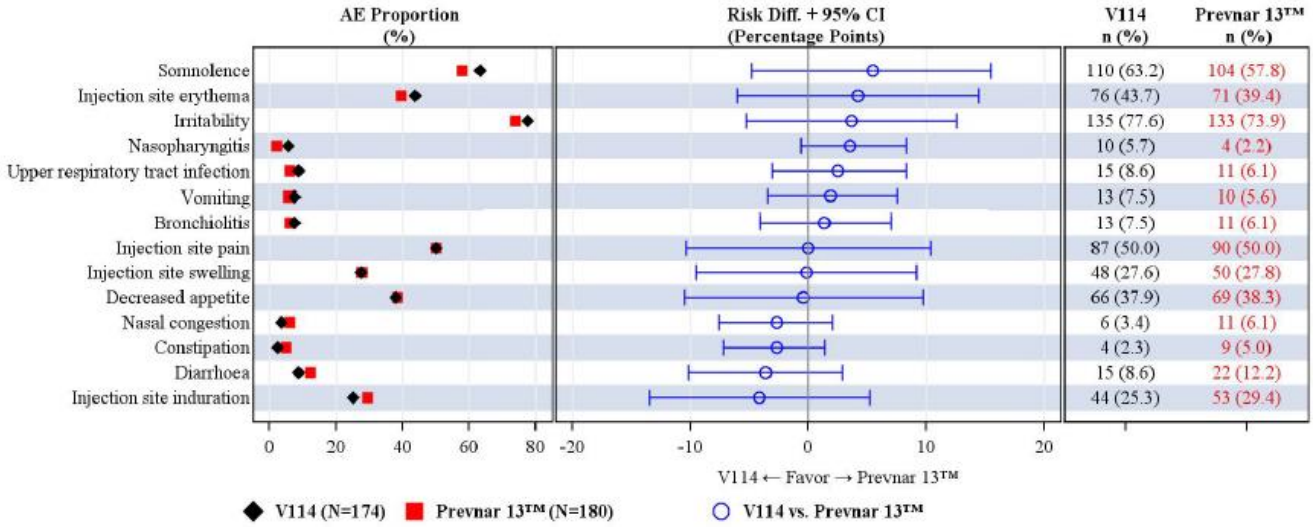



**Figure 22 Rainfall Plot of Adverse Events occurring ≥5% in either treatment group following any dose – Preterm Infants (V114-025, V114-027, V114-029, V114-031) (Source: Figure 5.3.5.3.3-pedspneumo: 10)**

The proportions of participants with AEs (solicited and unsolicited) by maximum intensity were generally comparable in both intervention groups after each dose. Of the participants with AEs graded by intensity, the majority experienced AEs with a maximum intensity of mild to moderate in both intervention groups.

The proportions of preterm infants with injection-site erythema, induration, or swelling by maximum size after each dose were generally comparable in both intervention groups. Of the participants with solicited AEs, the majority had events of short duration (≤3 days).

Vaccine-related AEs

The proportions of participants with injection-site AEs (solicited and unsolicited) and vaccine-related systemic AEs (solicited and unsolicited) after each dose in the primary series, after the toddler dose, and after any dose were generally comparable in both intervention groups.

Nearly all injection-site AEs in both intervention groups were considered by the investigator to be vaccine related. The most frequently reported (≥1%) vaccine-related injection-site AEs after any dose of V114 were the solicited injection-site AEs (injection-site pain, injection-site erythema, injection-site swelling, and injection-site induration).

The most frequently reported (≥1%) vaccine-related systemic AEs after each dose of V114 in preterm infants were the solicited systemic AEs (irritability, somnolence, and decreased appetite) and the unsolicited AEs of pyrexia, diarrhoea (following Dose 3 of the primary series), and vomiting (following Dose 1 of the primary series).

The proportions of preterm infants with maximum body temperature measurements based on the Brighton Collaboration cut points after each dose in the primary series, after the toddler dose, and after any dose were generally comparable in both intervention groups. The proportion of preterm infants in each intervention group reporting a maximum body temperature ≥40.0°C (104.0°F) was low (<2%) following any dose

Serious adverse event/death

The proportions of participants with SAEs reported after any dose were generally comparable in both intervention groups. SAEs were reported across multiple SOCs and most frequently in the Infections and Infestations SOC. No SAEs were considered by the investigator to be related to study intervention.

There were no deaths reported for preterm infants in the integrated population.

*AE of special interest*

No AEs or SAEs of apnea (preferred terms: apnea, apneic attack, breath holding, or sleep apnea syndrome) were reported in the integrated preterm population within the protocol-specified reporting periods.

***CHMP's comment***

In total 211 pre-term infants were exposed to V114. The pre-term infants were part of the healthy infant population described above. The safety database of 221 pre-term infants is considered limited, but sufficient to determine the safety profile as it can be compared to the safety profile in the healthy infants.

The safety profile in preterm infants was largely comparable to the safety profile as seen for the healthy infants. In line with the results for the healthy participants, the vast majority of participants experienced at least 1 AE in both treatment arms, of which the majority experienced at least 1 vaccine-related AE. The majority of AEs was mild to moderate in intensity. The most frequently reported AEs were identical in the preterm infants as compared to the total population, with the most frequently reported AEs being pyrexia, injection-site pain, injection-site erythema, injection-site induration, injection site swelling, irritability, somnolence and decreased appetite. Vaccine-related AEs were also comparable between both treatment groups and preterm infants and total population. The proportion of participants with maximum body temperature measurements based on the Brighton Collaboration cut points were comparable between intervention groups and total healthy infant population.

There was a slight numerical increase in the percentage of participants who experienced at least 1 AE in both treatment arms, indicating a slight increase in reactogenicity in preterm infants.

The percentage of participants experiencing SAEs was comparable between the treatment arms. None of the SAEs was considered related to the vaccine.

Apnea is considered a risk after intramuscular injection of vaccines in preterm infants. No AEs or SAEs related to apnea were observed during the studies. Considering the fact that only 221 preterm infants were included in the studies, it is appreciated that a warning is in place in section 4.4 of the SmPC.

***Sickle cell disease***

The proportions of participants with AEs, including injection-site AEs, systemic AEs, and SAEs, were generally comparable in both intervention groups Table 50. No vaccine-related SAEs, deaths, or discontinuations from study intervention due to AEs were reported.

**Table 50 Summary of Adverse Events - V114-023**

| | V114 | | | PCV13 | | |
|---|---|---|---|---|---|---|
| | n | (%) | 95% CI[b] | n | (%) | 95% CI[b] |
| Participants in population | 69 | | | 34 | | |
| with one or more AEs | 56 | (81.2) | (69.9, 89.6) | 27 | (79.4) | (62.1, 91.3) |
| injection-site | 48 | (69.6) | | 26 | (76.5) | |
| systemic | 42 | (60.9) | | 19 | (55.9) | |
| with no AE | 13 | (18.8) | | 7 | (20.6) | |
| with vaccine-related[a] AEs | 51 | (73.9) | (61.9, 83.7) | 26 | (76.5) | (58.8, 89.3) |
| injection-site | 48 | (69.6) | | 26 | (76.5) | |
| systemic | 28 | (40.6) | | 7 | (20.6) | |
| with SAE | 13 | (18.8) | (10.4, 30.1) | 8 | (23.5) | (10.7, 41.2) |
| with vaccine-related SAEs | 0 | (0.0) | (0.0, 5.2) | 0 | (0.0) | (0.0, 10.3) |
| who died | 0 | (0.0) | (0.0, 5.2) | 0 | (0.0) | (0.0, 10.3) |

[a] Determined by the investigator to be related to the vaccine.
[b] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through completion of study participation.
AE= adverse event; CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or PCV13); SAE=serious adverse event.

The most frequently reported AEs in both groups were solicited injection-site and systemic events. The five (5) most commonly reported AEs in each group were injection site pain, injection site swelling, headache, myalgia, and fatigue.

