EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2021
EMA/620380/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vaxneuvance

Common name: pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure No. EMEA/H/C/005477/0000

Note

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

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List of abbreviations

Quality terms:

^{1}H NMR	One-dimensional proton nuclear magnetic resonance
AEX	Anion Exchange
APA	Aluminum Phosphate Adjuvant
BI-RCV	Boehringer Ingelheim RCV
BPR	Bubble Point Ratio
BSE/TSE	Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies
CAD	Charged aerosol detector
CCI	Container closure integrity
CD	Circular dichroism
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CRM UF-FR	CRM197 Ultrafiltration Final Retentate
CRM_{197}	Cross-Reactive Material 197
DMSO	Dimethyl sulfoxide
FP	Finished Product
AS	Active Substance
DSC	Differential Scanning Calorimetry
DT	Diphtheria toxin
EtOH	Ethanol
FBI	Final Bulk Intermediate
FFB	Final formulated bulk
HVLD	High Voltage Leak Detection
INN	International Nonproprietary Name
KOP	Key Operating Parameter
KPA	Key Process Attribute
MBC	Monovalent Bulk Conjugate(s)
MCB	Master cell bank
Meq	Molar equivalents
MMC	Multimodal Cation
NaOH	Sodium hydroxide
P-188	Poloxamer 188
PACB	Pre-Adsorbed Conjugate Blend
PFA	Perflouroalkoxy
PFS	pre-filled syringe
PnP	Pneumococcal Polysaccharide
PnPs/Pw	Polysaccharide to powder weight ratio
PPQ	Process Performance Qualification
PS-20	Polysorbate-20
PS-80	Polysorbate- 80
TOS	Time out of storage
UF/DF	Ultrafiltration /Diafiltration
V114	Pneumococcal 15-valent conjugate vaccine
VBSF	Vaccine Biologics Sterile Facility
WCB	Working cell bank
WFI	Water for Injection
WP	West Point

Clinical Terms:

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 and Control
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. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 19 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Vaxneuvance, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

The applicant applied for the following indication:

"*Tradename* is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults 18 years of age and older".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0244/2019, P/0347/2018 and P/0339/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0244/2019 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP: **EMEA-C1-002215-PIP01-17**.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.4.2. Derogation(s) from market exclusivity

Not applicable

1.4.3. New active Substance status

The conjugates of serotypes 22F and 33F are biological active substances that are not previously approved as part of a medicinal product for human use in the European Union. The applicant's revised claim is agreed upon, as there is no product on the EU market which includes conjugated polysaccharides of serotype 22F and 33F.

1.5. Scientific advice

The applicant did seek Scientific advice from the CHMP on several occasions between 2010 and 2019. These are detailed below:

EMEA/H/SA/1492/1/2010/PED/III. The applicant sought advice on the development of the assays to measure serotype-specific IgG and OPA and bridging these assays to the WHO reference ELISA. Compliance with existing guidelines and completion of validation programme was stressed. Important aspects for the current application are the acceptance of PCV13 as a comparator by CHMP, and the recommendation to use Prevenar 7 to bridge back to the data on efficacy for the seven serotypes in the Prevenar 7 vaccine.

This SA also included a question regarding the use of bioburden reduced instead of sterile bulks of individually conjugated polysaccharides.

EMEA/H/SA/1492/1/FU/1/2017/III. The previous scientific advice was followed, and approaches comply with the guideline on bioanalytical method validation. It is commented that the validation reports should contain information on calibration standards, QC samples, assay stability data, assay robustness and assay interference. Finally, sera used during validation and bridging should represent the sera from the intended phase 3 programme. In addition, scientific advice was sought on the proposed clinical development programme. It was agreed that efficacy studies are not feasible and that an approval may be based on comparative immunogenicity. It was agreed that the Phase 3 study designs, subject populations, sample sizes, safety endpoints and immunogenicity endpoints appropriately supported the registration of V114 for the mentioned indication.

This SA also included a follow-up question on sterility testing of monovalent bulks.

EMEA/H/SA/1492/1/FU/2/2019/I. With this advice, the applicant sought feedback on various quality aspects spanning upstream intermediates, drug substance and drug product. The scientific advice focussed on in-process sterility testing of monovalent bulk conjugate, release and stability specifications for drug product and level of detail required for upstream intermediates in the MAA.

EMEA/H/SA/1492/1/FU/3/2019/I. The applicant sought feedback on a subset of quality topics. The scientific advice focussed on the equivalence of CRM197 drug substance intermediate sourced from two different suppliers, initial shelf life and strategy to ensure storage period extension.

Overall, the clinical development programme has been in agreement with general guidance on the clinical development of vaccines.

At present, there is no correlate of protection. The approach to licensure for V114, depending on immunobridging to a licensed PCV is agreed. The FDA agreed to a non-inferiority margin of 0.50, however, the clinical importance of meeting or not meeting this margin is unknown.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Daniela Philadelphy

The application was received by the EMA on	19 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 June 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vaxneuvance on	14 October 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 August 2021

2. Scientific discussion

2.1. Problem statement

V114 is a protein conjugated polysaccharide vaccine intended for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older.

2.1.1. 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.

2.1.2. Epidemiology

Streptococcus pneumoniae is a major cause of vaccine-preventable disease worldwide, resulting in considerable morbidity and mortality, particularly in older adults (≥65 years of age), adults ≥18 years of age with certain comorbid conditions (e.g., chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma), and immunocompromised adults (e.g., HIV, HSCT patients). According to the Global Burden of Disease Study 2016 (GBD 2016 Lower Respiratory Infections Collaborators, The Lancet), *S. pneumoniae* was "the leading cause of lower respiratory infection morbidity and mortality globally, contributing to more deaths than all other aetiologies combined in 2016 (1,189,937 deaths, 95% UI 690,445–1,770,660)".

In total 247,663 confirmed cases of IPD were reported by 29 countries in the EU in 2018 (ECDC, annual epidemiological report 2018). IPD was predominantly reported in the elderly and infant population, with age-specific notification rates being highest in those aged ≥65 years (18.7 confirmed cases per 100,000 population). In the United States (US), in 2018, there were an estimated 31,400 cases of IPD, with the majority occurring in adults. The estimated incidence in adults ≥65 years was 24 per 100,000. The case-fatality rate of IPD in the US is approximately 11%, accounting for approximately 3,480 deaths annually, with the majority of deaths occurring in adults. In Europe, among the 10,486 cases with known outcome in 2018, 15% (1,609) died. Mortality rates increased with age (ECDC, annual epidemiological report 2018). The case-fatality rate of IPD has not decreased over the past 2 decades.

Next to IPD, pneumococcal pneumonia is also responsible for significant morbidity and mortality. The incidence of pneumococcal pneumonia increases with age, with the highest rates reported in adults 80 years or older. Recent studies have shown that case fatality rates of pneumococcal pneumonia range from 2-7%, with higher rates noted among older adults. A recent prospective study found that, among adults hospitalised for non-bacteraemic pneumococcal pneumonia, 12.8% had a poor outcome, defined as a need for mechanical ventilation and/or shock/and or in-hospital death. The risk factors for pneumococcal pneumonia are similar to those for IPD, and include older age, immunocompromising conditions (e.g., HIV infection, primary immunodeficiency) and certain chronic illnesses (e.g., chronic respiratory disease, chronic renal disease, liver disease, heart disease, diabetes, and alcoholism). Studies conducted in the US and Europe show that pneumococcal pneumonia remains a considerable

public health problem in adults, despite the impact of infant vaccination with pneumococcal conjugate vaccines (PCVs) on disease caused by vaccine types.

2.1.3. Aetiology and pathogenesis

Streptococcus pneumoniae is a gram-positive encapsulated diplococcus, commonly asymptomatically colonizes the human nasopharynx. Carriage rates decline with age (approx. 1/3rd to 2/3rds of children and ≤10% of adults are colonised). 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.

The overall incidence of PD due to serotypes covered by current vaccines, excluding serotype 3, has significantly decreased in all age groups in regions where PCVs have been introduced into infant immunisation schedules. PCV use has led to an increase in the burden of disease due to non-vaccine serotypes. This phenomenon of serotype replacement has been observed especially in adult populations.

A recent review of available literature and surveillance data in Western Europe reported that 22F and 33F were among the key non-vaccine serotypes leading to disease (Htar et al. 2019 Expert review of vaccines). Data from 2018, which were reported in the 2020 annual epidemiological report on IPD by the European Centre for Disease Prevention and Control (ECDC), showed an increase in the proportion of IPD caused by non-Prevenar 13^{TM} serotypes, including serotype 22F, among adults 65 years and older (ECDC, annual epidemiological report 2018). Data from the US Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance network (ABCs) IPD surveillance network showed that the proportion of IPD due to serotypes 22F and 33F has increased following the introduction of PCVs. This increasing trend has also been noted in other countries. In 1998-1999 (prior to the introduction of PCVs), serotypes 22F and 33F caused 5.4% of cases among adults ≥65 years of age in the US. By 2018, serotypes 22F and 33F accounted for 15.4% of IPD cases in this age group (≥65 years) (Unpublished CDC ABCs 2018 data). These data indicate that serotypes 22F and 33F are increasingly causing IPD in several regions and countries.

2.1.4. Clinical presentation, diagnosis

IPD can lead to meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis. In adults, approximately 80-90% of cases of IPD present as bacteraemic pneumococcal pneumonia. Complications from bacteriaemic pneumococcal pneumonia can be severe and include adult respiratory distress syndrome (ARDS), sepsis, septic shock and death.

Community-acquired pneumonia (CAP) is a common disease resulting in considerable morbidity and mortality in older adults, and *S. pneumoniae* has been identified as one of the most common causes.

Studies conducted in the US and Europe show that pneumococcal pneumonia remains a considerable public health problem in adults, despite the impact of infant PCV vaccination on disease caused by vaccine types.

2.1.5. Management

Treatment options:

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data.

Most cases with clinical symptoms consistent with IPD (meningitis, pneumonia, sepsis) require initiation of empiric treatment before bacterial culture results are known. As a result, initial treatment generally includes broad-spectrum antibiotics that have efficacy against *S. pneumoniae* as well as other likely pathogens. The increasing rates of pneumococcal resistance to penicillin and other commonly used antimicrobial agents complicate treatment decisions and may lead to treatment failures with subsequent increased morbidity and healthcare costs.

Treatment of CAP caused by S. *pneumoniae* requires rapid initiation of appropriate antibiotic therapy and may require additional supportive care such as supplemental oxygen and sufficient fluid intake.

- For the outpatient treatment of healthy patients without comorbidities, recommended antibiotic therapy includes amoxicillin, doxycycline, or a macrolide. For outpatients with comorbidities (eg, diabetes, alcoholism, liver disease), combination therapy or a monotherapy consisting of a fluroquinolone is recommended.
- For inpatients, a fluoroquinolone or a combination of a β-lactam plus a macrolide are the preferred options.

Prevention options:

Prevention of PD in adults currently includes vaccination with pneumococcal polysaccharide vaccine (PPV) and/or PCV, as well as prophylactic use of antibiotics in certain clinical settings. The mechanism of action of all licensed pneumococcal vaccines is the induction of protective, serotype-specific, anti-capsular antibodies. Pneumococcal vaccines have demonstrated efficacy and effectiveness against invasive disease caused by the serotypes contained in the vaccines in both children and adults. Recommendations for pneumococcal vaccination in adults are typically based on age or risk for pneumococcal disease.

Pneumovax23 (pneumococcal vaccine polyvalent; PPV23) was licensed in the US in 1983 and nationally in the EU in the 80s. It is indicated for use in persons 2 years of age and older for whom there is an increased risk of morbidity and mortality from pneumococcal disease due to ageing and/or underlying medical conditions. It covers serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F.

Three PCVs have been licensed since 2000 across major markets, directly and indirectly resulting in a substantial reduction of pneumococcal disease caused by serotypes contained in the vaccines in countries where infant PCV immunisation programs exist. Prevenar was introduced in 2000 and has been widely adopted in national childhood vaccination schedules worldwide. Synflorix and Prevenar 13™ (PCV13) were licensed in 2009 and 2010, respectively, and replaced Prevenar for paediatric immunisation worldwide. PCV13 is the only PCV licensed for use in adults and covers serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

2.2. 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 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.

2.3. Quality aspects

2.3.1. Introduction

The finished product (referred to as Vaxneuvance) is presented as suspension for injection in prefilled syringes containing 15 distinct pneumococcal capsular polysaccharides (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F), each conjugated to the carrier protein cross-reactive material 197 (CRM197) originating from Corynebacterium diphtheriae C7. The content expressed as polysaccharide per serotype is 2 µg / 0.5 ml dose for all serotypes except 6B which is present in an amount of 4 µg / 0.5 ml dose.

Other ingredients are aluminium phosphate adjuvant, polysorbate, L-histidine, sodium chloride and water for injection.

The product is available in pack sizes of 1 or 10, with or without needles. A CE certificate has been provided for the needles.

2.3.2. Active Substance

The active substance is manufactured by conjugation of CRM197 to the pneumococcal capsular polysaccharides. Both of these are defined as intermediates in the process and included as separate sections in the report below.

2.3.2.1. Pneumococcal polysaccharide (PnP) intermediate

General Information

The Vaxneuvance polysaccharides are the purified pneumococcal polysaccharides (PnPs) from 15 serotypes of *Streptococcus pneumoniae*. The serotype designations using the Danish naming system are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. Each of the PnP types has a unique monomeric repeat unit structure. Capsular polysaccharide is polydisperse within a given batch,

consisting of a distribution of polysaccharide molecules of differing chain lengths (i.e., varying number of repeat units). Native polysaccharide average molecular masses range from across the 15 serotypes.

Pneumococcal polysaccharide vaccines specifically elicit a T-cell independent antibody response, which is not very effective in children under the age of two. Covalent conjugation of the pneumococcal polysaccharides to a carrier protein (such as CRM_{197} in Vaxneuvance) converts the immune response to a T-cell dependent response with improved immunological memory in pneumococcal vaccine-naïve children, thus priming the immune system for a future natural exposure to *S. pneumoniae* or a subsequent dose of vaccine. Compared to pneumococcal polysaccharide vaccines, pneumococcal conjugate vaccines are more effective in infants and generally elicit a stronger functional antibody response in older adults.

The applicant requested new active substance status for the product as a whole, but there is already one product on the market in the EU (Prevenar 13) containing pneumococcal polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7V, 9F, 14, 18C, 19A, 19F and 23F conjugated to CRM_{197}. Upon request the applicant has revised the claim for New Active Substance to include only conjugates of serotypes 22F and 33F which is accepted.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The intermediates, PnPs powders of the 15 serotypes are manufactured at a site where satisfactory GMP compliance has been demonstrated. Each serotype is manufactured independently utilising a common manufacturing platform with slight variations to accommodate differences in strains, PnPs, and process stream properties. Of the 15 Vaxneuvance PnPs serotypes, 14 are shared with the sponsor's currently licensed 23-valent pneumococcal polysaccharide vaccine and are referred to as legacy serotypes and are manufactured in the same way. One serotype, 6A, is not included in the sponsor's currently licensed 23-valent pneumococcal polysaccharide vaccine and is a novel serotype for Vaxneuvance.

The manufacture of PnPs AS intermediates is achieved in two main parts: (1) Upstream fermentation and inactivation modules, which produce the inactivated pneumococcal bacteria and, (2) Downstream purification process which consists of clarification, ultrafiltration, polishing and recovery modules to produce purified PnPs. There are no in-process or intermediate hold steps in the PnPs manufacturing process. Regarding batch and scale definitions for the Pneumococcal polysaccharides (PnP's), the applicant has indicated the target batch size in grams for each serotype of final purified powder.

One or more working cell bank vials are thawed and expanded in a fermentor until reaching a target cell density. The entire volume of the fermentor is transferred to the production fermentor and further cultivated. Optical density, dextrose, and lactate concentrations are recorded periodically. Additionally, in-process samples are drawn for culture purity and identity. The fermentation process is terminated when liquefied phenol is added to inactivate the culture in the fermentor. After phenol is added, the batch is incubated with constant agitation for a defined time period. After it is confirmed that the phenol concentration has reached the target, the batch is transferred to the inactivation tank where it is held for inactivation.

The inactivated broth is then purified by clarification (including flocculation and centrifugation), ultrafiltration (including endonuclease treatment of serotypes 1 & 3), polishing (including phenol precipitation, low cut alcohol fractionation and centrifugation) and product recovery (including high cut alcohol precipitation, centrifugation, ethanol trituration and drying and rehydration to minimise hygroscopicity.) The purified powder is stored at controlled temperature. The containers are the same

as already in use for the approved 23 valent Pneumococcal vaccine, and the information submitted is acceptable. The manufacture of the polysaccharides is adequately described in satisfactory detail.

The CRM_{197} manufacturing process includes an optional refiltration step that can be performed once in the event of a filter integrity test failure. Commercial and small-scale data demonstrates that the optional refiltration step is consistently capable of producing a product meeting its predetermined specifications and quality attributes.

Considering that serotype 6A utilised the historical platform manufacturing process and considering the successful manufacturing history of the process for the other 23 serotypes in the legacy vaccine, the process control strategy for serotype 6A maintained consistency with the approach used for the other serotypes. The testing has been described in sufficient detail. Depending on the chemical differences between the serotypes certain parameters differ between serotypes. The proposed limits have been accurately supported by development data.

The carrier protein CRM197 was first manufactured for early clinical use. The process was then transferred to a further manufacturing site and successfully validated. GMP batches were then successfully manufactured before the manufacturing site closed and material from this location has been used to support clinical trials. The process was then transferred, where engineering batches, PPQ and commercial manufacture batches were initiated to support the Phase 3 pivotal and lot consistency clinical trials, as well as routine commercial supply. During clinical development, the following changes were noted.

- Major changes between the two clinical sites were besides scale and site adjustments, inclusion of additional chromatography step (MMC), optimised control set points and composition of media/buffers for the production fermentation and purification steps and change of resin type.
- Major changes between the clinical and commercial sites were, besides scale and site adjustments, purifications steps HA and MMC divided into two cycles each, new WCB (originating from same MCB).

Regarding development of the pneumococcal polysaccharide intermediate, manufacture is based on technology already available to the applicant. Conjugation of the CRM197 to the pneumococcal polysaccharide has been optimised during development and described in the dossier. Appropriate comparability studies have been performed at the various stages of development.

Control of materials

Original wild-type isolates for all Vaxneuvance serotypes were received and utilised in production. Information on the source of the original wild-type isolates for the *S. pneumoniae* serotypes is provided. No animal-derived products were used in the production of the current master cell banks (MCBs) and working cell banks (WCBs) for all serotypes. The raw materials are the same as already approved for the 23 valent non-conjugated pneumococcal vaccine.

PnPs process performance qualification (PPQ) batches spanning all 15 serotypes contained in Vaxneuvance were manufactured to successfully validate the PnPs platform process. The redeveloped process for the original 23 PnPs serotypes was approved first in 2004 (USA) and subsequently globally. There have been no major process changes to the 14 PnPs serotypes used in Vaxneuvance since they were successfully validated for the Sponsor's currently licensed 23-valent pneumococcal polysaccharide vaccine.

The 15th Vaxneuvance PnPs serotype 6A has been developed specifically for Vaxneuvance and was introduced as the 24th PnPs manufactured at the commercial site. The serotype 6A control strategy leveraged a risk assessment evaluation of all process parameters, using ranges of the commercially manufactured serotype 6B as initial ranges for evaluation. Process parameter range-finding

experiments were then conducted. The established platform manufacturing process was deemed suitable for serotype 6A, and the same universal set of critical process parameters (CPPs) and critical quality attributes (CQAs) was applied with only minor variations in specification ranges. The PPQ data show that the production is consistent, controlled and robust.

Characterisation

The chemical structures of the repeating units of the pneumococcal polysaccharides included in this vaccine are well established. The repeating unit structures contain between two (serotype 3) and seven (serotype 7F) monosaccharides and exhibit considerable structural diversity in terms of monosaccharide composition, glycosidic linkages, and the presence or absence of short branched features. Repeating units for six of the serotypes contain either backbone (serotypes 6A, 6B, 19A, and 19F) or sidechain (serotypes 18C and 23F) phosphate groups. Serotypes 1, 7F, 9V, 18C, 22F, and 33F repeating units contain potentially labile *O*-acetate functional groups. Finally, the serotype 4 repeating unit contains a unique pyruvate moiety, and the serotype 5 repeating unit contains a unique ketone moiety.

One-dimensional proton nuclear magnetic resonance (^{1}H NMR) is used for routine PnPs release testing. The identity region of the ^{1}H NMR spectrum contains signals from the anomeric protons in the PnPs repeat unit. These PnPs spectral profiles are unique for each serotype, making it possible to distinguish one polysaccharide type from another. The serotype identity of the characterisation batches was established by a numerical point-by-point correlation with their associated reference batches, confirming the polysaccharides have the proper serotype repeating unit structures and demonstrates the consistency of manufacture for the chemical structure.

O-acetate is a component of the PnPs repeating unit structure for six of the Vaxneuvance serotypes (1, 7F, 9V, 18C, 22F, and 33F). While *O*-acetate content is not considered a critical immunological feature of these polysaccharides, it is a potentially labile moiety, making it an excellent marker for manufacturing consistency.

The polysaccharide content, or purity, of each PnPs bulk powder batch listed, was measured directly by quantitative ^{1}H NMR assay. This assay yields capsular polysaccharide content that is reported as a polysaccharide to powder weight ratio (PnPs/Pw).

The molecular size or weight-average molecular mass of each PnPs bulk is measured by high-performance size-exclusion chromatography with multi-angle light scattering and refractive index detection (HPSEC/MALS/RI). This method is a routine release test. For all these tests, the characterisation batch data are representative of pneumococcal polysaccharide bulks produced in the commercial facility. The data indicate that the attribute levels are consistent from batch to batch within a serotype. As stated by the Ph. Eur. monograph on Conjugated Pneumococcal Vaccines, depending on the chemical composition of the specific serotype of the polysaccharides, the following attributes should also be included: Total nitrogen, phosphorus content, uronic acid content, Hexosamines content, and methylpentose content. The applicant was asked to submit such data or justify its absence. It was raised by the company that the NMR assay applied in routine testing would replace the tests mentioned. The answer did not discuss the quantitative aspects of the assay but in the description of the method it is stated that similarity between each pairwise comparison is assessed by a calculated correlation coefficient. A comparison of two profiles positively identifies the sample with a homologous profile in the database, thereby matching the sample identity with that of a known serotype. Even if not expressing the content of the different functional groups in quantitative terms this will verify that the sample is comparable to the reference and thus fulfil the requirements.

Specification, analytical procedures, batch analysis, and container closure

The release and stability specifications for pneumococcal polysaccharide serotypes are provided. Overall, the tests (appearance and description, identification, impurities and microbiological quality) conducted are considered adequate.

The methods have been accurately described and appropriately validated.

The analytical methods to test the PnP's were properly described or reference was made to pharmacopoeial monographs.

Batch data have been shown in total from 79 batches of the different serotypes, varying from 4 to 8 batches per serotype. All batches fulfil the acceptance criteria. The acceptance criteria for molecular size and residual protein show differences from available batch analysis data. Results close to the outer ranges of the attribute would therefore, even if within specifications, indicate that the attribute is out of trend. The applicant was asked to explain action taken in such out of trend cases. The applicant explains that the results for molecular size and residual protein are not questioned in case they fall within the specifications and actions taken to clarify the reason for the out of trend result, if any, are not described. Further clarifications were requested in the D180 LOI: The applicant has committed to include serotype specific alert limits based on historical performance for relevant tests and has also described the action taken in case a result is with the specification but beyond the alert limit. These actions are considered acceptable.

Container closure

The PnPs Active substance Intermediates are stored in plastic bottles. The bottles are compliant with ISO 10993. The company has provided data to ensure that this material also meets the requirement of Ph. Eur. 3.1 and 3.2.

A risk assessment leveraging the results of an extractables study, the low-temperature storage and solid phase, concludes that the risk of carry-over of potential leachables into the final finished product is negligible.

Stability

A defined storage period is claimed for all serotypes.

For each serotype except 6A three batches have been stored ; for serotype 6A four batches are included in the study where initially only one of the batches has been stored , the remaining three batches have been stored r. Updated stability data for the batches of serotype 6A has now been submitted supporting a defined storage period. Attributes tested are described. The data submitted shows that the relevant parameter is stable over time, even if some variability is shown over time due to the method. In the stability studies neither the acceptance criteria in force at the time of the study nor the current requirements are given. In this case the results all fulfil the proposed acceptance criteria and no further information is needed in relation to this but for future applications information of acceptance criteria for the attributes should be considered as it simplifies the assessment. This applies to the PnP and CRM_{197} intermediates and the AS and FP.

The applicant was asked to further justify the number of freeze-thawing cycles allowed for PnPs in the production of the conjugates. In their response, data to support defined freeze thaw cycles were submitted and the results indicated that this number can be accepted.

Based on the assessment of the data provided the claimed shelf life and storage conditions claimed for all serotypes are accepted.

2.3.2.2. Cross-Reactive Material 197 (CRM_{197}) intermediate

General Information

Cross-Reactive Material 197 (CRM_{197}) protein is an intermediate used in the manufacture of the Pneumococcal 15-Valent Conjugate Vaccine (Vaxneuvance) active substance. CRM_{197} is a nontoxic (enzymatically inactive) form of diphtheria toxin (DT), wherein the native glycine at position 52 in DT is replaced with a glutamic acid. Covalent conjugation of the pneumococcal polysaccharides to a carrier protein (such as CRM_{197} in Vaxneuvance) converts the immune response to a T-cell dependent response with improved immunological memory in pneumococcal vaccine-naïve children, thus priming the immune system for a future natural exposure to *S. pneumoniae* or a subsequent dose of vaccine. The general information provided on CRM_{197} is found acceptable.

Manufacture, process controls and characterisation

Manufacturing and process controls

The intermediate CRM_{197} is manufactured at a site where satisfactory GMP compliance has been demonstrated.

The CRM_{197} protein manufacturing process is based upon a specified process utilising *Pseudomonas fluorescens* as a host.

The CRM_{197} protein manufacturing process is initiated by the fermentation of the *Pseudomonas fluorescens* cells, followed by harvest, osmotic shock to release the CRM_{197} protein from the *P. fluorescens* periplasm and flocculation of cell debris. Further purification steps include clarification of the cell debris, three sequential chromatographic steps, ultrafiltration, membrane chromatography and a bioburden reduction filtration prior to CRM_{197} final bulk intermediate (FBI) filling. The CRM_{197} batch size is based on a post-inoculation working volume in production reactor. The FBI is stored.

The manufacturing process of CRM_{197} is described in flow diagrams, stating process intermediates and in-process controls (IPCs), as well as CPPs and CQAs for each step. Only two IPC and two CPPs are proposed for the entire CRM_{197} process. However, details about key operating parameters (KOP), CQA and key process attributes (KPA) are provided in the dossier. The KOPs proposed for each step are adequate, with corresponding acceptable criteria. Reprocessing is proposed for the bioburden reduction filtration step, in the event of a filter integrity test failure.

Process validation and/or evaluation

The manufacturing process for CRM_{197} was validated at a specified site and data have been presented. Validation results from KOPs, KPAs, CQAs and CPPs are provided for all steps. All validation criteria were met. The process validation was found acceptable.

Hold times were validated for specified process intermediates and the proposed hold times are found acceptable.

The CRM_{197} manufacturing process includes an optional refiltration step that can be performed once in the event of a filter integrity test failure. Commercial and small-scale data demonstrates that the optional refiltration step is consistently capable of producing a product meeting its predetermined specifications and quality attributes.

Commercial-scale studies for chromatography resin re-use are ongoing. The data at commercial scale supports the proposed lifetimes.

Manufacturing process development

Three sites have historically been used for the clinical and commercial production of the intermediate CRM_{197}.

The differences between processes at the three sites are sufficiently described and justified.