**Table 51 Participants With Adverse Events by Descending Frequency in the V114 Group (Incidence ⩾ 5% in One or More Vaccination Groups) – V114-023**

| | V114 | | PCV13 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Participants in population | 69 | | 34 | |
| with one or more adverse events | 56 | (81.2) | 27 | (79.4) |
| with no adverse events | 13 | (18.8) | 7 | (20.6) |
| | | | | |
| Injection site pain[a] | 42 | (60.9) | 23 | (67.6) |
| Injection site swelling[a] | 19 | (27.5) | 12 | (35.3) |
| Headache[a] | 17 | (24.6) | 6 | (17.6) |
| Myalgia[a] | 16 | (23.2) | 4 | (11.8) |
| Fatigue[a] | 9 | (13.0) | 7 | (20.6) |
| Sickle cell anaemia with crisis | 7 | (10.1) | 6 | (17.6) |

| | | | | |
|---|---|---|---|---|
| Injection site induration[a] | 6 | (8.7) | 3 | (8.8) |
| Back pain | 4 | (5.8) | 1 | (2.9) |
| Pyrexia | 4 | (5.8) | 1 | (2.9) |
| Injection site erythema[a] | 3 | (4.3) | 2 | (5.9) |
| Arthralgia[a] | 2 | (2.9) | 3 | (8.8) |

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through completion of study participation.
[a] Injection site erythema, injection site induration, injection site pain, injection site swelling, arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.
MedDRA version 23.1 was used in the reporting of this study. PCV=pneumococcal conjugate vaccine (V114 or PCV13).

All injection-site AEs were considered vaccine-related.

The proportions of participants with vaccine-related solicited systemic AEs were generally comparable across intervention groups with the exception of myalgia, which was reported more frequently for participants in the V114 group compared with the PCV13 group.

**Table 52 Participants With Systemic Adverse Events Related to Study Vaccine (Incidence > 0% in One or More Vaccination Groups) – V114-023**

| | **V114** | | **PCV13** | |
|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** |
| Participants in population | 69 | | 34 | |
| with one or more systemic AEs related to study vaccine | 28 | (40.6) | 7 | (20.6) |
| with no systemic AEs related to study vaccine | 41 | (59.4) | 27 | (79.4) |
| **Gastrointestinal disorders** | **3** | **(4.3)** | **1** | **(2.9)** |
| Abdominal pain upper | 0 | (0.0) | 1 | (2.9) |
| Nausea | 1 | (1.4) | 0 | (0.0) |
| Vomiting | 2 | (2.9) | 1 | (2.9) |
| **General disorders and administration site conditions** | **12** | **(17.4)** | **6** | **(17.6)** |
| Axillary pain | 0 | (0.0) | 1 | (2.9) |
| Fatigue[a] | 8 | (11.6) | 5 | (14.7) |
| Pyrexia | 4 | (5.8) | 1 | (2.9) |
| **Musculoskeletal and connective tissue disorders** | **14** | **(20.3)** | **3** | **(8.8)** |
| Arthralgia[a] | 1 | (1.4) | 1 | (2.9) |
| Myalgia[a] | 14 | (20.3) | 2 | (5.9) |
| **Nervous system disorders** | **12** | **(17.4)** | **3** | **(8.8)** |
| Headache[a] | 12 | (17.4) | 3 | (8.8) |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **(1.4)** | **0** | **(0.0)** |
| Throat irritation | 1 | (1.4) | 0 | (0.0) |
| **Skin and subcutaneous tissue disorders** | **1** | **(1.4)** | **1** | **(2.9)** |
| Rash | 1 | (1.4) | 0 | (0.0) |
| Urticaria[a] | 0 | (0.0) | 1 | (2.9) |

Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through completion of study participation.
[a] Arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.
Relatedness to study vaccine was determined by the investigator. MedDRA version 23.1 was used in the reporting of this study.
PCV=pneumococcal conjugate vaccine (V114 or PCV13).

Of the participants with solicited AEs graded by intensity, the majority of participants experienced solicited AEs with a maximum intensity of mild or moderate in both intervention groups.

***CHMP's comment***

The safety of V114 was evaluated in study V114-023, in which children 5 through 17 years of age with SCD were exposed to V114 (69 children) or PCV13 (34 children).

In both intervention groups the majority of participants experienced at least 1 or more AEs and even 1 or more vaccine-related AEs. Vaccine-related injection-site AEs were experienced by the majority of participants in both treatment groups, with the proportion being slightly lower in the V114 group

compared to the PCV13 group; 69.6% vs 76.5% respectively. The most commonly reported AEs in both treatment groups were injection site pain and injection-site swelling.

Vaccine-related systemic AEs were more commonly reported in the V114 group compared to the PCV13 group: 40.6% vs 20.6%. This difference was mainly driven by myalgia, which was reported for 20.3% of participants in the V114 group compared to 5.9% in the PCV13 group. The most commonly reported systemic AEs were myalgia, headache and fatigue in both treatment groups, though in different proportions, with in the V114 group 20.3% of participants experienced myalgia, 17.4% headache and 11.6% fatigue, while in the PCV13 group 14.7% of participants experienced fatigue, 8.8% headache and 5.9% myalgia.

A slight difference was observed between the sex subgroups in the V114 group, with V114 being more reactogenic in females compared to males. Due to small numbers no firm conclusions can be drawn. Due to small numbers no comparison between race or ethnic subgroups can be made, as only 1 subgroup met predefined criteria of at least 5% of population for both race and ethnic subgroups.

Black or African American participants reported higher frequencies of systemic vaccine-related AEs after V114 compared to PCV13 (43.2% vs 16.0%). Similar tendencies were also observed for Hispanic or Latino participants who reported higher vaccine-related systemic AEs after V114 compared to Prevenar 13 (38.6% vs 25.0%). These differences have not been observed in the general healthy population. Due to the small sample size no firm conclusions can be drawn.

In the 5 to 9 year old population, the proportion of participants experiencing injection-site AEs was higher compared to the 10-14 year old population, while the proportion of participants experiencing systemic AEs was lower. The proportion of participants with SAEs was higher in the 5 to 9 year old population compared to 10-14 year olds. However, again the subgroups are small, making firm conclusions difficult.

The safety profile in children with SCD was largely comparable to the safety profile as seen for the healthy infants. The most commonly reported AEs were injection-site pain and injection site swelling. Vaccine-related systemic AEs were more commonly reported in the V114 group compared to the PCV13 group, with the difference being driven by more frequently reported myalgia. No new safety signals were identified.

***HIV-1 infected subjects***

The proportions of participants with 1 or more AEs were generally comparable in both intervention groups. Vaccine-related injection-site and systemic AEs were reported for a higher proportion of participants in the V114 group following vaccination with PCV.

AEs were reported for the majority (>69%) of participants in both intervention groups. One participant in the V114 group and 1 participant in the PCV13 group experienced 1 or more SAEs; no SAEs were considered to be vaccine-related, Table 53. No deaths were reported during the study.

### Table 53 Summary of Adverse Events – V114-030

| | V114 | | | PCV13 | | |
|---|---|---|---|---|---|---|
| | n | (%) | (95% CI)[a] | n | (%) | (95% CI)[a] |
| Participants in population | 203 | | | 204 | | |
| with one or more AEs | 160 | (78.8) | (72.5, 84.2) | 142 | (69.6) | (62.8, 75.8) |
| Injection-site | 145 | (71.4) | | 122 | (59.8) | |
| systemic | 107 | (52.7) | | 90 | (44.1) | |
| with no adverse event | 43 | (21.2) | | 62 | (30.4) | |
| with vaccine-related[b] AEs | 159 | (78.3) | (72.0, 83.8) | 137 | (67.2) | (60.3, 73.6) |
| Injection-site | 145 | (71.4) | | 122 | (59.8) | |
| Systemic | 97 | (47.8) | | 77 | (37.7) | |
| with SAEs | 1 | (0.5) | (0.0, 2.7) | 1 | (0.5) | (0.0, 2.7) |
| with vaccine-related SAEs | 0 | (0.0) | (0.0, 1.8) | 0 | (0.0) | (0.0, 1.8) |
| who died | 0 | (0.0) | (0.0, 1.8) | 0 | (0.0) | (0.0, 1.8) |
| discontinued vaccine due to an AE | 0 | (0.0) | (0.0, 1.8) | 1 | (0.5) | (0.0, 2.7) |
| discontinued vaccine due to a vaccine- related AE | 0 | (0.0) | | 1 | (0.5) | |
| discontinued vaccine due to a SAE | 0 | (0.0) | | 0 | (0.0) | |
| discontinued vaccine due to a vaccine-related SAE | 0 | (0.0) | | 0 | (0.0) | |

[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through Week 8 (prior to vaccination with PPV23).
CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™); PPV23=pneumococcal polysaccharide vaccine (PNEUMOVAX™23).
Source CSR V114-030 Table 12-1

The 3 most frequently reported AEs in both intervention groups were injection-site pain, myalgia, and injection-site swelling.