An extended comparability exercise has been executed using material from clinical and commercial sites and. It should be noted that both sites have been used in clinical phase 3 trials. The comparability exercise included a comparison of release data from 20 vs 14 batches. All batches met the release specification acceptance criteria. Additional characterisation analyses were also included in the comparability package. Even though some differences are noted between the two sites/processes the differences have been acceptably justified, and comparability for materials produced at the two sites is agreed upon. Stability studies performed using materials from both sites, support the claim of comparability.

The control strategy for each step of the CRM_{197} process was based on the clinical control strategy, risk assessment, and lab-scale studies. Risk evaluation/parameter classification justifications are provided for each parameter (information on severity and risk priority number score). Acceptable information on laboratory process characterisation studies has been provided.

All KOPs, CPPs, KPAs and CQAs are listed for each step with corresponding acceptance criteria. The KOP/KPA acceptance criteria have been changed since the PPQ runs, based on data generated at a laboratory scale. The changes to the CRM_{197} control strategy (changes in the classification of parameters and changes to acceptance criteria) after the PPQ runs have now been summarised, justified, and supported by data.

Characterisation

CRM_{197} is a nontoxic (enzymatically inactive) form of diphtheria toxin (DT), wherein the native glycine at position 52 in DT is replaced with a glutamic acid. This single amino acid substitution occurs in the active site of the catalytic domain and is the basis for the nontoxicity of CRM_{197}. CRM_{197} retains the other structural features of DT.

Diphtheria toxin is a 535 amino acid protein. DT is composed of two subunits that can be proteolytically cleaved into the A fragment containing the catalytic domain and the B fragment containing the transmembrane domain and receptor-binding domain. From the published crystal structure, DT is a Y-shaped molecule. The base of the Y contains the transmembrane domain, while the two arms of the Y contain the catalytic and receptor-binding domains.

The primary, secondary, tertiary, and quaternary structures of carrier protein CRM_{197} were evaluated using a series of biochemical and biophysical characterisation techniques. The three CRM_{197} PPQ batches manufactured at commercial-scale were used for the characterisation analyses.

In general, the methods chosen, and the results provided demonstrate that CRM_{197} has been well characterised.

The presence of A and B fragments were elucidated since CRM_{197} has the same features as diphtheria toxins (proteolytical-susceptible clipping sites). The results demonstrated that the commercial-scale purification process limits the production of these fragments and/or effectively removes them.

The lack of diphtheria toxin activity was also investigated by ADP-ribosylation activity analysis. The three PPQ batches were found to exhibit acceptably lowADP ribosylation activity relative to that of DT. This supports the consistent lack of toxicity in commercial-scale CRM_{197} batches.

Process related impurities elucidated were determined and specified. The levels of each process-related impurity demonstrated clearance, with concentrations at an acceptable level. No analysis of process-related impurities is proposed in the release specification. This was initially endorsed except for two specified impurities. To further support the initial claim the applicant provided more data showing consistently very low levels of these impurities and it can be endorsed that these attributes are also not included in routine testing.

The raw materials used during the manufacture of CRM_{197} are included in the dossier. Further, CRM197 fermentation process media are described (list of components included with corresponding concentrations). Purification buffers and solutions and chromatography resins and materials used in CRM197 purification are presented and are satisfactory.

Specification, analytical procedures, batch analysis, and container closure

The specification for CRM_{197} complies with Ph. Eur. 5.2.11 (*carrier proteins for the production of conjugated polysaccharide vaccines for human use*) and includes analysis of identity, pH, protein content and bacterial endotoxins.

The following compendial methods are used for release of CRM_{197}; bioburden (Ph. Eur. 2.6.12), Endotoxin (Ph. Eur. 2.6.14), pH (Ph. Eur. 2.2.3), Appearance (Ph. Eur. 2.2.1 and 2.2.2). Results from method verification are presented for each compendial analysis.

Detailed descriptions of the non-compendial analytical procedures included in the CRM_{197} specification are provided. Information on equipment, reagents, controls, method acceptance criteria (system suitability tests and sample acceptance) and reportable results are given. Validation of non-compendial methods was performed in accordance with ICH Q2 requirements.

The description and validation of analytical methods for CRM_{197} are found acceptable.

The specification for CRM_{197} has been established based mainly on Ph. Eur. requirements and batch data (release and stability). The acceptance criteria proposed are in general considered acceptably justified based on historical data and are in line with Ph. Eur. 5.2.11 Carrier proteins for the production of conjugated polysaccharide vaccines for human use.

The limit for the monomer showed differences to the results seen in the data submitted. The limit proposed) is set based on the minimal requirement in Ph. Eur. 5.2.11. Thus, results close to the proposed release limits would be considered outliers. The applicant was asked to describe the actions taken when out of trend results are noted and these actions are considered adequate.

Batch analysis

Three manufacturing sites have historically produced CRM_{197} intermediate. Batches from two sites have been used in clinical phase 3 trials. Results from seven batches from the currently used commercial site, have been presented. Furthermore, results from two batches and 18 batches from these sites are shown. All results are within the proposed acceptance criteria for each CQA.

Container closure system

The CRM_{197} FBI is filled into plastic bottles. A dimensional drawing is provided in the dossier. Further, a specification of the is shown. The irradiated bottles meet the requirements of ISO 10993-5.2009. The information on the container closure system is found acceptable.

Stability

The applicant proposed a shelf life of for CRM_{197} intermediate when stored at the recommended temperature.

To support this claim, the applicant provided data from three representative PPQ batches from clinical site stored under long term conditions. Additionally, data from three commercial site batches stored for defined period were also provided. The results demonstrated that the CRM_{197} intermediate can be stored for a specified period and conditions.

The stability testing protocol for the PPQ batches is planned for a specified period. Thus, a post-approval commitment to continue these stability studies has been included in the dossier.

Accelerated studies demonstrated that a time out of storage (TOS) could be allowed for a specified period. The intact monomer is a stability indicating parameter and decreased at accelerated conditions.

Stressed studies demonstrated that a TOS could be allowed for a specified period and conditions.

Since the manufacturing process description for MBC includes refreezing of the CRM_{197} containers after thawing, the applicant was requested to discuss the aggregation of CRM_{197} and further justify the number of freeze-thawing cycles allowed of CRM_{197}. Such data have been submitted and a specified number of freeze thaw cycles can be accepted.

In conclusion, the claimed shelf life and storage conditions for CRM_{197} intermediate is considered to be accepted.

2.3.2.3. Active Substance Monovalent bulk conjugate

General Information

The Vaxneuvance active substances are composed of pneumococcal polysaccharide (PnPs) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A,19F, 22F, 23F, and 33F individually conjugated to CRM_{197} carrier protein. Each purified conjugate bulk is a distinct active substance referred to as the serotype-specific monovalent bulk conjugate (MBC).

Conjugation of PnPs and the CRM_{197} carrier protein is achieved via reductive amination. However, native PnPs do not contain the necessary reactive aldehyde groups. Rather, aldehydes are first introduced in the polysaccharides via oxidation in a step referred to as activation. For many serotypes, a percentage of polysaccharide repeating units is activated, although the manufacturing target is intentionally varied with serotype. Reductive amination chemistry is then used to link the recently introduced aldehydes on activated polysaccharide molecules with primary amines on CRM_{197}, predominantly in the side chains of lysine residues.

Given the numerous activation sites introduced to each polysaccharide molecule and the 39 lysine residues in each protein molecule, conjugates form complex networks of covalently cross-linked polysaccharide and protein molecules. Within each conjugate molecule, polysaccharide chains may contain varying numbers of repeating units. Additionally, each conjugate molecule may contain different numbers of polysaccharide and protein molecules. There may also be different numbers of cross-links between polysaccharide and CRM_{197} molecules. As such, a single monovalent bulk conjugate batch of a single serotype is a polydisperse distribution of heterogeneous conjugate molecules.

Crosslinking achieved between polysaccharide, and CRM_{197} molecules is generally in the specified ranges. The weight-average molecular mass of the MBC is monitored by HPSEC/UV/MALS/RI. Weight-average molecular masses measured by this assay ranges were specified across the 15 serotypes.

Manufacture, process controls and characterisation

Description of manufacturing process and controls

The MBC is produced by the stated manufacturer. EMA initially determined that the current MIA and GMP certificate for this site did not cover the manufacture of vaccines intermediates. This was therefore raised as a major objection. Updated documentation including the manufacturing operations related to immunological conditions was submitted and the major objection resolved.

The pneumococcal 15-valent conjugate vaccine contains 15 distinct PnPs serotypes. In this process, the PnPs powder is dissolved, size reduced to a target molecular mass, chemically activated, and buffer-exchanged by ultrafiltration. The CRM_{197} protein carrier is then conjugated to the activated PnPs. The resulting conjugate is purified before a final bioburden reduction filtration step. Due to the nature and structure of the different PnPs serotypes, there are serotype-specific process steps and operating parameters throughout the manufacturing process to ensure the resulting MBC meets all required specifications. The bulk conjugate manufacturing process has been adequately described, including conjugation, purification and filling. No reprocessing is described.

MBC process parameters were identified through process risk assessment and subsequent small-scale process characterisation (PC) studies. PC experiments were generally designed to evaluate ranges wider than the expected normal operating range (which was designed around the target) based on ease of control and development knowledge. Statistical models were used to evaluate the PC data, considering both statistical and practical significance to identify critical process parameters (CPP). During the PC studies, several unit operations were determined to be sensitive to process variability and enhanced in-process control strategies were established, as needed by serotype, to ensure process consistency. The control of critical steps and intermediates has been acceptably described as are the methods used in the control and their validation.

Process validation and/or evaluation

PPQ data demonstrate that all batches met the pre-defined validation criteria. The process validation data supports the design of the processes resulting in a reproducible output. All PPQ lots fulfilled the pre-set criteria. The MBCs are produced via a low bioburden process which have been discussed in earlier scientific advices with EMA as the monovalent conjugates will be sterile filtered in preparation of the finished product. The shipping validation supports that the packaging configurations will give sufficient thermal and physical protection.

Manufacturing process development

The applicant has submitted a very comprehensive and detailed description of the manufacturing process development. The basis for classification of criticality of attributes and parameters allows a proper assessment of the claimed criticality and the proposed control strategy to avoid certain risk factors.

Characterisation

The structural features of the activated PnPs intermediate and of the MBCs for each serotype were evaluated using a series of biochemical characterisation techniques. Additionally, levels of MBC matrix components were assessed.

Data are in most cases reproducible within serotypes and also when comparing earlier process versions. Where some differences are seen, these have been acceptably explained.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Analytical test methods and acceptance criteria (release and stability) used to assure the quality of Vaxneuvance MBC are provided. These include appropriate tests for physicochemical attributes, appearance, identity, assay (polysaccharide and protein content), purity conjugated and free polysaccharide), and microbiological aspects. The specification reflects the company proposal after requests for further justifications of certain attribute acceptance criteria.

The test attributes in the specifications follow what is stated in Ph. Eur. for the monovalent conjugate bulk. The description of the analytical methods and their validation is acceptable. Historical and currently used CRM_{197} reference standards have been sufficiently described (manufacturing, qualification, re-testing and stability testing).

The PPQ batches all show results well within the applied acceptance criteria and very good reproducibility between batches. A similar picture is seen for the other supporting data submitted, indicating that the process is under good control. Release data from attributes with numerical limits were statistically analysed to set commercial product specifications. GMP batches manufactured at commercial scale were the primary dataset used in the formal statistical analysis of process risk and were the focus of any proposed updates to numerical specification limits.

The applicant did initially not consider clinical aspects in proposing the acceptance criteria except for residual cyanide and endotoxins, and the acceptance criteria were in many cases different from the levels seen in PPQ and earlier batches, including clinical ones. Many of these tests can have a clinical impact but are not tested at the finished product stage. These include conjugate molecular size, polysaccharide to protein ratio, free protein and free polysaccharide. The applicant was asked to justify that the proposed limits will lead to a safe and efficacious product representative of what has been used in clinical trials. In their response the applicant proposed tightening of the limits for certain attributes. The proposed acceptance criteria for free protein and PnP:Pr ratio were considered acceptable, but the ones for conjugate size and free-polysaccharide were requested to be further revised unless justified. The applicant subsequently presented revised acceptance criteria and supported these with results from batches used in clinical trials.

Container closure

The MBC active substance is filled into plastic bottles. Sterilisation of the material has been described. Extractables studies performed with various solvents under extreme condition found no substance greater than the threshold for safety concern.

Stability

The stability data submitted is a blend of PPQ batches, commercial batches, scaled down pilot/clinical batches manufactured at specified site using the same process as now proposed and batches for 5 serotypes produced at specified site using the same manufacturing process as now proposed. Updated stability data have been submitted.

Stability studies for PPQ batches were conducted at: long-term condition, accelerated condition, and stress condition. The accelerated and stress storage conditions are performed to support distribution

and Time Out of Storage (TOS) events. Additional studies were included and a photostability study to determine photosensitivity in alignment with ICH Q1B.

PPQ batches per serotype batches and 2-3 representative clinical batches per serotype were placed on stability to support shelf-life. Stability indicating methods have been used for the stability studies.

In summary, the monovalent bulk conjugates of serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 18C, 19A, 19F and 23F have a specified shelf life of at long-term condition. The shelf life of serotypes 3, 14 and 33F is also specified at long-term condition.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Vaxneuvance finished product (FP) is a sterile opalescent liquid suspension for injection. The FP provides a total of 64 µg/ml of total pneumococcal polysaccharide (PnPs) antigens conjugated to CRM_{197} (~ 60 µg/mL) as monovalent bulk conjugate (MBC) in the final formulated bulk (FFB).

The composition for the Vaxneuvance formulation per 0.5 mL dose is presented below.

Table 1 Composition

Description	Input Material	Content per Dose (0.5 mL)	Function	Quality Standard
Active Ingredients (MBC)	**Total PnPs (Serotype)**	2 µg	Active	Internal Specification
	1			
	3			
	4			
	5			
	6A			
	6B	4 µg		
	7F	2 µg		
	9V			
	14			
	18C			
	19A			
	19F			
	22F			
	23F			
	33F			
Carrier Protein	CRM_{197}	~ 30 µg		
Inactive Ingredients	Aluminum Phosphate Adjuvant (APA)	125 µg[a]	Adjuvant	Internal Specification
	Polysorbate-20	*	Surfactant	*Ph. Eur.*/NF
	L-Histidine	*	Buffer	*Ph. Eur./USP*
	Sodium Chloride	*	Isotonicity	*Ph. Eur./USP*
	Water for Injection	*	Solvent	*Ph. Eur./USP*

[a] Al^{3+} ions

The FP is filled into a 1.5 mL glass syringe and stored at 2–8ºC.

In some markets, sterile Luer lock needles may be co-packaged with the prefilled syringe. Three sizes of CE marked needles are available and 1 to 2 needles are co-packaged based on market preferences. The gauge and length of the needles are as follows: 25G X 5/8 inch (0.5 X 16mm), 25G X 1 inch (0.5 X 25mm) or 23G X 1 inch (0.6 X 25mm)

Pharmaceutical development

Aluminium phosphate adjuvant (APA) is used to enhance the immunogenicity of Vaxneuvance.

Manufacturing process development

The formulation and filling processes have been maintained, with minor optimisations, throughout the development of Vaxneuvance.

The applicant was asked to discuss if the adsorption and the manufacturing process impacts the level of free polysaccharides as determined on the monovalent conjugated bulk. In the response it was justified that no significant impact on the level of free polysaccharide is foreseen, which was accepted.

Vaxneuvance FP contains no overages.

The recoverable volume was shown to by far fulfil the minimum capability value. No leaks were detected by High Voltage Leak Detection Test.

A toxicological assessment of the extractables was performed. Based on the amounts observed, there were no extractables found that would present an increased risk to patient safety during acute or chronic dosing.

The applicant initially submitted some information in relation to nitrosamines as leachables/ extractables but not performed a risk assessment on the presence of nitrosamine impurities in the product in accordance with the published Art. 5(3) Referral on Nitrosamines (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf) including both active substance and finished product. This was raised as a Major objection. The applicant has now submitted an extensive and detailed nitrosamine risk assessment. This document describes an analysis of the risks at the level of the raw materials, water and the chemical conjugation process. Also, potential sources from excipients and primary packaging were extensively discussed. No sources of potential nitrosamine risk were identified. As such it is deemed acceptable that no confirmatory testing is required.Metal impurities were studied in the conjugated polysaccharide bulks substances while the formulation with additional excipient and package components are of pharmacopoeial grade and have not contributed further to impurity content of the finished product.

Presentations with or without needles are described in the SmPC. An EC certificate issued by TüV Rheinland, Nûrnberg, for K-Pack II hypodermic needles produced by Terumo has been provided.

2.3.3.2. Manufacture of the product and process controls

Description of the manufacturing process and controls

The finished product and APA (adjuvant) are manufactured at the specified site. The formulation batch size range for Vaxneuvance is qualified. Satisfactory GMP compliance has been provided for this manufacturer.

The Vaxneuvance FP manufacturing process consists of four main steps: 1) Buffer and Intermediate preparations 2) Thawing and transfer of monovalent bulk conjugates (MBCs) 3) Formulation and 4) Filling, visual inspection and storage.

The duration of the adsorption to APA and the agitation applied during this process to produce the FFB was requested in the initial assessment. The applicant has described the duration and agitation and studies on which these parameters are set but there were still some concerns in relation to this following the D121 response. In response and based on the validation data provided, the minimal period of agitation has been indirectly justified. The data submitted indicates that the agitation applied will result in a homogenous suspension. The data on serotype specific adsorption kinetics indicate that there is a slight increase in adsorption through mixing but not significantly higher compared to unmixed sample. Data have also been shown indicating that longer agitation does not increase the degree of adsorption. This taken together with the introduction of the test for degree of adsorption in the specifications with the updated acceptance criteria will allow for a degree of adsorption which is under control.

Aseptic filling and stoppering of the Vaxneuvance FP in syringes occur under defined conditions for microbiological control. An automatic filling machine, equipped with sterile components, aseptically fills the FFB into syringes such that each syringe contains a minimum recoverable volume. The syringes are stoppered automatically. During filling, in-process weight checks are performed.

The combination product assembly process is an automated process. The assembly of the plunger rod into the PFS is completed by torquing the un-labelled syringe into the plunger rod. The unlabelled syringe assembly is labeled by the syringe labeller.

A thermoformed tray is molded inline, and the finished assembled syringe is placed into the tray. The lidding stock is sealed onto the tray and trimmed. The sealed trays are placed into a carton with a package insert.

Process validation and/or evaluation

All CPPs that were evaluated as part of the PPQ met specifications, all in-process controls evaluated as part of the PPQ were met, and all CQAs that were evaluated as part of the PPQ met specifications.

The results of the PPQ study provide documented evidence that establishes, with a high level of assurance, that the manufacturing process for Vaxneuvance FP, consistently produces product meeting predetermined quality attributes. The ranges seen in the statistical analysis is often considerably tighter than the proposed acceptance criteria.

Shipping qualification studies of Vaxneuvance FP bulk and finished product in PFS were conducted to demonstrate that the selected commercial packaging components (e.g., cartons, shippers, thermal containers) will maintain structural and product-image integrity from both typical and dynamic transportation hazards. Different active and passive thermal containers have been qualified that support the shipments of Vaxneuvance filled finished product and packaged finished product. These containers are currently in use with other commercial products.

The final assembly and packaging PPQ study demonstrates that the process of assembling the Vaxneuvance FP PFS with the plunger rod produces a combination product meeting all predefined performance acceptance criteria. The assembly and packaging PPQ were performed on validated equipment designed for the final assembly operation of the Vaxneuvance combination product.

2.3.3.3. Product specification

The description of the analytical methods and their validations are acceptable.

The applicant has acceptably described the establishment of the primary reference standard and the secondary reference standards, and these are considered relevant for their intended use.

Batch analysis

Batch results have been presented. Overall, the results indicate excellent reproducibility. Some tests, are no longer included in the specification, but results are included in the batch data showing good reproducibility.

Justifications of specifications

The specifications for the FP were established based on regulatory guidelines, analytical capability, process capability, clinical manufacturing experience, and stability performance. The applicant subsequently tightened the shelf life limits to 70-130% throughout the shelf life. The saccharide content is stable during storage and there is no need for tighter release limits to compensate for potential loss during the shelf life.

The applicant was also asked to justify that the acceptance criteria applied in the aluminium content assay which can be considered clinically qualified. The applicant proposed to tighten the release acceptance criteria for aluminum content and was considered acceptable.

Justification of Methods Not Included in the Commercial Specifications

The proposed specifications are considered acceptable.

2.3.3.4. Stability of the product

Stability information for Vaxneuvance finished product stored under recommended 5°C / Ambient Humidity (2-8°C) and supportive conditions are provided. Stability studies were performed under ICH conditions, using stability indicating assays.

All data remained within the stability specifications at the time of testing. The submitted data indicate there have been no significant changes in terms of potency, quality or purity for the Vaxneuvance FP, when stored at the long-term storage condition of 5°C (2 to 8°C). The data to date indicate there have been no significant changes in quality for the Vaxneuvance FP in the PFS image when stored at 1°Cand 25°C for 30 days and 8 weeks respectively, to support short duration excursions to these temperatures.

The results of the photostability study demonstrated that the confidence interval for the unlabeled syringe unprotected by the secondary pack was not met for 3 serotypes indicating photosensitivity; however, the secondary pack provided appropriate protection from the effects of light exposure specified in ICH Q1B. The study supports the recommended storage condition for the Vaxneuvance FP syringes outside the secondary pack to be "protected from light."

During the procedure the applicant has submitted further stability dataBased on the data submitted the proposed shelf life of 24 months when stored at 2-8°C can be accepted. The product can support time out of storage up to 25°C and 48 hours for the clinician/end user and the latter is reflected in the SmPC.

In conclusion: the finished product shelf life is 24 months when stored at (2-8°C). The product should not be frozen and the pre-filled syringe stored in the outer carton in order to protect from light.

Vaxneuvance should be administered as soon as possible after being removed from the refrigerator. In the event of temporary temperature excursions, stability data indicate that Vaxneuvance is stable at temperatures up to 25°C for 48 hours.

2.3.3.5. Adventitious agents

Raw materials of animal origin have been addressed in this part of the dossier. BSE/TSE risk assessment for each raw material is provided, and the risk was considered negligible, this is endorsed.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has provided a very comprehensive documentation of the 4 different parts in the quality section- Pneumococcal polysaccharides of 15 serotypes, the CRM_{197} carrier, the 15 MBC and the finished product. It describes in detail the different components of the vaccine, the development of their manufacturing processes and the control strategy to verify that the processes are under control leading to a product of good and consistent quality. Quality by design principles have been applied in the development of the product and is also used in production. The quality of the resulting product is highly consistent with a very low batch to batch variability in most attributes. There is also a good historical comparability within the serotypes when looking at earlier versions of the processes.

Two major objections were identified in the initial assessment. One related to the manufacturer of the MBC, where the manufacturing and importation authorisation needed to be updated to include manufacturing operations related to immunological products, the other related to an insufficiently detailed risk assessment in relation to the possible presence of nitrosamines in the product emanating from the Active substance and Finished product processes. Both of these have now been resolved.

In addition, 53 other concerns were initially identified. These are now resolved, and the product can be recommended for approval from a quality point of view.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

No quality recommendations have been raised.

2.4. Non-clinical aspects

2.4.1. Introduction

The pivotal nonclinical toxicology studies of V114 were performed according to GLP and were conducted in an OECD member country.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

For the pharmacodynamics (PD) of this product, no protection studies have been conducted. Only data on immunogenicity are present, while the immunogenicity has been tested on the functionality of the antibody response. So, protection measures are rather indirect. However, a direct protection animal model is not possible.

The applicant has shown that the response at the 13-15 serotypes with this product as Formulation B is similar to the immune titers of Prevenar, in both New Zealand Rabbits and in infant monkeys (2-6 months of age). The data in the animals suggest that the new vaccine V114 is as active as Prevenar.

The immunogenicity data in rabbits and infant rhesus monkeys have shown that V114 in Formulation B induces functional antibody activity, which is expected to protect against pneumococcal infection. From a regulatory point of view, this is the most important conclusion from these studies. Ten (10) other rabbit studies have been devoted to earlier formulations during the development of this product.

There is no further discussion on the choice of an adjuvant or whether an adjuvant is needed. The increase of the immunogenicity by aluminium phosphate has been shown in early developmental studies, not shown in this assessment report. It is noted that this adjuvant is also used in Prevenar.

Data on the immune system parameters such as B- and T-cell response, or the response of various interleukins are not present, simply as this type of studies has not been conducted. Since this product is very similar to Prevenar, such data are not considered necessary.

2.4.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not performed for V114 since the vaccine did not show any systemic effects apart from the expected immune response. This is conformed to the relevant Guidance.

2.4.2.3. Safety pharmacology programme

Standalone safety pharmacology studies were not performed for V114. According to WHO "Guidelines on Nonclinical Evaluation of Vaccines" (2005) [Ref. 4.3: 03R07T] and "Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines" (2013) [Ref. 4.3: 04NHDV], safety pharmacology tests for vaccines should be performed only if data from nonclinical and/or clinical studies suggest that the vaccine may affect physiological functions (central nervous system, respiratory, cardiovascular, or renal functions) other than the immune system. V114 was tested in nonclinical toxicity studies in rats and physical signs, clinical pathology endpoints, or pathology endpoints did not indicate any adverse effects on the central nervous, cardiovascular, renal or respiratory systems. In addition, V114 has been tested in human clinical studies and apart from the expected immune response, there has not been any evidence of systemic effects (such as effects on the circulatory and respiratory system) caused by V114.

Taken together, these data indicate that V114 had no effect on physiological functions in nonclinical or clinical studies. Therefore, standalone nonclinical safety pharmacology studies were determined not to be necessary for V114.

2.4.2.4. Pharmacodynamic drug interactions

Studies evaluating pharmacodynamic drug interactions with V114 have not been conducted. The potential interaction with other drugs or vaccines can only be addressed in clinical studies.

2.4.3. Pharmacokinetics

No pharmacokinetics studies have been conducted for V114. This is consistent with WHO Guidelines on non-clinical evaluation of vaccines (2005), indicating that pharmacokinetics are not required for vaccines.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single dose toxicity studies were performed. This is agreed upon.

2.4.4.2. Repeat dose toxicity

Three repeated dose toxicity studies were performed in rats with V114. In the first, 2 different adjuvants were compared (APA [32 ug PnPs with 125 ug APA/dose and 64 ug PnPs with 187.5 ug APA/dose] vs MAA). This study was conducted with an early-stage formulation. The second and third were conducted with 32 µg /dose in 250 µg/mL APA (formulation B, the current proposed marketed formulation). In the third, V114 was administered via the subcutaneous route. In all studies, the vaccine was administered once every 3 weeks for a total of 5 doses. APA only groups were included in the first and third studies. Assessment of immunogenicity is discussed below.

In both studies using intramuscular administration (the intended clinical route), no effects other than slight to moderate effects in the lymphoid tissues and treated injection sites were observed. Such effects are expected following a vaccine-induced immune response and are of limited toxicological significance. These effects included haematological findings (very slight to slight increases in leukocyte, neutrophil, and monocyte counts; slightly decreased reticulocyte counts in males and slightly increased counts in females), very slight changes in coagulation parameters (increased fibrinogen and decreased prothrombin and partial thromboplastin time), biochemical changes (slight decreases in albumin and slight increases in globulin, and associated slight decreases in the total albumin/globulin ratio; very slight decreases in total protein in females). All these changes were partially or fully resolved during the treatment-free period.

Furthermore, slight to marked inflammation at the injection sites was observed, correlating with grossly noted focal red or tan discolouration of quadriceps muscles. Although the inflammation persisted in the 4-week treatment-free period, severity was reduced and was consistent with partial and ongoing resolution of the inflammatory response. In fact, all these findings can be interpreted as an inflammatory and immunological response to the vaccine, which is transient and to be expected from a vaccine.