### Table 54 Summary of Adverse Events – V114-030

| | V114 | | PCV13 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Participants in population | 203 | | 204 | |
| with one or more adverse events | 160 | (78.8) | 142 | (69.6) |
| with no adverse events | 43 | (21.2) | 62 | (30.4) |
| Injection site pain[a] | 112 | (55.2) | 110 | (53.9) |
| Myalgia[a] | 69 | (34.0) | 52 | (25.5) |
| Injection site swelling[a] | 58 | (28.6) | 44 | (21.6) |
| Headache[a] | 30 | (14.8) | 22 | (10.8) |
| Injection site induration[a] | 21 | (10.3) | 13 | (6.4) |
| Arthralgia[a] | 19 | (9.4) | 21 | (10.3) |
| Injection site erythema[a] | 19 | (9.4) | 12 | (5.9) |
| Fatigue[a] | 16 | (7.9) | 17 | (8.3) |

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through Week 8 (prior to vaccination with PPV23).
[a] Injection site erythema, injection site induration, injection site pain, injection site swelling, arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.
MedDRA version 24.0 was used in the reporting of this study.
Source: V114-030 CSR Table 12-2
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™); PPV23=pneumococcal polysaccharide vaccine (PNEUMOVAX™23).

The proportion of participants with systemic vaccine-related AEs was higher in the V114 group compared with the Prevnar 13™ group. However, this difference was not attributable to any specific AE.

**Table 55 Participants With Systemic Adverse Events Related to Study Vaccine (Incidence >0% in One or More Vaccination Groups) - V114-030**

| | V114 | | PCV13 13™ | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Participants in population | 203 | | 204 | |
| with one or more systemic adverse events related to study vaccine | 97 | (47.8) | 77 | (37.7) |
| with no systemic adverse events related to study vaccine | 106 | (52.2) | 127 | (62.3) |
| **General disorders and administration site conditions** | **14** | **(6.9)** | **14** | **(6.9)** |
| Asthenia | 0 | (0.0) | 1 | (0.5) |
| Fatigue[a] | 10 | (4.9) | 10 | (4.9) |
| Hyperthermia | 1 | (0.5) | 0 | (0.0) |
| Pyrexia | 3 | (1.5) | 4 | (2.0) |
| **Investigations** | **1** | **(0.5)** | **0** | **(0.0)** |
| Body temperature increased | 1 | (0.5) | 0 | (0.0) |
| **Musculoskeletal and connective tissue disorders** | **78** | **(38.4)** | **60** | **(29.4)** |
| Arthralgia[a] | 19 | (9.4) | 20 | (9.8) |
| Myalgia[a] | 66 | (32.5) | 51 | (25.0) |
| Pain in extremity | 0 | (0.0) | 1 | (0.5) |
| **Nervous system disorders** | **27** | **(13.3)** | **14** | **(6.9)** |
| Headache[a] | 27 | (13.3) | 14 | (6.9) |
| **Skin and subcutaneous tissue disorders** | **1** | **(0.5)** | **5** | **(2.5)** |
| Pruritus | 0 | (0.0) | 2 | (1.0) |
| Rash erythematous | 1 | (0.5) | 0 | (0.0) |
| Urticaria[a] | 0 | (0.0) | 3 | (1.5) |

Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred from Day 1 (following vaccination with PCV) through Week 8 (prior to vaccination with PPV23).
[a] Arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.
Relatedness to study vaccine was determined by the investigator. MedDRA version 24.0 was used in the reporting of this study.
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™); PPV23=pneumococcal polysaccharide vaccine (PNEUMOVAX™23).
Source CSR V114-030 Table 14.3-12

The proportions of participants with AEs (solicited and unsolicited) by maximum intensity were generally comparable in both intervention groups following vaccination with PCV. Of the participants with solicited AEs graded by intensity, the majority had events with a maximum intensity of mild in both intervention groups. The proportions of participants with solicited AEs that were severe in maximum intensity were low and comparable in both the V114 and PCV13 groups (2.5% and 2.0%, respectively). Of the participants with solicited AEs in both intervention groups, the majority had events of short duration (≤3 days) following vaccination with PCV.

***CHMP's comment***

The safety of V114 was evaluated in study V114-030, in which children 6 through 17 years of age living with HIV (CD4+ Tcell count ≥200 cell/µL and plasma HIV RNA of <50,000 copies/mL) were exposed to V114 (203 children) or PCV13 (204 children).

In both intervention groups the majority of participants experienced at least 1 or more AEs and even 1 or more vaccine-related AEs. The most commonly reported AEs, >20% of participants, in both treatment groups were injection site pain, myalgia and injection-stie swelling.

Vaccine-related injection-site AEs were experienced by the majority of participants in both treatment groups, with the proportion being higher in the V114 group compared to the PCV13 group; 71.4% vs 59.8% respectively. Vaccine-related systemic AEs were more commonly reported in the V114 group compared to the PCV13 group: 40.6% vs 20.6%. These differences were driven by an overall slightly more reactogenic profile of V114.

The safety profile observed in participants with CD4+ T-cell counts of ≥200 to <500 cells/μL and ≥500 cells/μL was largely comparable. Considering the small number of participants with CD4+ T-cell counts of ≥200 to <500 cells/μL (n=17) no firm conclusions can be drawn.

No clear trends were observed in between the age subgroups. A slight difference was observed between the sex subgroups in the V114 group, with V114 being more reactogenic in females compared to males. However, considering the small differences, no impact is expected. Comparable to the total population, a trend towards higher reactogenicity in White subjects was observed for both intervention groups compared to Asian participants. Reactogenicity was even higher in Black subjects. However, again due to small numbers no firm conclusions can be drawn.

The safety profile in children with HIV was largely comparable to the safety profile as seen for the healthy infants. No new safety signals were identified.

***Age: determined using the catch-up vaccination study***

The safety profiles of 1 (2 to 17 years of age), 2 (12 through 23 months of age), or 3-dose (7 through 11 months of age) catch-up regimens of V114 were generally comparable to those of PCV13.

The proportions of participants with AEs following any dose were generally comparable between intervention groups for each age group evaluated. The majority of reported injection-site and systemic AEs in both intervention groups were transient and of mild to moderate intensity.

While the proportions of participants with AEs was higher in the V114 group compared with the PCV13 group for participants 12 through 23 months of age (mainly due to higher proportions of participants with solicited AEs of injection-site pain and irritability these results may not be clinically meaningful given the small sample size analysed in this age group.

| Participants | Category | V114 n (%) | PCV13 n (%) |
|---|---|---|---|
| 7 to 11 months of age | Participants in population | 64 | 64 |
| | with ≥1 AE | 49 (76.6) | 50 (78.1) |
| | injection site | 25 (39.1) | 27 (42.2) |
| | systemic | 45 (70.3) | 43 (67.2) |
| | with vaccine-related AEs | 41 (64.1) | 41 (64.1) |
| | with SAEs | 7 (10.9) | 5 (7.8) |
| | with vaccine-related SAEs | 0 (0.0) | 0 (0.0) |
| | who died | 0 (0.0) | 0 (0.0) |
| | who discontinued vaccine due to an AE | 0 (0.0) | 0 (0.0) |
| 12 to 23 months of age | Participants in population | 62 | 64 |
| | with ≥1 AE | 49 (79.0) | 38 (59.4) |
| | injection site | 32 (51.6) | 24 (37.5) |
| | systemic | 40 (64.5) | 29 (45.3) |
| | with vaccine-related AEs | 42 (67.7) | 31 (48.4) |
| | with SAEs | 4 (6.5) | 4 (6.3) |
| | with vaccine-related SAEs | 0 (0.0) | 0 (0.0) |
| | who died | 0 (0.0) | 0 (0.0) |
| | who discontinued vaccine due to an AE | 0 (0.0) | 0 (0.0) |
| 2 to 17 years of age | Participants in population | 177 | 175 |
| | with ≥1 AE | 132 (74.6) | 134 (76.6) |
| | injection site | 118 (66.7) | 119 (68.0) |
| | systemic | 93 (52.5) | 92 (52.6) |
| | with vaccine-related AEs | 125 (70.6) | 125 (71.4) |
| | with SAEs | 4 (2.3) | 4 (2.3) |
| | with vaccine-related SAEs | 0 (0.0) | 0 (0.0) |
| | who died | 0 (0.0) | 0 (0.0) |

AE=adverse event; PCV=pneumococcal conjugate vaccine; SAE=serious adverse event
Reported AEs include nonserious AEs that occurred within 14 days of vaccination and SAEs that occurred after vaccination (Day 1) through completion of study participation.