The study using subcutaneous administration showed similar results.

According to the applicant, the NOAEL for formulation B was 32 µg Ps/dose, providing a 200-fold exposure multiple on a µg/kg basis.

2.4.4.3. Genotoxicity

Studies on genotoxicity or carcinogenicity were not performed because these are not generally required for vaccines according to the WHO Guidelines on the non-clinical evaluation of vaccines, 2005.

2.4.4.4. Carcinogenicity

Studies on carcinogenicity were not performed because these are not generally required for vaccines according to the WHO Guidelines on the non-clinical evaluation of vaccines, 2005.

2.4.4.5. Reproductive and developmental toxicity

To evaluate the potential effects of V114 on reproduction and development, an embryo-fetal developmental (EFD) and preweaning toxicity study and a postnatal developmental (PND) toxicity study were performed in rats. Assessment of immunogenicity is discussed below. A second EFD study, which was initiated to evaluate further the potential effects of V114 on kidney and urinary tract development observed in the first EFD study, was terminated early because the observation of RPD was not reproduced in the postnatal development study. All studies were performed with Formulation B.

The absence of stand-alone fertility studies is agreed since they are not routinely required for vaccines. The histopathology data from the repeat-dose GLP toxicity studies in rats do not raise any concerns that the V114 vaccine adversely affects male or female reproductive organs.

In an EFD and preweaning toxicity study in rats with intramuscular administration of 32 µg/dose in 250 µg/mL APA 28 and 7 days prior to mating and on GD6 and LD7, no V114-related maternal toxicity was observed. In addition, there were no effects on fetal outcomes, except for an increased incidence of RPD in F1 pups examined on PND 21 (in 14% of the pups, versus 0% in control pups). Due to the lack of historical controls, lack of microscopic evaluation of the affected kidneys, and the absence of fetal kidney findings in the pups analysed at caesarean section, the relationship to treatment with V114 was questioned.

In a PND study in rats with a similar dosing schedule as in the performed EFD study, no effects were observed on maternal toxicity, natural delivery or litter parameters or on-pup external morphology, viability, or body weights. Importantly, the finding of an increased incidence of RPD in the EFD study was not reproduced. No V114-related macroscopic findings in the kidney, ureters, or urinary bladder in any of the F0 females (on LD21) or F1 pups (on PND21) were noted.

No special juvenile toxicity studies were performed because no target organs of toxicity have been identified. Juvenile Rhesus monkeys have been used in the PD part.

2.4.4.6. Local Tolerance

Local tolerance was assessed as part of the repeat-dose studies. This is agreed with. No other effects than expected as vaccination response were observed.

2.4.4.7. Other toxicity studies

<u>Immunogenicity</u>

Immunogenicity was assessed in the repeated dose toxicity studies and reproductive toxicology studies. Pooled serum (harvested on day 42) from 5 male and 5 female rats that received an intramuscular injection with 32 µg/dose V114 on day 1 and day 21 was used as a positive control in the immunogenicity

assay. In the pivotal repeated dose toxicity study (TT#16-1044) the proportion of V114-treated animals that generated V114-specific antibodies was between 10 and 100% across all serotypes on day 15 and between 90% and 100% across all serotypes 2 weeks after the last dose. In the EFD and PND studies, at least ten serotypes were detected in 90-95% of the F0 female samples after V114 treatment. F1 pups showed similar trends.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, due to their nature, vaccines, and lipids are unlikely to result in a significant risk to the environment.

2.4.6. Discussion on non-clinical aspects

Immunogenicity data in rabbits and infant rhesus monkeys have shown that V114 in Formulation B induces functional antibody activity, which is expected to protect against pneumococcal infection.

The applicant's approach to focus on three rabbit studies (out of 13) and two infant monkey studies (out of 9) is regarded acceptable, as these studies used vaccine formulations that were very similar or identical, respectively, to the final drug formulation selected for clinical studies and the intended marketed presentation, respectively. All other studies are regarded as supportive data and were summarised briefly in the dossier.

When V114 Formulation B, lot 2 was compared versus Prevnar 13 for the 13 serotypes contained in both vaccines, the responses appeared to be better comparable to Prevnar 13 responses than in study NZWR-16, especially for the MOPA responses.

In repeated dose toxicity studies, no effects other than those expected following a vaccine-induced immune response were observed, including slight to moderate effects in the lymphoid tissues and treated injection sites. Such effects are of limited toxicological significance. No adverse effects on fertility, embryonic/foetal development or development of the offspring were observed in an EFD and preweaning toxicity study and a PND study.

In regards to the observed renal pelvic dilations in F1 pups, the applicant speculated in study TT #19-7090 that the relationship of this finding to V114 administration was uncertain due to a lack of historical control data, the lack of microscopic evaluation of kidneys from the affected pups, and the absence of fetal kidney findings at caesarean section or any other urogenital findings in V114-treated pups. Indeed, non-reproducibility of the findings in study TT #19-7090 was demonstrated in the subsequent postnatal developmental toxicity study TT #19-7170 in rats, suggesting that the observed renal pelvic dilations in study TT #19-7090 were an isolated finding and thus probably not clinically relevant. This conclusion is additionally supported by the fact that renal pelvic dilations are occasionally observed in test article groups in postnatal rat development studies. Considering all these aspects, no concern was raised on this issue.

2.4.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that V114 induces functional antibody activity, which is expected to protect against pneumococcal infection. In addition, the toxicology programme revealed no effects other than those expected for a vaccine.

From a non-clinical point of view, there are no objections against the market approval of V114.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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

Study ID # study centres/ location	Design	No. of subjects by group	Study Population	Primary Objectives
Main studies				
V114-019 30 sites Canada, Japan, Spain, Taiwan, US	Phase 3, randomised, double-blind, active comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114	Randomisation ratio V114:PCV13 = 1:1 V114: Randomised: 604 Vaccinated with PCV: 602 Completed: 596 PCV13: Randomised: 601 Vaccinated with PCV: 600 Completed: 594	Pneumococcal vaccine-naïve adults ≥50 years of age Gender: 513 M/ 689 F Median Age: 66.0 years	To evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs. To compare the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with V114 versus PCV13. To compare serotype-specific proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses for the 2 unique serotypes in V114 for participants administered V114 versus participants administered PCV13.
V114-017 79 sites Australia, Canada, Chile, New Zealand, Poland, Russia, US	Phase 3, randomised, double-blind, active comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114 followed by PPV23 6 months later in immunocompetent adults with or without risk factors for pneumococcal disease	Randomisation ratio V114:PCV13 = 3:1 V114: Randomised: 1135 Vaccinated with PCV: 1133 Vaccinated with PPV23: 1035 Completed: 1038‡ PCV13: Randomised: 380 Vaccinated with PCV: 379† Vaccinated with PPV23: 346 Completed: 350‡	Pneumococcal vaccine-naïve adults ≥18 to ≤49 years of age with or without risk factors for pneumococcal disease Gender: 731 M/ 781 F Median Age: 36.0 years	To evaluate the safety and tolerability of V114 and PCV13 with respect to the proportion of participants with AEs within each vaccination group separately. To evaluate the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with V114 and PCV13 within each vaccination group separately.

Study ID # study centres/ location	Design	No. of subjects by group	Study Population	Primary Objectives
Supportive studies				
V114-007 17 sites US	Phase 2, randomised, double-blind, active comparator-controlled, study to evaluate safety, tolerability, and immunogenicity of V114	Randomisation ratio V114:PCV13 =1:1 V114: Randomised: 127 Vaccinated with PCV: 127 Completed: 127 PCV13 Randomised: 126 Vaccinated with PCV: 126 Completed: 126	Adults ≥65 years of age who were previously vaccinated with PPV23 ≥1 year prior to study entry Gender: 102 M/ 151 F Median Age: 72.0 years	To describe the safety and tolerability profiles of V114 and PCV13 when administered as a single dose in adults ≥65 years of age with a prior history of PPV23 To summarize the serotype-specific IgG responses measured at Day 1 and Day 30 postvaccination in recipients of V114 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and the 2 serotypes unique to V114 (22F and 33F)
V114-016 22 sites Spain, South Korea, Taiwan, US	Phase 3, randomised, double-blind, active comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114 followed by PPV23 1 year later	Randomisation ratio V114:PCV13 = 1:1 V114: Randomised: 327 Vaccinated with PCV: 326 Vaccinated with PPV23: 298 Completed: 303‡ PCV13: Randomised: 325 Vaccinated with PCV: 325† Vaccinated with PPV23: 302 Completed: 306‡	Pneumococcal vaccine-naïve adults ≥50 years of age Gender: 281 M/ 370 F Median Age: 65.0 years	To evaluate the safety and tolerability of V114 compared with PCV13 with respect to the proportion of participants with AEs. To evaluate the safety and tolerability of PPV23 administered 12 months following V114 compared with PPV23 administered 12 months following PCV13 with respect to the proportion of participants with AEs. To evaluate the serotype specific OPA GMTs at 30 days postvaccination with PPV23 (Month 13) for participants administered V114 compared with participants administered PCV13 12 months before receipt of PPV23.
V114-018 13 sites France, Peru, South Africa, Thailand, US	Phase 3, randomised, double-blind, active comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114 followed by PPV23 8 weeks later in adults infected with HIV	Randomisation ratio V114:PCV13 = 1:1 V114: Randomised: 152 Vaccinated with PCV: 152 Vaccinated with PPV23: 150 Completed: 145 PCV13: Randomised: 150 Vaccinated with PCV: 150 Vaccinated with PPV23: 148 Completed: 147	Pneumococcal vaccine-naïve adults ≥18 years of age infected with HIV Gender: 238 M/ 64 F Median Age: 41.0 years	To evaluate the safety and tolerability of V114 and PCV13 with respect to the proportion of participants with AEs within each vaccination group separately. To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination (Day 30) with V114 and PCV13 within each vaccination group separately

Study ID # study centres/ location	Design	No. of subjects by group	Study Population	Primary Objectives
V114-020 55 sites Australia, Chile, Denmark, Finland, United Kingdom, US	Phase 3, randomised, double-blind, active comparator-controlled, lot-to-lot consistency study to evaluate the safety, tolerability, and immunogenicity of V114	Randomisation ratio V114 Lot 1:V114 Lot 2: V114 Lot 3:PCV13 = 3:3:3:1 V114 Lot 1: Randomised: 702 Vaccinated with PCV: 698 Completed: 683 V114 Lot 2: Randomised:704 Vaccinated with PCV: 704 Completed: 689 V114 Lot 3: Randomised: 701 Vaccinated with PCV: 700 Completed: 683 PCV13: Randomised: 233 Vaccinated with PCV: 231† Completed: 227	Pneumococcal vaccine-naïve adults ≥50 years of age Gender: 990 M/ 1343 F Median Age: 65.0 years	To evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs. To compare the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) across 3 different lots of V114.
V114-021 45 sites US	Phase 3, randomised, double-blind, placebo-controlled to evaluate safety, tolerability, and immunogenicity of V114 when administered concomitantly with inactivated influenza vaccine	Randomisation ratio concomitant: non-concomitant = 1:1 Concomitant group: Randomised: 600 Vaccinated with QIV: 599 Vaccinated with PCV: 599 Received placebo: 583 Completed: 583 Non-concomitant group: Randomised: 600 Vaccinated with QIV: 598 Received placebo: 597 Vaccinated with PCV: 587 Completed: 583	Adults ≥50 years of age with (>1 year prior to study entry) or without prior PPV23 vaccination Gender: 525 M/ 672 F Median Age: 65.0 years	To evaluate the safety and tolerability of V114 and QIV when administered concomitantly compared with V114 and QIV when administered non-concomitantly with respect to the proportion of participants with AEs. To compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 administered concomitantly with QIV versus V114 administered non-concomitantly with QIV. To compare the strain-specific HAI GMTs at 30 days postvaccination with QIV administered concomitantly with V114 versus QIV administered non-concomitantly with V114.

AE=adverse event; CAIH=Centre for American Indian Health; CD4=cluster of differentiation 4; F=female; GMC=geometric mean concentration; GMT=geometric mean titre; HAI=hemagglutination inhibition; HIV=human immunodeficiency virus; IgG=immunoglobulin G; M=male; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine; PCV13= Prevenar 13™ ; PPV23=PNEUMOVAX™23; QIV=quadrivalent influenza vaccine; US=United States.

† One participant randomised to the PCV13 group inadvertently received V114 in each of the following studies: V114-016, V114-017, and V114-020 (Lot 1).

‡ For studies with multiple vaccinations, participants could discontinue study vaccine (i.e., not receive the second vaccination), but remain in the study and be counted as Completed.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetic studies were conducted with the V114 vaccine regimen. 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).

2.5.2.2. Pharmacodynamics

Mechanism of action

Induction of protective immunity by V114 is thought to occur mainly through a T-cell dependent immune response which induces antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

Primary and Secondary pharmacology

The pharmacodynamic profile of V114 is defined by the immunogenicity profile, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005). Immunogenicity results are described in the Clinical Efficacy sections.

Assays

In the V114 adult clinical programme, vaccine-induced, serotype-specific immune responses in the form of functional antibodies as measured by opsonophagocytic activity (OPA) and all serotype-specific IgG antibodies for all 15 serotypes included in V114 were measured using validated multiplex opsonophagocytic assay (MOPA) and pneumococcal electrochemiluminiescence (Pn ECL) assays, respectively. Evaluation of serotype-specific OPA responses was the primary objective of the V114 Phase 3 studies supporting licensure; evaluation of serotype-specific total IgG responses was generally a secondary objective (except for Study V114-018, where IgG and OPA responses are co-primary endpoints).

The assays were validated and considered fit for purpose.

2.5.3. Discussion on clinical pharmacology

The evaluation of the protective effect of V114 is based on bridging clinical immunogenicity results to PCV13, which has been shown to be effective.

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

The applicant utilised two assays to characterise the vaccine-induced immune response: MOPA and Pn ECL. MOPA measures functional antibodies as the assay is designed to mimic the opsonophagocytosis process. The Pn ECL measures all antibodies against specific serotypes. The MOPA was chosen as the main immune parameter to bridge towards PCV13 and to predict clinical benefit. Both assays were validated and shown to be fit for purpose.

The strategy to translate V114 immunogenicity data into the likelihood of protection based on immunobridging to PCV13 has been accepted by CHMP in scientific advice procedure **EMEA/H/SA/1492/1/FU/1/2017/III** and is further described in the Efficacy section of this report.

2.5.4. Conclusions on clinical pharmacology

The evaluation of the beneficial effect of V114 is based on bridging clinical immunogenicity results to PCV13, which has been shown to be effective. This strategy has been agreed upon by CHMP in scientific advice procedure **EMEA/H/SA/1492/1/FU/1/2017/III.** The assays used to determine immunogenicity results have been validated and are considered fit for purpose.

2.5.5. Clinical efficacy

An overview of the clinical studies included in the present submission is provided in the table above. A total of 6 phase 3 studies (V114-007, -016, -017, -018, -019, -020 and -021) and 1 phase 2 study (V114-007) were conducted with V114, enrolling over 7,400 adults across more than 260 clinical study sites in 18 countries.

The overall objective of the clinical development programme was to evaluate the safety, tolerability, and immunogenicity of V114 administered as a single dose in adults ≥18 years of age. Immunogenicity was investigated as efficacy studies with V114 were not considered feasible, which was endorsed by the CHMP. The purpose of the clinical development programme was consequently to support immunobridging of V114 to the licensed PCV13. There is no correlate of protection known for IPD or pneumonia caused by *Streptococcus pneumoniae* in adults. However, the opsonophagocytic assay reflects in vivo protection by the vaccine-induced functional antibodies, which are therefore considered surrogate markers for vaccine efficacy. OPA GMT results have been found to correlate with protection against disease (Song et al. J. Infect Chemother. 2013).

PCV13 was included as a comparator in 6 of the 7 studies, during which subjects either received V114 or PCV13 alone (V114-007, V114-019, V114-020) or as part of a sequential regimen with PPV23 (V114-016, V114-017, V114-018). In 1 study, V114-021, participants received a single dose of V114 concomitantly or non-concomitantly with a single dose of inactivated quadrivalent influenza vaccine (QIV).

2.5.5.1. Dose response studies

Studies from the early development phase with different formulations are not submitted in this dossier.

No dose response studies have been submitted for evaluation with the current formulation of the V114 vaccine. As the dose of each of the shared polysaccharide serotypes and the administration regimen of V114 is comparable to PCV13, this absence is not critical for the evaluation. For the 2 unique serotypes, 22F and 33F, the amount per dose chosen was 2 µg.

2.5.5.2. Main studies

Immunogenicity data obtained from study V114-017 and V114-019 were considered to provide pivotal evidence. Combined, the two studies represent the entire population that might be exposed to this vaccine, as study V114-019 enrolled subjects ≥ 50 years of age while study V114-017 included subjects 18-49-year-old with and without risk factors for pneumococcal disease. The methods of these 2 studies are described below, and where possible the presentation of results has been compiled side-by-side.

V114-019: A randomized, double-blind, active comparator-controlled, parallel assignment, multicentre, Phase 3 clinical study to evaluate the safety, tolerability and immunogenicity of V114 in healthy adults over 50 years of age.

V114-017: A randomized, double-blind, active comparator-controlled, multicentre, Phase 3 clinical study to evaluate the safety, tolerability and immunogenicity of V114 followed by administration of PPV23 6 months later in immunocompetent adults between 18 and 49 years of age at increased risk for pneumococcal disease.

Methods

- **Study Participants**

Both studies enrolled adult men and women from whom written informed consent was obtained. Any underlying chronic condition was documented to be stable, according to the investigator's clinical judgement. Women of childbearing potential were eligible if not pregnant and had to use adequate birth control methods as described in the study protocols.

Study V114-019 enrolled healthy (in the investigator's clinical judgment) adults **≥50 years of age**.

Study V114-017 enrolled adults **18 to 49 years of age (inclusive)**. The subjects enrolled should either be in good health (according to the investigator) and /or have ≥1 of the following risk conditions for pneumococcal disease: diabetes mellitus, chronic liver disease, chronic obstructive pulmonary disease (COPD), asthma, chronic heart disease or current smoker.

The main exclusion criteria for both studies were:

- History of IPD or known history of other culture-positive pneumococcal disease within 3 years of Visit 1 (Day 1)
- Known or suspected impairment of immunological function.
- Received any pneumococcal vaccine or was expected to receive any pneumococcal vaccine during the study outside of the protocol
- Received systemic corticosteroids.
- Received immunosuppressive therapy.

- **Treatments**

During both studies **V114-019** and **V114-017**, subjects either received a single dose of V114 or PCV13 via intramuscular injection (IM), which is identical to the proposed posology.

During study **V114-017,** subjects also received a single dose of PPV23 IM at 6 months after primary vaccination.

- **Objectives and Outcomes**

The objectives and corresponding endpoints of Study V114-019 and Study V114-017 are presented in Table 2 and Table 3, respectively.

Table 2 Objectives and endpoints of Study V114-019

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs.	Solicited injection site AEs from Day 1 through Day 5 postvaccination. Solicited systemic AEs from Day 1 through Day 14 postvaccination. Vaccine-related SAEs from Day 1 to Month 6 postvaccination.
To compare the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with V114 versus PCV13.	Serotype-specific OPA responses for the 15 serotypes in V114 at Day 30.
To compare serotype-specific proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses for the 2 unique serotypes in V114 for participants administered V114 versus participants administered PCV13.	Serotype-specific OPA responses for the 2 unique serotypes in V114 at Day 1 and Day 30.
Secondary Objectives	**Secondary Endpoints**
To compare the serotype 3 OPA GMT at 30 days postvaccination (Day 30) with V114 versus PCV13.	OPA responses for serotype 3 at Day 30.
To compare proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for the serotype 3 OPA responses for participants administered V114 versus participants administered PCV13	OPA responses for serotype 3 at Day 1 and Day 30.
To evaluate the serotype-specific IgG GMCs at 30 days postvaccination (Day 30) with V114 compared to PCV13	Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30.
To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and separately for participants administered PCV13.	Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Day 30.

AE=adverse event; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titer; IgG=Immunoglobulin G; OPA=opsonophagocytic activity; PCV13=Prevenar 13™; SAE=serious adverse event

Table 3 Objectives and endpoints of Study V114-017

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of V114 and PCV13 with respect to the proportion of participants with AEs within each vaccination group separately.	Following PCV vaccination: Solicited injection site AEs from Day 1 through Day 5 postvaccination. Solicited systemic AEs from Day 1 through Day 14 postvaccination. Vaccine-related SAEs from Day 1 to Month 6 postvaccination.
To evaluate the serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with V114 and PCV13 within each vaccination group separately.	Serotype-specific OPA responses for the 15 serotypes in V114 at Day 30.
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of PPV23 administered 6 months following V114 and PCV13 with respect to the proportion of participants with AEs within each vaccination group separately	Following PPV23 vaccination: Solicited injection site AEs from Day 1 through Day 5 postvaccination. Solicited systemic AEs from Day 1 through Day 14 postvaccination. Vaccine-related SAEs from Month 6 to Month 7.
To evaluate the serotype-specific IgG GMCs at 30 days postvaccination (Day 30) with V114 and PCV13 within each vaccination group separately	Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30.
To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and PCV13 within each vaccination group separately	Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Day 30.
To evaluate the serotype-specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Month 7), (2) GMFRs and proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination with PPV23 (Month 7) for both OPA and IgG responses, (3) GMFRs and proportions of participants with a ≥4-fold rise from prevaccination with PPV23 (Month 6) to 30 days postvaccination with PPV23 (Month 7) for both OPA and IgG responses for participants administered V114 and separately for participants administered PCV13 6 months before receipt of PPV23	Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1, Month 6, and Month 7.

AE=adverse event; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titre; IgG=Immunoglobulin G; OPA=opsonophagocytic activity; PCV13=Prevenar 13™; SAE=serious adverse event

- **Randomisation and Blinding (masking)**

Treatment allocation/randomization occurred centrally using interactive response technology (IRT) system. Participants were assigned randomly in a 1:1 ratio to receive either V114 or PCV13 during study **V114-019** or 3:1 ratio to receive either V114 or PCV13 for study **V114-017**, respectively.

For Study **V114-019,** randomization was stratified based on:

- Age at time of randomization: 50 to 64 years of age, 65 to 74 years of age and ≥75 years of age. At least 800 participants were ≥65 years of age.

For Study **V114-017,** randomization was stratified based on:

- the type/number of risk factors for pneumococcal disease as defined in the protocol a participant has at the time of randomization.

- Enrolment at Centre for American Indian Health (CAIH) or not

Both studies used a double-blinding technique. V114 and PCV13 were prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator involved in the clinical evaluation of the participants remained blinded to the group assignments.

Because V114 and PCV13 have a different physical appearance, a member of the study site staff was unblinded for the purposes of receiving, maintaining, preparing and/or dispensing, and administering these study vaccines. Procedures for handling, preparing, and administering the unblinded vaccines were located in the Investigator Trial File Binder. To avoid bias, the unblinded study personnel had 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 were not present in the examination room when study vaccines were administered. Contact between participants and unblinded study personnel after vaccination administration was strictly prohibited. Blinded site personnel were responsible for all safety and immunogenicity follow-up procedures after vaccine administration.

An unblinded Clinical Research Associate monitored vaccine accountability at the study site. All other Sponsor personnel or delegate(s) and Merck Research Laboratories employees directly involved with the conduct of this study remained blinded to the participant-level intervention assignment.

- **Statistical methods**

V114-019

The study was considered to have met its primary immunogenicity objectives if non-inferiority of V114 compared to PCV13 was demonstrated with respect to OPA GMTs for the 13 shared serotypes (lower bound of the 2-sided 95% CI of the estimated OPA GMT ratio [V114/PCV13] ≥0.5) and superiority of V114 compared to PCV13 was demonstrated with respect to both OPA GMTs (lower bound of the 2-sided 95% CI of the estimated OPA GMT ratio [V114/PCV13] ≥2.0) and the proportions of participants with ≥4-fold rises in OPA responses (lower bound of the 2-sided 95% CI of the difference in percentages [V114-PCV13] >0.1) for the 2 unique serotypes. In addition, the superiority of response to serotype 3 of V114 compared to PCV13 was investigated concerning OPA GMTs (lower bound of the 2-sided 95% CI of the estimated OPA GMT ratio [V114/PCV13] ≥1.2) and proportions of participants with ≥4-fold rises in OPA responses (lower bound of the 2-sided 95% CI of the difference in percentages [V114-PCV13] ≥0.0). 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 is required.

In general, missing data were not imputed. However, for analyses of OPA GMTs and IgG GMCs at Day 30, the Kenward-Roger adjustment was used with restricted (or residual) maximum likelihood to make proper statistical inference. This model allows the inclusion of participants who are missing either the baseline or post-baseline measurements, thereby increasing efficiency.

V114-017

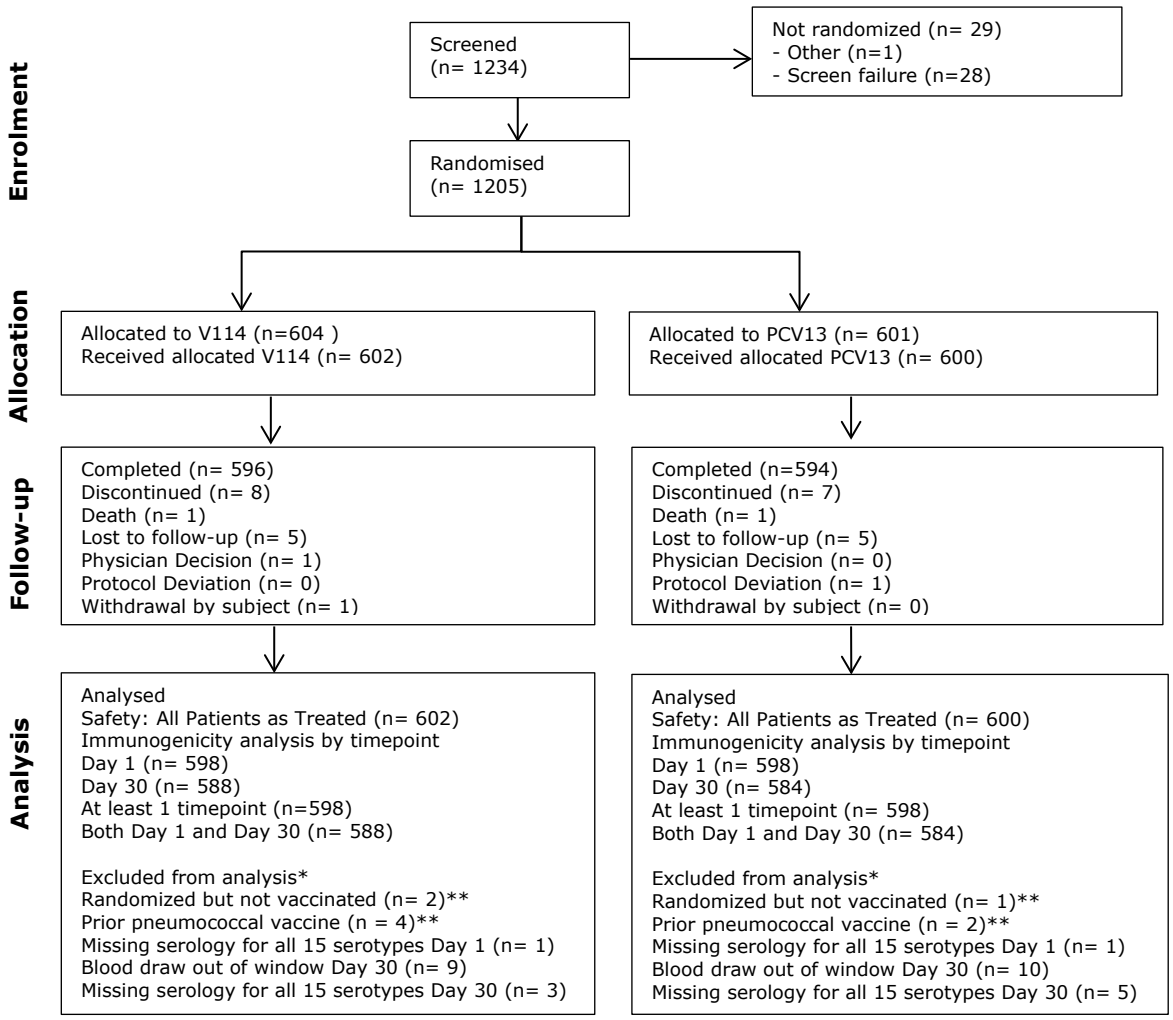
Study V114-017 is a descriptive study. In order to address the primary immunogenicity objective, evaluation of the OPA GMTs at 30 days postvaccination with V114 or Prevnar 13™ (Day 30) included descriptive summaries, and within-group 95% CIs calculated for each vaccination group. Point estimates for the OPA GMTs calculated by exponentiating the estimates of the mean of the natural log

values. The within-group CIs derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