Across all age groups evaluated, the proportions of participants with SAEs after any dose were generally comparable between intervention groups and no vaccine-related SAEs, deaths, or discontinuations from study intervention due to an AE were reported.

Catch-up vaccination with V114 in participants 2 through <6 and ≥6 through 17 years of age showed a lower proportion of participants reporting AEs in the ≥2 to <6 years of age group compared with ≥6 through 17 years of age group, regardless of intervention group.

| | 2 to <6 Years of Age | | | | ≥6 to 17 Years of Age | | | |
|---|---|---|---|---|---|---|---|---|
| | V114 | | PCV13 | | V114 | | PCV13 | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 114 | | 112 | | 63 | | 63 | |
| with one or more AEs | 72 | (63.2) | 75 | (67.0) | 60 | (95.2) | 59 | (93.7) |
| injection-site | 62 | (54.4) | 62 | (55.4) | 56 | (88.9) | 57 | (90.5) |
| systemic | 43 | (37.7) | 47 | (42.0) | 50 | (79.4) | 45 | (71.4) |
| with no AE | 42 | (36.8) | 37 | (33.0) | 3 | (4.8) | 4 | (6.3) |
| with vaccine-related[a] AEs | 66 | (57.9) | 66 | (58.9) | 59 | (93.7) | 59 | (93.7) |
| injection-site | 62 | (54.4) | 62 | (55.4) | 56 | (88.9) | 57 | (90.5) |
| systemic | 28 | (24.6) | 27 | (24.1) | 45 | (71.4) | 35 | (55.6) |
| with SAEs | 4 | (3.5) | 3 | (2.7) | 0 | (0.0) | 1 | (1.6) |
| with vaccine-related SAEs | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[a] Determined by the investigator to be related to the vaccine.
Reported adverse events include nonserious adverse events that occurred within 14 days of vaccination and serious adverse events that occurred after vaccination (Day 1) through completion of study participation.
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Across all age groups evaluated in V114-024 (7 through 11 months, 12 through 23 months, and 2 through 17 years), the most frequently reported AEs after each dose of PCV were mainly the solicited injection-site and systemic events in both intervention groups and were generally comparable in both intervention groups.

***CHMP's comment***

Overall, in line with the healthy infant population, the safety profile per age group was comparable between the treatment groups. In addition, the most frequently reported AEs after each dose were mainly the solicited injection-site and systemic events and the unsolicited AE of pyrexia. No new safety signals were observed in older children.

Of note, in children aged 2 to <6 years of age a substantially lower reactogenicity was observed compared to the healthy infant population, while the reactogenicity profile in children aged >6 to 17 years of age was found to be largely comparable to the healthy infant population. This is thought to be due to small numbers in the different age groups.

## Safety related to drug-drug interactions and other interactions

Concomitant vaccines were administered in both the V114 and PCV13 intervention groups in Studies V114-025, V114-027, and V114-029, as prespecified in the study protocols. Studies V114-008, V114-024, and V114-031 permitted the administration of non-study routine childhood vaccines according to the recommended schedule for paediatric vaccination.

***CHMP's comment***

The safety of V114 was evaluated while childhood vaccines could be concomitantly administered.

## Discontinuation due to adverse events

In total, 4 participants had AEs leading to study vaccine discontinuation during the protocol specified reporting period in studies V114-008, V114-027, and V114-030.

During study V114-008, 2 participants discontinued study vaccine due to an AE. One participant in the V114 Lot 1 group discontinued V114 following vaccination 1 due to a nonserious, vaccine-related AE of rash, and 1 participant in the V114 Lot 2 group discontinued V114 following vaccination 1 due to a serious, vaccine-related AE of febrile convulsion.

During study V114-027 1 participant enrolled in group 3 discontinued study intervention due to a vaccine-related SAE (epilepsy) that occurred within the protocol-defined reporting period. The SAE occurred after dose 2 (PCV13). Dose 3, V114, was administered prior to withdrawal of the participant.

During study V114-030, 1 participant in the PCV13 group discontinued study intervention (ie, did not receive PPV23 at Week 8) due to vaccine-related AEs of injection-site erythema, injection-site induration, and injection-site swelling following PCV13.

***CHMP's comment***

It is acknowledged that the number of discontinuations due to AEs is low (n=4 in total) and comparable between intervention groups. AEs were reported across multiple SOCs with no AEs being reported more than once.

## Post marketing experience

Not applicable.

## 2.5.1. Discussion on clinical safety

The clinical safety of V114 was evaluated in 8 clinical trials in which in total, 5,366 infants and children received at least 1 dose of V114 and 3,491 infants and children received at least 1 dose of PCV13. The active comparator PCV13 was included in all 8 studies (V114-008, V114-023, V114-024, V114-025, V114-027, V114-029, V114-030 and V114-031).

Reactogenicity was followed for 14 days when concerning solicited injection-site and systemic reactions and for 7 days concerning body temperature, which is considered appropriate (see Guideline on clinical evaluation of vaccines). Subjects were followed for 6 months, which is considered a sufficient period of time to collect relevant adverse events (except for study V114-008 where follow-up was limited to 30 days). This strategy led to a sufficient period of time to collect information on the outcome of the adverse events.

An integrated safety analysis was performed for 4 studies, including healthy infants from approximately 2 months of age: V114-025, V114-027 [Groups 1 and 5 only], V114-029, and V114-031. Safety results obtained from the other studies were analysed separately.

**Exposure**

Overall, 5,366 participants received at least 1 dose of V114, of which 211 were preterm infants. In total 303 participants received V114 as a catch-up regimen, 69 had sickle cell disease (SCD) and 203 were HIV infected. The majority of studies allowed for concomitant vaccination with routine childhood vaccines. The size and composition of the safety database is considered sufficient for the assessment of the safety profile of V114. However, the size of the safety database limits the detection of more rare adverse events. In addition, as only 177 healthy children aged 2 to 17 years of age were administered V114, the information on the safety profile in this population is limited. The MAH has committed to collect information on rare but serious AEs systemically post-licensure.

**Adverse Events**

*Integrated safety population*

The safety profile in the integrated safety population for V114 was generally comparable to the safety profile of PCV13. The majority of participants in both treatment groups experienced at least 1 AE. AEs were experienced by a comparable proportion of participants in both treatment groups, as the percentage of participants experiencing the different AEs did not differ more than 10%. V114 was slightly more reactogenic compared to PCV13, as the majority of AEs occurred slightly more frequently after injection with V114 compared to PCV13. The most commonly reported vaccine-related AEs were mostly solicited AEs and identical in both the V114 and PCV13 group: irritability (67.7% vs 62.8%), somnolence (48.5% vs 45.7%), injection-site pain (44.4% vs 39.4%), injection-site erythema (41.7% vs 40.5%), decreased appetite (29.8% vs 26.2%), pyrexia (29.8% vs 28.2%), injection-site induration (28.3% vs 30.8%), and injection-site swelling (28.2% vs 25.3%). In both intervention groups, the majority of participants had solicited AEs which were mild to moderate in intensity, with a size ≤2 inches (5.1 cm) and short duration (≤3 days).

The safety profile as determined using the integrated safety population was largely comparable to the profile as determined in the underlying studies. In all studies the safety profile of V114 was comparable to PCV13, with the most frequently reported AEs following any dose being solicited AEs. The majority of the AEs were mild to moderate in intensity and of short duration. Differences in the PTs reported and the proportion of participants experiencing AEs occurred across the studies, however no clear trends or safety signals could be observed in the separate studies.

*Sex, race and ethnicity*

In the integrated analysis, no clear trends were observed with respect to reactogenicity between males and females or ethnic subgroups in the V114 group. A trend towards higher reactogenicity in White subjects was observed for both intervention groups compared to Asian and multiple race participants. However, these results do not give rise to concern.

Overall, the safety profile in the different subgroups of sex, race and ethnicity was similar to the safety profile in the entire population and no new safety signals are observed.