Results

- **Participant flow**

V114-019



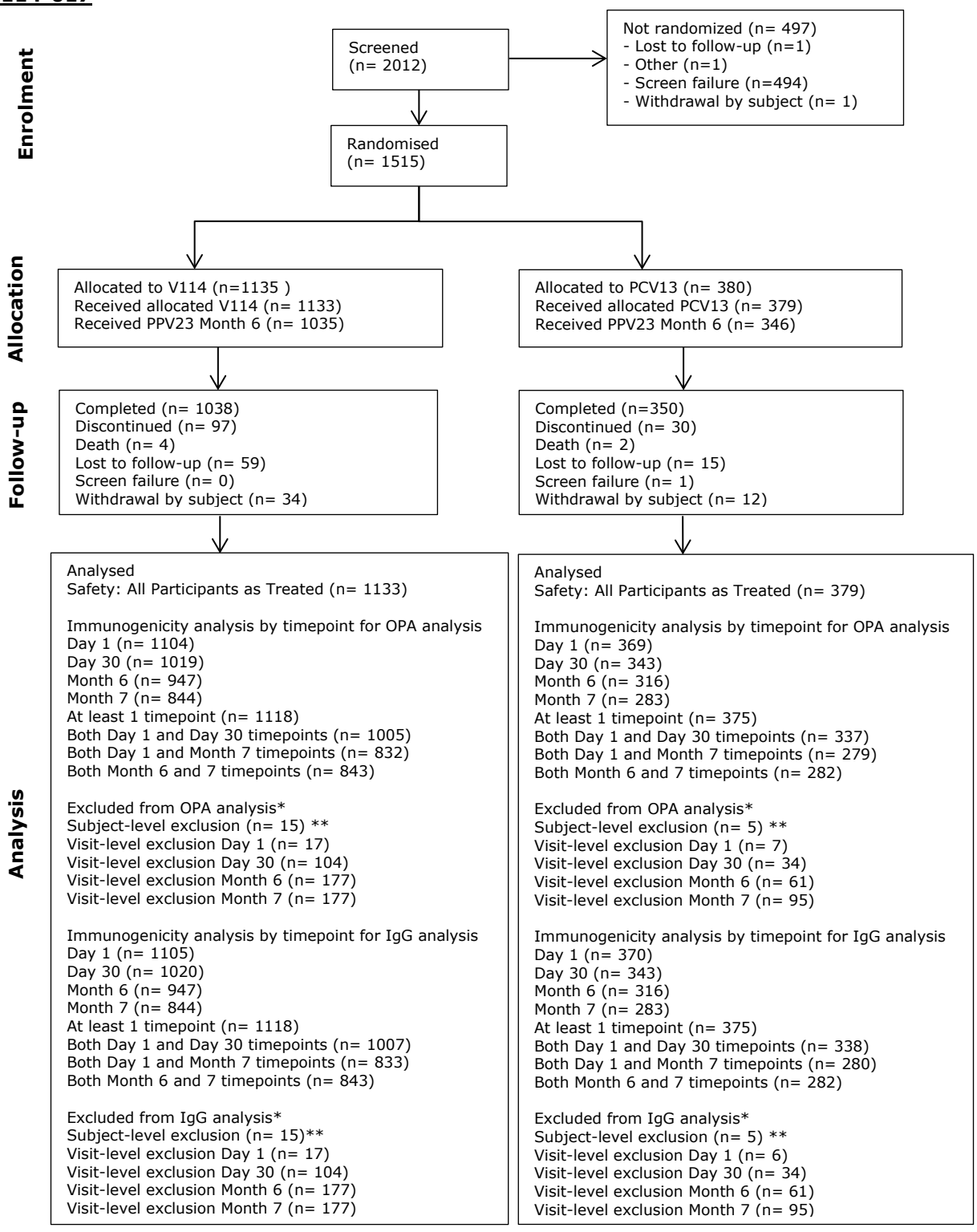
*Subjects may have more than 1 reason for exclusion. Subjects are displayed in all applicable categories.
**Subject level exclusion results in exclusion from analyses at all timepoints

- **Recruitment**

The study was conducted at 30 sites in 5 countries; 6 sites in Canada, 5 sites in Japan, 3 sites in Spain, 2 sites in Taiwan and 14 sites in the USA.

First subject first visit: 13 June 2019, Last subject last visit: 30 March 2020.

V114-017



*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

- **Recruitment**

The study was conducted at 79 sites, of which 77 randomised participants, in 7 countries; 7 sites in Australia, 9 in Canada, 5 in Chile, 8 in New Zealand, 8 in Poland, 3 in the Russian Federation and 37 in the USA.

First subject first visit: 16 July 2018, Last subject last visit: 20 January 2020.

- **Conduct of the study**

V114-019

Amendments

There was **1 amendment** to the original study protocol (13-FEB-2020; 6 weeks before the end of the study), which encompassed the addition of 2 secondary immunogenicity objectives relating to the demonstration of superiority for serotype 3 and the stringency of the superiority testing for the new serotypes 22F and 33F was updated from >0 to >0.1. The amendment was implemented prior to the last visit and database lock and therefore would not affect the type I error during superiority testing of serotypes 22F and 33F. The addition of 2 secondary endpoints investigating the superiority of serotype 3 once non-inferiority has been demonstrated is acceptable. The amendment does not impact subject wellbeing or study conduct.

Additional changes:

- Removal of IK status as a precondition for OPA testing:

The presence of bactericidal substances in serum could potentially inflate OPA titers as measured by MOPA assay. An intrinsic killing (IK) test was initially included to detect the presence of bactericidal agents, mainly antibiotics, in serum samples in the V114 studies. The percentage of IK-positive samples in earlier V114 studies were in a range generally consistent with reported systemic antibiotic use.

Blinded performance monitoring of the IK test revealed a higher than expected number of serum samples testing IK-positive following a change to a critical reagent which affected this study. As a result and given the low proportion of participants reporting systemic antibiotic use around the time of blood draws for immunogenicity testing, IK status as a precondition for OPA testing and analysis was removed, and the evaluation of OPA-related endpoints in this study was based on results from all available OPA data. Subsequently, the IK test was modified, and a separate report was prepared to summarize primary and key secondary OPA endpoints, excluding samples that tested positive in the modified IK test. Overall, the results of the analyses included in that report were consistent with those presented in the individual study CSRs, which included all available OPA data.

- Changes Related to the COVID-19 Pandemic:

Source data review and/or verification prior to database lock was/were waived for some participants (<2%) in this study (13-MAR-2020). Based on the very small quantity of data points without source data verification (SDV) (<2%), the finding that missing data verification was not related to a specific site and the fact that the study data were cleaned for at least 1 prior eDMC review, it was considered that waiving of SDV of these data points would not have impacted study interpretability or conclusions.

Protocol deviations

Important protocol deviations were reported for 29 (2.4%) participants in the study, of which 4 participants (0.3%) had protocol deviations that were considered clinically important. Clinically important deviations were safety events that were not reported within the protocol-defined reporting

period and a woman of childbearing potential who did not have a pregnancy test conducted prior to receipt of the study vaccine.

V114-017

Amendments

There were **3 amendments** to the original study protocol all of which did not impact subject well-being, study conduct or outcome of the study. More information on the amendments is presented in the clinical assessment report.

Additional changes:

- Removal of IK status as a precondition for OPA testing (as above)
- Changes Related to the COVID-19 Pandemic
    - Source data review and/or verification prior to database lock was/were waived for some participants (<2%) in this study (13-MAR-2020); see comment Study V114-019.
- Electronic vaccine rapport card (eVRC) related changes

Protocol deviations

Important protocol deviations were reported for 417 (27.5%) participants in the study, of which the protocol deviations in 20 participants (1.3%) were considered clinically important: 15 (1.3%) in the V114 group and 5 (1.3%) in the PCV13 group. The clinically important protocol deviations included: safety events not reported within the protocol-defined reporting period, improperly stored study intervention that was deemed unacceptable for use, dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment, and no pregnancy test conducted prior to receipt of study vaccine.

- **Baseline data**

The treatment groups were balanced for baseline demographics in both studies, as seen in Table 4.

Table 4 Summary of baseline and demographic characteristics for subjects in Study V114-019 and V114-017

Demographic Characteristic	V114-019		V114-017	
	V114 N=602	PCV13 N=600	V114 N = 1133	PCV13 N = 379
Age (yrs)				
Mean	66.2	65.7	35.8	35.8
Standard Deviation	7.7	7.4	8.9	8.9
Median	67.0	66.0	36.0	36.0
Min	50	50	18	18
Max	92	82	49	49
Age, Groups (yrs)				
50 to 64	186 (30.9%)	186 (31.0%)		
65 to 74	346 (57.5%)	346 (57.7%)		
≥75	70 (11.6%)	68 (11.3%)		
18 to 29			329 (29.0%)	105 (27.7%)
30 to 39			351 (31.0%)	112 (29.6%)
40 to 49			453 (40.0%)	162 (42.7%)
Sex at Birth, n (%)				
Female	358 (59.5%)	331 (55.2%)	581 (51.3%)	200 (52.8%)
Male	244 (40.5%)	269 (44.8%)	552 (48.7%)	179 (47.2%)
Ethnicity, n (%)				
Hispanic / Latino	135 (22.4%)	129 (21.5%)	135 (11.9%)	39 (10.3%)
Not Hispanic / Latino	467 (77.6%)	470 (78.3%)	982 (86.7%)	337 (88.9%)
Not reported	0 (0.0%)	1 (0.2%)	8 (0.7%)	1 (0.3%)
Unknown			8 (0.7%)	2 (0.5%)
Race, n (%)				
American Indian or Alaskan Native	0 (0.0%)	1 (0.2%)	445 (39.3%)	149 (39.1%)
Asian	150 (24.9%)	152 (25.3%)	15 (1.3%)	8 (2.1%)
Black or African American	36 (6.0%)	37 (6.2%)	43 (3.8%)	18 (4.7%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	0 (0.0%)	33 (2.9%)	11 (2.9%)
White	408 (67.8%)	406 (67.7%)	580 (51.2%)	191 (50.4%)
Multiple	7 (1.2%)	4 (0.7%)	17 (1.5%)	3 (0.8%)
Race Subgroups, n (%)				
African American/African Heritage	47 (17)	56 (20)	62 (20)	77 (25)
Asian	12 (4)	15 (5)	22 (7)	13 (4)
White	216 (76)	201 (71)	214 (69)	207 (67)
Other	8 (3)	9 (3)	10 (3)	11 (4)
Planned stratums for study V114-017 (CAIH enrolment and risk factors), n (%)				
CAIH no risk factors			280 (24.7%)	93 (24.5%)
CAIH single risk of diabetes mellitus			26 (2.3%)	9 (2.4%)
CAIH single risk of chronic heart disease			1 (0.1%)	1 (0.3%)
CAIH single risk of current smoker			53 (4.7%)	18 (4.7%)
CAIH single risk of AUDIT-C ≥5			58 (5.1%)	19 (5.0%)
CAIH 2 risks: liver/diabetes/lung/heart /current smoker/AUDIT-C ≥5			20 (1.8%)	7 (1.8%)
CAIH ≥3 risks: liver/diabetes/lung/ heart/current smoker/AUDIT-C ≥5			1 (0.1%)	1 (0.3%)
Non CAIH single risk of diabetes mellitus and AUDIT-C less than 5			120 (10.6%)	40 (10.6%)
Non CAIH single risk of chronic liver disease and AUDIT-C less than 5			26 (2.3%)	9 (2.4%)
Non CAIH single risk of chronic lung disease and AUDIT-C less than 5			161 (14.2%)	53 (14.0%)
Non CAIH single risk of chronic heart disease and AUDIT-C less than 5			55 (4.9%)	19 (5.0%)
Non CAIH single risk of current smoker and AUDIT-C less than 5			111 (9.8%)	37 (9.8%)
Non CAIH 2 risks: liver/diabetes/lung/ heart/current smoker/AUDIT-C ≥5			200 (17.7%)	66 (17.4%)
Non CAIH ≥3 risks: liver/diabetes/ lung/heart/current smoker/AUDIT-C ≥5			21 (1.9%)	7 (1.8%)

- **Numbers analysed**

V114-019

The participant flow, including participants randomised, vaccinated, discontinued and completed, is presented above.

Primary immunogenicity analyses were conducted using the per protocol (PP) population, which was defined as all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analysis. Supportive immunogenicity analyses were conducted for the primary immunogenicity endpoint using the full analysis set (FAS) population, defined as all randomised participants who received either V114 or PCV13 and had at least 1 serology result. Safety analyses were based on all participants as treated population (APaT) population (see Table 5).

Table 5 Analysis populations study V114-019

Population	V114	PCV13
Subjects randomised	604	601
APaT	602 (99.7%)	600 (99.8%)
Subjects included in analyses by timepoint		
Day 1	598 (99.0%)	598 (99.5%)
Day 30	588 (97.4%)	584 (97.2%)
At least 1 timepoint	598 (99.0%)	598 (99.5%)
Both Day 1 and Day 30 timepoint	588 (97.4%)	584 (97.2%)

APaT=All participants as treated; PCV13=Prevenar 13^{TM}

V114-017

The participant flow, including participants randomised, vaccinated, discontinued and completed, is presented above. Of note, participants could be considered to have completed the study without receipt of PPV23.