*Potential effect of antipyretics use*

The use of antipyretics differs between studies (e.g. paracetamol V114-025: ~48%, V114-029: ~67%, V114-024: ~25-35%, V114-027: ~6%, 008: no use of paracetamol). The use of antipyretics was balanced between treatment arms. Additional tables were provided and in each study the percentage of individuals with AE was higher in the group receiving antipyretics compared with no antipyretic intake. Although only overall numbers of participants receiving antipyretics were presented per study, not individual timepoints of antipyretic intake per subject, the presented data indicate that there are

no differences between treatment groups.

*Special population*

*Preterm infants*

In total 211 pre-term infants were exposed to V114. The safety database for pre-term infants is considered limited, but sufficient to determine the safety profile as it can be compared to the safety profile in the healthy infants included in the same study.

The safety profile in preterm infants was largely comparable to the safety profile as seen for the healthy infants. The most frequently reported vaccine-related AEs were identical in the preterm infants as compared to the total population, with the most frequently reported AEs being pyrexia, injection-site pain, injection-site erythema, injection-site induration, injection site swelling, irritability, somnolence and decreased appetite. There was a slight numerical increase in the percentage of participants who experienced at least 1 AE in both treatment arms compared to the total healthy infant population, indicating a slight increase in reactogenicity in preterm infants.

The percentage of participants experiencing SAEs was comparable between the treatment arms. None of the SAEs was considered related to the vaccine in the preterm infant population.

No new safety signals were identified.

*Immunocompromised*

The safety of a single administration of V114 in children 5 through 17 years of age with SCD was evaluated in study V114-024. In total, 69 children were exposed to V114 and 34 to PCV13. The safety profile in children with SCD was largely comparable to the safety profile as seen for the healthy infants. The most commonly reported AEs were injection-site pain and injection site swelling. Vaccine-related systemic AEs were more commonly reported in the V114 group compared to the PCV13 group, with the difference being driven by more frequently reported myalgia. No new safety signals were identified.

The safety of a single administration of V114 in children 6 through 17 years of age living with HIV (CD4+ T cell count ≥200 cell/µL and plasma HIV RNA of <50,000 copies/mL) was evaluated in study V114-030. In total, 203 children were exposed to V114 and 204 to PCV13. The safety profile in children with HIV was largely comparable to the safety profile as seen for the healthy infants. In both intervention groups the majority of participants experienced at least 1 or more AEs and even 1 or more vaccine-related AEs. The most commonly reported AEs, >20% of participants, in both treatment groups were injection site pain, myalgia and injection-stie swelling. Vaccine-related systemic AEs were more commonly reported in the V114 group compared to the PCV13 group: 40.6% vs 20.6%. This difference was driven by an overall slightly more reactogenic profile of V114. No new safety signals were identified.

The safety profile observed in participants with CD4+ T-cell counts of ≥200 to <500 cells/µL and ≥500 cells/µL was largely comparable. Considering the small number of participants with CD4+ T-cell counts of ≥200 to <500 cells/µL (n=17) no firm conclusions can be drawn.

Interestingly in both participants with SCD and living with HIV-1 infection, a slight difference was observed between the sex subgroups in the V114 group, with V114 being more reactogenic in females compared to males. However, considering the small differences, no impact is expected.

*Catch-up vaccination*

The safety profiles of 1-, 2- , or 3-dose catch-up regimens of V114 given to 2 to 17 years of age, 12 through 23 months of age or 7 through 11 months of age respectively was evaluated in study V114-

027. In total, 64 children 7 to 11 months were exposed to V114 and 64 to PVC13, 62 children aged 12 to 23 months of age were exposed to V114 and 64 to PCV13 and 177 children aged 2 to 17 years of age were exposed to V114 and 175 to PCV13.

Overall, in line with the healthy infant population, the safety profile per age group was comparable between the treatment groups. In addition, the most frequently reported AEs after each dose were mainly the solicited injection-site and systemic events and the unsolicited AE of pyrexia. No new safety signals were observed in older children.

Of note, the reactogenicity in children aged 2 to <6 years of age was substantially lower compared to the healthy infant population, while the reactogenicity profile in children aged >6 to 17 years of age was found to be largely comparable to the healthy infant population. This is thought to be due to small numbers in the different age groups.

**Serious Adverse Events and Death**

Overall, in all 8 studies submitted the proportions of participants experiencing SAEs were comparable across intervention groups and the majority of SAEs were in the SOC Infections and Infestations. In total 5 SAEs were considered related to the vaccine by the investigator. However, for 1 additional SAE of febrile convulsion experienced by a participant in the V114 group, the SAE is considered to be related to the vaccine taking into consideration that no other causality was provided and the timing of the event relative to vaccination. In addition, several observations of the assessment of relatedness to the vaccine were not followed with regards to PCV13. However, considering the fact that it involves PCV13, the issues are not further pursued as it is not considered relevant for the current procedure.

The number of deaths in the 8 studies is low and comparable between study interventions, as in the V114 group 3 out of 5366 participants (0.06%) died and 2 out of 3491 participants (0.06%) in the PCV13 group. The narratives of participants who died were reviewed and no indication of a causal relationship to the vaccine could be identified, although one death due to unknown cause which occurred during study V114-008 must be regarded as speculative due to the lack of additional information.

**Discontinuations**

During the 8 studies submitted during this procedure, 4 participants discontinued due to AEs. The number of discontinuations is low. The AEs causing the discontinuations were reported across multiple SOCs with no AEs being reported more than once.

## 2.5.2. Conclusions on clinical safety

The safety profile of V114 appears to be similar to the safety profile of PCV13. It is a reactogenic vaccine, with the majority of participants reporting 1 or more AEs; however, these were mostly mild or moderate in intensity and of short duration (≤3 days). The most frequently reported vaccine-related AEs by PT were the solicited AEs of irritability, somnolence, injection-site pain, injection-site erythema, decreased appetite, injection-site swelling, and injection-site induration and the unsolicited AE of pyrexia. Overall, the proportions of participants with SAEs were comparable across intervention groups. Very few SAEs were considered related to the study vaccine.

In conclusion, V114 is well tolerated in infants and children. However, compared to PCV13, V114 is slightly more reactogenic. This increase in reactogenicity has no further clinical implications.

## 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## 2.5.4. Risk management plan

The MAH submitted an updated RMP version 1.1 with this application. The main proposed RMP changes were the following:

This RMP was updated to reflect completion of 8 clinical trials to support the supplemental marketing application for use of Pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed) in infants, children and adolescents from 6 weeks to less than 18 years of age.

There are no new or reclassified safety concerns.

During the assessment, the MAH submitted an updated RMP version 1.2 for adding V114-032 as a post-authorisation efficacy study.

Prior to opinion, the MAH submitted a further update, RMP (version 2.0) including the V114-032 amended protocol as Annex 5 (PAES). The Applicant confirmed that there is no other change proposed to the RMP (from version 1.2 to version 2.0) besides the administrative changes associated to this amended protocol.

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

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

### *Safety concerns*

No changes were proposed. The summary of safety concerns remains unchanged as reflected below:

**Table SVIII.1: Summary of Safety Concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Use in **adult** HSCT recipients |

## *Pharmacovigilance plan*

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| Study V114-022: Safety and Immunogenicity of V114 in Recipients of Allo-HSCT<br>Ongoing | To evaluate the safety and tolerability of 3 doses of V114 and 3 doses of PCV13 with respect to the proportion of participants with adverse events (AEs) within each vaccination group | Use in **adult** HSCT recipients | Final report | 4Q2022 |

## *Risk minimisation measures*

**Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Use in **adult** HSCT recipients | Routine risk minimisation measures:<br>Special warnings and precautions for use section of the product information<br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance<br>Additional pharmacovigilance:<br>Study V114-022: Safety and Immunogenicity of V114 in Recipients of Allo-HSCT (final report due date 4Q2022) |

No new risk minimisation measures or pharmacovigilance activities have been proposed.

### *PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES*

**Table IV.1: Planned and On-Going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations**

| Study Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Date |
|---|---|---|---|---|
| Efficacy studies which are conditions of the marketing authorisation | | | | |
| Study V114-032: A Study of V114 and Acute Otitis Media **in Children** (PNEU-ERA)<br>Ongoing | To evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal AOM in children. | Efficacy against AOM | Final report | 2Q2027 |

## *2.6. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to include editorial changes in the product information.

Annex II has been amended to include V114-032, as a post-authorisation efficacy study (PAES) in the EU-RMP.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

### 2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- A user consultation (full testing report of the 855x450mm patient leaflet [06DKGB] and a bridging report to a 210x550mm patient leaflet [06DQJY]) has recently been conducted as part of the Marketing Authorisation granted for the vaccine Vaxneuvance in December 2021.
- The proposed additions related to the safe use of this vaccine are not expected to impact the package leaflet readability for patients and are limited to the proposed paediatric indication. The following additions have been made:
  - section 1: to reflect the proposed indication for the paediatric population
  - section 2: to include information references to the paediatric population and align with the proposed updates made to the SmPC using patient-friendly terms
  - section 3: to add the different vaccination schedules (depending on the age of the paediatric population) and administration site relevant to children
  - section 4: to list the possible side effects encountered in the paediatric population. The additional side effects are presented in patient-friendly terms
  - tear-off portion intended for the Healthcare Professionals: updates made in accordance with the SmPC.
- The design, layout and format of the package leaflet are not affected by the proposed updates.
- No new presentation is associated with the proposed paediatric indication for this vaccine
- The vaccine is to be administered exclusively by Healthcare Professionals

### 2.6.2. Labelling and package leaflet exemptions

None

### 2.6.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vaxneuvance (pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

### 2.6.4. Quick Response (QR) code

None

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The proposed added indication is:

*Vaxneuvance is indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to less than 18 years of age.*

*Streptococcus pneumoniae* (pneumococcus), which causes pneumococcal disease (PD), remains a major cause of vaccine preventable PD worldwide with considerable morbidity and mortality, in infants, children, and adults. Clinical manifestations of pneumococcal disease include invasive pneumococcal disease (IPD) and non-invasive disease. IPD can lead to meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis. The non-invasive disease can present as, e.g. acute otitis media, sinusitis and non-bacteraemic pneumonia.

### 3.1.2. Available therapies and unmet medical need

*Treatment options:*

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data. Initial treatment of IPD generally includes broad-spectrum antibiotics, that have efficacy against *S.pneumoniae* as well as other likely pathogens. The increase in pneumococcal resistance to penicillin and other commonly used antimicrobial agents complicates treatment decisions and may lead to treatment failures with subsequent increased morbidity and healthcare costs.

*Prevention options:*

Prevention of PD in children includes routine childhood vaccination with pneumococcal conjugate vaccines (PCVs) as well as prophylactic use of antibiotics and pneumococcal polysaccharide vaccine (PPV) in special populations (e.g., children with functional or anatomic asplenia).

Currently two vaccines are licensed for this indication in children in the EU: Prevenar13 (PCV13) and Synflorix (only for children up to 5 years of age). Another unconjugated pneumococcal vaccine is licensed but not for the intended infant population (PNEUMOVAX23; PPV23).

*Unmet medical need:*

Since the introduction of pneumococcal vaccines, there has been an overall reduction in the incidence of IPD, however pneumococcal disease remains a major cause of mortality and morbidity. A decrease in the incidence of pneumococcal disease caused by serotypes included in the currently licensed vaccines, except serotype 3, was observed across all age groups. However, strain replacement is a concern as in multiple regions, a significant increase in disease caused by non-vaccine serotypes in both children and adults has been observed.

IPD cases caused by 2 serotypes not included in vaccines currently licensed for use in children, 22F and 33F, have increased in frequency in several regions and countries. The two serotypes 22F and 33F cause 8.5% and 6.8% of IPD in children <1 and children 1 to 4 years of age in the EU. Serotype 22F and 33F are known to be among the serotypes with the highest invasive capacity (Yildirim I et al. Vaccine 2011) and are associated with serious clinical outcomes.

Due to the disease severity of IPD and the healthcare burden of residual disease due to non-vaccine serotypes, prevention of pneumococcal disease remains an unmet medical need.

### 3.1.3. Main clinical studies

The main clinical studies for evaluating the immunogenicity of V114 are the 2 Phase 3 studies V114-025 and V114-029. Both studies are randomized, multicentre, double-blind, active comparator controlled (PCV13) studies evaluating the safety, tolerability and immunogenicity of V114.

Study V114-025 enrolled healthy infants at approximately 2 months of age (from 42 to 90 days [inclusive]) who were randomized (1:1) to receive either V114 or PCV13. Treatment consisted of a 2-dose primary series in full-term infants administered IM at 2 and 4 months of age approximately followed by a toddler dose at 11 to 15 months of age, and in preterm infants a 3 dose primary series was administered IM at approximately 2, 3, and 4 months of age from date of birth (not corrected) followed by a toddler dose at 11 to 15 months of age. In total, 588 participants received at least 1 dose of V114 IM, and 592 received at least 1 dose of PCV13.

Study V114-029 enrolled healthy infants at approximately 2 months of age (from 42 to 90 days [inclusive]) who were randomized (1:1) to receive either V114 or PCV13. Treatment consisted of a 3-dose primary series in both full-term and preterm infants administered IM at 2, 4 and 6 months of age from date of birth (not corrected for preterm infants) approximately, followed by a toddler dose at 12 to 15 months of age. In total, 859 participants received at least 1 dose of V114 IM, and 856 received at least 1 dose of PCV13.

Overall, the design of the presented main studies is similar and considered adequate. In all studies the subjects received a regimen of V114 or PCV13 which is in line with the approved dosing regimen for PCV13 and the proposed regimen for V114. Immunogenicity was evaluated 30 days after primary series and immediately prior to the toddler dose and 30 days after the toddler dose. In the main studies, participants also received routine childhood vaccinations. The study populations included the main populations reflects the target population for vaccination with V114.

In line with EMA guidance, in a scientific advice (EMEA/H/SA/1492/1/FU/1/2017/III) it was agreed to base the clinical development programme on immunogenicity studies and that no efficacy studies are required. The non-inferiority margin of -0.1 for the difference (V114 minus PCV13) in response rate and 0.5 for the GMC ratio (V114/PCV13) for the 13 shared serotypes has been agreed in the scientific advice (EMEA/H/SA/1492/1/FU/1/2017/III).

The following supportive studies were submitted:

- Study V114-027 investigated the interchangeability of both PCV13 and V114 in infants aged approximately 2 months of age.
- Study V114-024 investigated the immunogenicity of catch-up vaccination with V114 in children aged 7 to 11 months, 12 to 23 months and 2 to 17 years of age.
- Study V114-023 investigated the immunogenicity of a single dose of V114 in children aged 5 to 17 years of age with sickle cell disease.
- Study V114-030 investigated the immunogenicity of a single dose of V114 in children 6 to 17 years of age living with HIV-1 infection.

- Study V114-008, a Phase II study to evaluate the safety, tolerability, and immunogenicity of 2 different lots of V114.

## *3.2. Favourable effects*

**Response rate**. At 30 days post toddler dose, the vast majority of participants achieved the threshold of 0.35 µg/mL for all serotypes included in V114, indicating adequate protection against IPD.

**Comparability to PCV13**. Both V114 and PCV13 were immunogenic in all studies and subgroups tested. V114 was shown to be non-inferior to PCV13 for the 13 shared serotypes at 30 days post toddler dose in both pivotal studies, based on the IgG GMCs with the predefined non-inferiority margin of the lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio [V114/ PCV13] being greater than 0.5 for each serotype. In addition, the difference in the response rates [V114 minus PCV13] were smaller than 10 percentage points for each serotype at 30 days post toddler dose in both pivotal studies. The RCDCs of the 13 shared serotypes showed a similar pattern for the V114 group and the PCV13 group. Visually, the curves show a similar distribution, indicating that both vaccines induced a comparable immune response.

**Serotype 3.** In both pivotal studies serotype 3 showed consistently higher IgG GMCs (Study 025: 1.28, Study 029: 1.35) and seroresponse rates (Study 025: 92% vs 84%, Study 029: 95% vs 80%) with Vaxneuvance. These aspects were observed in all studies.

**Additional serotypes 22F and 33F**. A substantial immune response was measured for both additional serotypes, which was non-inferior to the lowest response seen for the 13 shared serotypes (except serotype 3). At 30 days post toddler dose, the vast majority of participants achieved IgG GMCs which fell well above the threshold of 0.35 µg/mL in all studies, indicating an immune response that is likely to offer protection against IPD.

**Immune memory**. In all studies, the antibody concentration decreased over time as IgG GMCs immediately prior to the toddler dose were lower compared to 30 days post primary series (PPS) in both treatment arms. The toddler dose increased IgG GMCs to levels comparable to or higher than PPS. This indicates that immune memory is induced.

**Preterm infants**. Both 30 days PPS and 30 days PTD, the vast majority of participants achieved the threshold value of 0.35 µg/mL for all serotypes after vaccination with V114.

**Immunocompromised**. In both participants with SCD and living with HIV-1 infection, a single administration of V114 induced IgG GMCs against all serotypes contained in the vaccine which were well above the threshold of 0.35 µg/mL. This indicates that the response generated was substantial and clinically relevant.

**Interchangeability.** The interchangeability study (027) investigated the immune response after switching from PCV13 to V114 at different time points during the 3 + 1 regimen. IgG GMCs were overall comparable for the 13 shared serotypes between the groups which switched to V114 after the initial two doses with PCV13. Response rates for the shared serotypes remained high in all groups.

**Catch-up vaccination.** In general, catch-up vaccination with V114 elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days following the last dose of study intervention, for all 15 serotypes contained in the vaccine. The observed immune response is comparable to infants immunized in due time (data from pivotal studies).

**Concomitant vaccination with routine childhood vaccines**. The immune response to the concomitantly administered vaccines was comparable between the V114 and PCV13 group, indicating that the generation of the immune response was not impacted differently by the 2 treatment arms. All

responses for the concomitant vaccines showed a within 5 percentage points difference between the treatment arms.

## *3.3. Uncertainties and limitations about favourable effects*

**Efficacy/effectiveness data**. No efficacy or effectiveness data is available for V114 in infants and children. The evaluation of the protective effect of the V114 vaccine regimen is based on bridging clinical immunogenicity results to immunogenicity data of a licensed pneumococcal vaccine, PCV13, that has been shown to be effective.

**Correlate of protection**. There is no correlate of protection known for pneumonia or AOM. The indications of pneumonia and AOM were granted to PCV13 based on non-inferiority of immune response to PCV7. PCV13 has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed. However, no exact vaccine efficacy was determined, nor the immune response required to achieve protection. Therefore, the strategy of non-inferiority testing for V114 to PCV13 introduces the possibility of biocreep for the shared serotypes, considering that the immune response required to induce a protective effect is unknown. In addition, whether the correlate of protection also applies for the new serotypes included in V114, is currently unknown.

**Reduced immunogenicity response**. Generally, the immune response to V114 was numerically lower compared to PCV13 as assessed by IgG GMCs for the 13 shared serotype. When comparing IgG GMCs generated by V114 to PCV13, the GMC ratio fell below 1 for the majority of the shared serotypes. In addition, across all studies, the serotype 6A IgG GMCs elicited by V114 were substantially lower compared to the IgG GMCs elicited by PCV13. Finally, a lower immune response is seen in study V114-025, leading to slightly lower response rates, indicating that the immune reaction induced by the 2-dose primary series is reduced compared to the 3-dose primary series.

**Persistence of protective effect.** The data indicate that IgG concentrations decline at a similar rate after vaccination with V114 and PCV13 and consequently also the response rates. Given hat the initial concentrations were lower with V114, it could be assumed that the protective effect of V114 might wane earlier compared to PCV13. Since no data after a longer period are available

**Failed study**. In principle the pivotal study V114-029 failed, as not all of the primary objectives were met. The IgG GMC for serotype 6A did not meet non-inferiority criteria based on IgG GMCs at 30 days PPS.

**Serotype 6A.** In several studies, including the 2 pivotal studies, serotype 6A showed the most pronounced difference between V114 and PCV13. While after the primary series the GMC ratio was even below 0.5 in several studies, the ratios increased after the toddler dose, but remain the lowest of all 13 shared serotypes.

**Prophylactic use of antipyretics.** In a post-marketing study of PCV13, it has been observed that the prophylactic use of antipyretics (ibuprofen and paracetamol) reduced the immune response especially after the primary series. In general, the use of paracetamol was overall balanced between groups in all respective studies. Further, subgroup analyses based on antipyretic use showed similar pattern for both vaccines in changes in IgG GMCs in subjects with concomitant antipyretic use compared to subjects that did not use of antipyretics. A correlation with age could not be evaluated since data in older subjects was limited.

**Serotype 3 and 33F in the interchangeability study**. Switching the toddler dose from PCV13 to V114 does not impact the effect for the 13 shared serotypes, however, an additional benefit for serotype 3 and 33F cannot be assumed for subjects that only switched after the primary series.

**HIV-positive subjects**: The majority of participants (91.6%) had CD4+ T-cell count ≥500 cells/µL and the data for participants with CD4+ T-cell count <500 cells/µL i.e. are very limited.

## *3.4. Unfavourable effects*

**Adverse events**. The safety profile of V114 was comparable to the safety profile of PCV13. For both interventions, the majority of participants experienced 1 or more AEs in all studies and the most commonly reported AEs were solicited AEs.

In healthy infants approximately 2 months of age, 93.7% of participants experienced 1 or more AE, and 89.4% experienced a vaccine-related AE. The most commonly reported vaccine-related AEs were: irritability (67.7%), somnolence (48.5%), injection-site pain (44.4%), injection-site erythema (41.7%), decreased appetite (29.8%), pyrexia (29.8%), injection-site induration (28.3%), and injection-site swelling (28.2%).

In both intervention groups, the majority of participants had events which were mild to moderate in intensity, with a size ≤2 inches (5.1 cm) and short duration (≤3 days).

**SAEs and Deaths**. Overall, the proportions of participants with SAEs were comparable across intervention groups and the majority of SAEs were in the SOC Infections and Infestations. Very few SAEs were considered related to the vaccine, which is agreed. Five participant deaths were reported in the 8 studies. Narratives of participants who died were reviewed and no indication of a causal relationship to the vaccine could be identified.

**Discontinuations due to AE**. In total 4 participants had AEs leading to study vaccine discontinuation. AEs were reported across multiple SOCs with no AEs being reported more than once.

The safety profile in preterm infants, participants with SCD and participants living with HIV-1 infection was largely comparable to the safety profile as seen for the healthy infants. No new safety signals were identified.

## *3.5. Uncertainties and limitations about unfavourable effects*

**Safety database**. In total, 5,366 participants received at least 1 dose of V114, of which 211 were preterm infants. The size of the safety database limits the detection of more rare adverse events. In addition the safety database in children aged 2 to 17 years of age (n=177) is limited and limits assessment of safety profile in this age category. Information on rare but serious AEs should be systematically collected post-licensure.

**Immediate and vaccine-related AEs.** More information with regard to immediate and vaccine-related AEs is requested.

**Assessment of relatedness of SAEs**: The assessment provided by the investigator of non-relatedness to study vaccine was not followed for 1 SAE experienced by a participant in the V114 group.

## 3.6. Effects Table

**Table 56 Effects Table for Vaxneuvance**

| Effect | Short description | Unit | V114 | PCV13 | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Response rate 30 days PPS | 13-shared serotypes | % | Non-inferiority was met for all serotypes after 3-dose primary series[1)]<br>The difference in response rate was within 10 percentage points for 12 out of 13 shared serotypes after the 2-dose primary series[2)] | | | V114-029<br>V114-025 |
| | 2 additional serotypes | % | Response rate higher for the 2 additional serotypes in the V114 group compared to the PCV13 group | | | V114-029 and V114-025 |
| Response rate 30 days PTD | 13-shared serotypes | % | The difference in response rate was within 10 percentage points for all serotypes after both 2- and 3-dose primary series[3)] | | | V114-029 and V114-025 |
| | 2 additional serotypes | % | Response rate higher for the 2 additional serotypes in the V114 group compared to the PCV13 group | | | V114-029 and V114-025 |
| **Unfavourable Effects** | | | | | | |
| Solicited Injection-site AE | Pain | % | 44.4 | 39.4 | SoE: These were the most commonly reported AEs in the integrated safety population of healthy infants approximately 2 months of age | Integrated summary of safety |
| | Erythema | % | 41.7 | 40.5 | | |
| | Induration | % | 28.3 | 30.8 | | |
| | Swelling | % | 28.2 | 25.3 | | |
| Solicited Systemic AE | Irritability | % | 67.7 | 62.8 | | |
| | Somnolence | % | 48.5 | 45.7 | | |
| | Decreased appetite | % | 29.8 | 26.2 | | |
| Unsolicited AE | Pyrexia | % | 29.8 | 28.2 | | |

Abbreviations: PPS=post primary series; PTD=post toddler dose

[1)]V114-029 has met its primary immunogenicity objectives regarding non-inferiority of V114 compared to PCV13 with respect to response rate for the 13 shared serotypes; lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus PCV13] being greater than -10 percentage points for each serotype).
[2)] V114-025, for serotype 6A the difference in the response rates [V114 minus PCV13] was greater than 10 percentage points,-19.4%.
[3)] V114-025 met the primary immunogenicity objectives regarding non-inferiority of V114 compared to PCV13 with respect to response rate for the 13 shared serotypes; lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus PCV13] being greater than -10 percentage points for each serotype).
Since comparisons were made individually for each of the 15 serotypes, this approach controls the 1-sided type-I error rate at 0.025, and no multiplicity adjustment was required.

## 3.7. Benefit-risk assessment and discussion

### 3.7.1. Importance of favourable and unfavourable effects

This submission does not contain efficacy studies and is based on the inference of V114 effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of noninferior immune responses to the 13 shared serotypes in PCV13. A surrogate of protection, IgG of 0.35 µg/mL, has been established for invasive pneumococcal disease (IPD) in children, which can be used to infer protection against IPD. However, it needs to be taken into consideration that whether the correlate of protection also applies for the new serotypes included in V114, is currently unknown. In addition, for pneumonia and acute otitis media (AOM) no correlate or surrogate of protection exists. The indications of pneumonia and AOM were granted to PCV13 based on non-inferiority of immune response to PCV7. PCV13 has been shown to be effective, as a reduction in disease prevalence in vaccinated children has

been observed. However, no exact vaccine efficacy was determined, nor the immune response required to achieve protection. Therefore, the strategy of non-inferiority testing for V114 to PCV13 introduces the possibility of biocreep for the shared serotypes, considering that the immune response required to induce a protective effect is unknown. CHMP has already recommended that the MAH should conduct post-marketing studies to evaluate vaccine effectiveness against AOM and pneumonia. The post-marketing program should also include population-based surveillance of the incidence rates of IPD in several different countries for an appreciable number of years using national surveillance systems, in particular for the new serotypes for which efficacy against IPD is not known.

V114 induced an immune response to all serotypes included in the vaccine in all studies and subgroups tested. The immune response induced by V114 was consistent across studies, the FAS population showed results comparable to the PP population and the results as assessed by OPA antibodies were in line with the IgG GMCs, indicating a robust response. At 30 days post toddler dose the IgG GMCs for all serotypes was well above the threshold of 0.35 µg/mL for all serotypes in all studies. The response rate, defined as the proportion of participants achieving IgG of ≥0.35 µg/mL, was ≥92% for all serotypes. These results indicate that V114 induced a substantial immune response that is likely to offer protection against IPD.

The immune response induced by V114 as assessed by IgG GMCs for the 13 shared serotypes was numerically lower compared to the response induced by PCV13, with the GMC ratio falling below 1 for the majority of serotypes. However, the response rate, defined as the proportion of participants achieving ≥0.35 µg/mL, was largely comparable and indicated that the majority of participants in both treatment groups achieved the threshold of 0.35 µg/mL. Although given the high response rates no concerns about the immediate protective effect after completion of the dosing regimen are raised, the implications of this lower response on immune persistence are not known. Data collected prior to the administration of the booster dose (Pre toddler dose) indicate that IgG concentrations and consequently also the response rates decline at a similar rate after vaccination with V114 and PCV13. Given that the initial concentrations were lower with V114, it could be assumed that the protective effect of V114 might wane earlier compared to PCV13. PSURs, including information on breakthrough disease/vaccine failure, serotype distribution and incidence of IPD will provide an indication on impact of the lower titres on immune persistence as frequency of IPD is reported per age category.

At 30 days post primary series (PPS), the response to serotype 6A was substantially lower in the V114 group compared to the PCV13 group, leading to not meeting non-inferiority criteria in one of the two pivotal studies: IgG GMC non-inferiority criteria during study V114-029. However, as the IgG GMCs for serotype 6A in both pivotal studies was still well above the threshold of 0.35 µg/mL at 30 days PPS, the clinical impact on protection against IPD is considered limited.

The response induced by serotype 3 and the 2 additional serotypes was substantially higher after V114 vaccination compared to vaccination with PCV13. This is considered clinically relevant as these are serotypes that are still causing significant disease burden. While this has been established for both full vaccination regimen, the benefit might not be achieved when switching from PCV13 to V114 late in the dosing regimen.

Overall, the immune response induced by the 2-dose primary series evaluated in study V114-025 was lower compared to the immune response induced by the 3-dose primary series, leading to slightly lower response rates in study V114-025. However, at 30 days PPS and 30 days PTD, GMC ratios were comparable between both pivotal studies, indicating that while V114 generated the lowest immune response in study V114-025, the same holds true for PCV13.

The potential influence of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response, as observed in the post-marketing of PCV13, cannot be ruled out given the current data. The

presented results of subgroup analyses based on concomitant antipyretic use (yes/no) are similar for both vaccines, indicating a similar effect for both vaccines. Consequently, respective wording in the SmPC is required.

Further, the SmPC should include respective wording reflecting that an additional benefit for serotype 3 and 33F cannot be assumed for subjects that switched to V114 after the primary series.

The safety profile of V114 was in general similar to the safety profile of PCV13. In the 8 studies submitted in the dossier, no new safety signals were identified for V114 compared to PCV13. V114 was well tolerated but slightly more reactogenic, leading to a higher percentage of participants experiencing 1 or more AEs. For both interventions, the majority of participants experienced 1 or more AEs in all studies and the most commonly reported AEs were solicited AEs. The majority of the AEs were mild in intensity and of short duration (≤ 3 days). Overall, the proportions of participants with SAEs were comparable across intervention groups and very few were considered related to the vaccine. Discontinuations due to adverse events were low.

The safety profile in preterm infants, participants with SCD and participants living with HIV-1 infection was largely comparable to the safety profile as seen for the healthy infants. No new safety signals were identified.

### 3.7.2. Balance of benefits and risks

V114 induces an immune response to all 15 serotypes contained within the vaccine in all studies and subpopulations tested. At 30 days post toddler dose the IgG GMCs for all serotypes fell well above the threshold of 0.35 µg/mL and a non-inferior immune response of V114 against PCV13 was shown, therefore it is considered reasonable to conclude that V114 could provide protection against pneumococcal disease.

The safety profile of V114 is characterised by AEs that are mainly mild to moderate in intensity and of short duration. V114 is overall well tolerated with a slightly more unfavourable safety profile compared to PCV13. Overall, the beneficial effect associated with V114 outweigh the risks.

Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive from a clinical perspective. Therefore, the variation to extend the indication of Vaxneuvance is approvable.

## *3.8. Conclusions*

The overall B/R of Vaxneuvance is positive provided post-authorisation effectiveness data be collected within an agreed timeframe. As current limitations and uncertainties to the beneficial effects of its use, it is emphasised that no efficacy or effectiveness data is available for V114 in infants and children. The evaluation of the protective effect of the V114 vaccine regimen is based on bridging clinical immunogenicity results to immunogenicity data of a licensed pneumococcal vaccine, PCV13, that has been shown to be effective. There is no correlate of protection known for pneumonia or AOM, and indications of pneumonia and AOM were granted to the study comparator PCV13 based on non-inferiority of immune response to PCV7; hence the risk of biocreep for the shared serotypes, considering that the immune response required to induce a protective effect is unknown.

Specifically, in view of these considerations, the need to perform a post-marketing effectiveness study (PAES) has been identified as a key measure to the benefit risk balance of the new indication. The justification is informed by the fact that the current assessment on surrogate endpoints requires verification of impact on clinical outcome.

The following measures are considered necessary to address issues related to efficacy:

"The MAH should submit the final study report for study V114-032: A study to evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal Acute Otitis Media (AOM) in infants who receive V114 compared to infants not receiving V114."

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA and IIIB |

Extension of indication to include treatment of infants, children and adolescents from 6 weeks to less than 18 years of age for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media for Vaxneuvance. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to include editorial changes in the product information.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Study V114-032: To evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal Acute Otitis Media (AOM) in children. | Final study report due by 2Q2027 |

## *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0343/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.