Primary immunogenicity analyses were conducted using the PP population, which was defined as all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analysis. Supportive immunogenicity analyses were conducted for the primary immunogenicity endpoint using the FAS population, defined as all randomised participants who received either V114 or PCV13 and had at least 1 serology result at Day 30. Safety analyses were based on the all participants APaT population, which consists of all randomised participants who received the relevant study vaccination, see Table 6.

Table 6 Analysis populations study V114-017

Population	V114	PCV13
Subjects randomised	1135	380
APaT Day 30	1134 (99.9%)	378 (99.5%)
APaT after PPV23	1036 (91.3%)	345 (90.8%)
Subjects included in OPA analyses by timepoint		
Day 1	1104 (97.3%)	369 (97.1%)
Day 30	1019 (89.8%)	343 (90.3%)
Month 6	947 (83.4%)	316 (83.2%0
Month 7	844 (74.4%)	283 (74.5%)
At least 1 timepoint	1118 (98.5%)	375 (98.7%)
Both Day 1 and Day 30 timepoint	1005 (88.5%)	337 (88.7%)
Both Day 1 and Month 7 timepoints	832 (73.3%)	279 (73.4%)
Both Month 6 and Month 7 timepoints	843 (74.3%)	282 (74.2%)
Subjects included in IgG analyses by timepoint		
Day 1	1105 (97.4%)	370 (97.4%)
Day 30	1020 (89.9%)	343 (90.3%)
Month 6	947 (83.4%)	316 (83.2%)
Month 7	844 (74.4%)	283 (74.5%)
At least 1 timepoint	1118 (98.5%)	375 (98.7%)
Both Day 1 and Day 30 timepoint	1007 (88.7%)	338 (88.9%)
Both Day 1 and Month 7 timepoints	833 (73.4%)	280 (73.7%)
Both Month 6 and Month 7 timepoints	843 (74.3%)	282 (74.2%)

APaT=All participants as treated; PCV13=Prevenar 13™, PPV23=Pneumovax™ 23

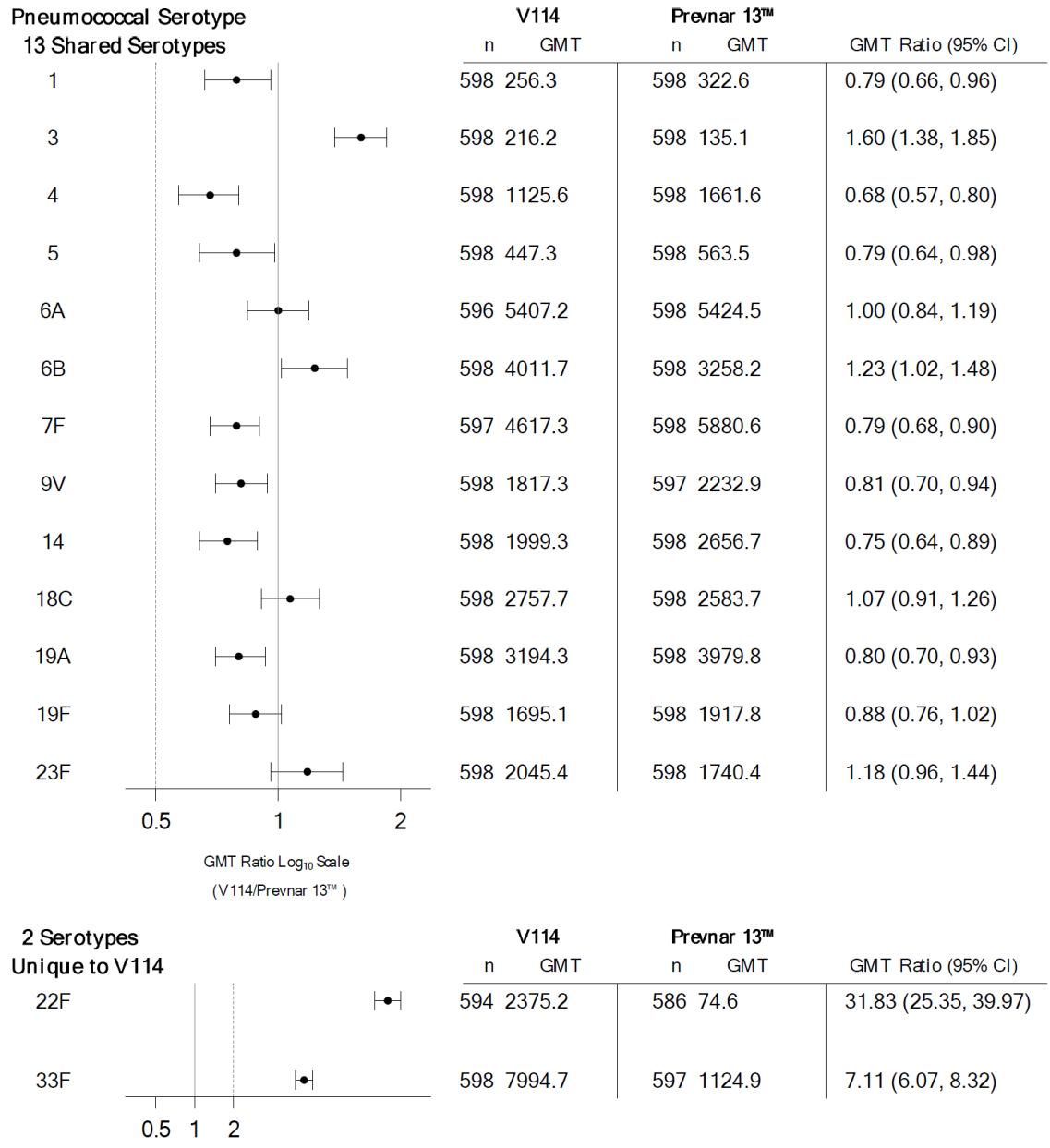
- **Outcomes and estimation**

V114-019

Primary Immunogenicity endpoints

V114 met non-inferiority criteria for the 13 shared serotypes (lower bound of 95% CI GMT ratio ≥0.5) and superiority criteria (lower bound of 95% CI GMT ratio ≥2.0) for the 2 unique serotypes as assessed by the serotype-specific OPA GMTs at 30 days postvaccination, see Figure 1.

Figure 1 Forest plot of OPA GMT ratios at Day 30 (PP population V114-019)



Data Source: Mod5.3.5.1/p019v114/Fig 11-1

V114 met superiority criteria for the 2 unique serotypes in V114 as assessed by the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from prevaccination to 30 days postvaccination, see Table 7. The lower bound of the 2-sided 95% CI of the differences (V114 – PCV13) between the proportions of participants with a ≥4-fold rise was >0.1 for both unique serotypes.

Table 7 Analysis of the proportions of participants with a ≥4-fold rise in OPA response at Day 30 for serotypes 22F and 33F - PP population V114-019

Pneumococcal Serotype	V114 (N = 602)	Prevnar 13™ (N = 600)	Percentage Point Difference (V114 - Prevnar 13™)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)†	p-Value† (1-sided)
22F	71.4 (374 / 524)	14.3 (71 / 498)	57.1 (52.0, 61.8)	<0.001
33F	56.7 (328 / 578)	6.3 (35 / 560)	50.5 (45.9, 54.9)	<0.001

† Estimated difference, 95% CI, and p-value are based on the stratified Miettinen & Nurminen method.

A conclusion of superiority is based on the lower bound of the 95% CI for the difference in percentages (V114 - Prevnar 13™) being > 10 percentage points (one-sided p-value < 0.025).

N=Number of subjects randomized and vaccinated; n=Number of subjects contributing to the analysis; m=Number of subjects with the indicated response.

Note: Per protocol, Day 30 is 30 days following vaccination with PCV.

Proportion of participants with a ≥4-fold rise is calculated from Day 1 to Day 30.

CI=confidence interval; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Data Source: Mod5.3.5.1/p019v114/Tab 11-2

Results for serotype-specific OPA GMTs and proportions of participants with a ≥4-fold rise in OPA responses from prevaccination to 30 days postvaccination in the FAS population were consistent with those observed in the PP population.

Secondary Immunogenicity endpoints

V114 met superiority criteria for serotype 3 as assessed by the OPA GMTs at 30 days postvaccination (see Figure 1, lower bound of 95% CI GMT ratio >1.2) and the proportions of participants with a ≥4-fold rise in OPA responses from prevaccination to 30 days postvaccination (see Table 8 lower bound of 95% CI V114 – PCV13 >0). Results for the FAS population were consistent with those for the PP population.

Table 8 Analysis of the proportions of subjects with a ≥4-fold rise in OPA responses at Day 30 for Serotype 3 – PP population

Pneumococcal Serotype	V114 (N = 602)	Prevnar 13™ (N = 600)	Percentage Point Difference (V114 - Prevnar 13™)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)†	p-Value† (1-sided)
3	70.2 (407 / 580)	58.7 (338 / 576)	11.5 (6.0, 16.9)	<0.001

† Estimated difference, 95% CI, and p-value are based on the stratified Miettinen & Nurminen method.

A conclusion of superiority is based on the lower bound of the 95% CI for the difference in percentages (V114 - Prevnar 13™) being > 0 percentage points (one-sided p-value < 0.025).

N=Number of subjects randomized and vaccinated; n=Number of subjects contributing to the analysis; m=Number of subjects with the indicated response.

Note: Per protocol, Day 30 is 30 days following vaccination with PCV.

Proportion of participants with a ≥4-fold rise is calculated from Day 1 to Day 30.

CI=confidence interval; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Trends observed for serotype-specific IgG GMCs at 30 days postvaccination were consistent with the primary analysis of OPA GMTs, with results being generally comparable for 12 of the shared serotypes between V114 and PCV13 and higher in the V114 group for the 2 unique serotypes and serotype 3. Similar trends were observed for serotype-specific GMFRs and proportions of participants with a ≥4-

fold rise from prevaccination to 30 days postvaccination for both OPA responses (see Table 9) and IgG responses.

Table 9 OPA antibody responses – PP population V114-019

Pneumococcal Serotype	Endpoint	Timepoint	V114 (N = 602)			Prevnar 13™ (N = 600)		
			n	Observed Response	95% CI[†]	n	Observed Response	95% CI[†]
13 Shared Serotypes								
1	GMT	Day 1	593	12.0	(10.6, 13.6)	594	11.2	(10.0, 12.6)
		Day 30	588	259.2	(225.4, 298.1)	577	319.7	(276.1, 370.2)
	GMFR	Day 1 to Day 30	583	14.3	(12.5, 16.4)	573	18.7	(16.2, 21.5)
	% ≥ 4-fold rise	Day 1 to Day 30	583	75.1% (438/583)	(71.4, 78.6)	573	77.7% (445/573)	(74.0, 81.0)
3	GMT	Day 1	596	18.1	(16.5, 19.8)	593	16.5	(15.1, 17.9)
		Day 30	582	219.4	(197.4, 243.8)	581	132.9	(119.1, 148.3)
	GMFR	Day 1 to Day 30	580	7.7	(7.0, 8.6)	576	5.2	(4.7, 5.7)
	% ≥ 4-fold rise	Day 1 to Day 30	580	70.2% (407/580)	(66.3, 73.9)	576	58.7% (338/576)	(54.5, 62.7)
4	GMT	Day 1	597	41.2	(36.8, 46.1)	594	45.9	(40.6, 51.9)
		Day 30	587	1106.7	(975.5, 1255.4)	582	1672.3	(1487.6, 1880.0)
	GMFR	Day 1 to Day 30	586	17.8	(15.7, 20.3)	578	24.4	(21.3, 27.8)
	% ≥ 4-fold rise	Day 1 to Day 30	586	79.5% (466/586)	(76.0, 82.7)	578	84.8% (490/578)	(81.6, 87.6)
5	GMT	Day 1	598	23.1	(21.0, 25.3)	598	23.2	(21.1, 25.4)
		Day 30	588	444.8	(379.7, 521.1)	584	561.7	(481.2, 655.6)
	GMFR	Day 1 to Day 30	588	12.3	(10.7, 14.2)	584	15.3	(13.2, 17.6)
	% ≥ 4-fold rise	Day 1 to Day 30	588	71.6% (421/588)	(67.8, 75.2)	584	75.3% (440/584)	(71.6, 78.8)
6A	GMT	Day 1	566	294.4	(265.9, 325.9)	572	263.7	(239.0, 290.9)
		Day 30	575	5469.4	(4824.9, 6200.0)	576	5284.2	(4614.4, 6051.3)
	GMFR	Day 1 to Day 30	545	13.0	(11.4, 14.9)	550	13.3	(11.6, 15.2)
	% ≥ 4-fold rise	Day 1 to Day 30	545	76.5% (417/545)	(72.7, 80.0)	550	74.9% (412/550)	(71.1, 78.5)
6B	GMT	Day 1	590	111.5	(95.8, 129.8)	592	113.5	(97.6, 131.9)
		Day 30	587	4001.0	(3493.7, 4581.9)	582	3237.5	(2806.3, 3735.0)
	GMFR	Day 1 to Day 30	579	26.3	(22.4, 30.8)	576	21.6	(18.5, 25.2)
	% ≥ 4-fold rise	Day 1 to Day 30	579	81.2% (470/579)	(77.7, 84.3)	576	79.2% (456/576)	(75.6, 82.4)
7F	GMT	Day 1	577	306.9	(264.7, 355.8)	569	335.8	(288.4, 391.0)
		Day 30	586	4601.1	(4168.4, 5078.8)	584	5891.4	(5336.2, 6504.4)
	GMFR	Day 1 to Day 30	566	12.0	(10.3, 13.9)	555	14.1	(12.1, 16.5)
	% ≥ 4-fold rise	Day 1 to Day 30	566	66.4% (376/566)	(62.4, 70.3)	555	72.4% (402/555)	(68.5, 76.1)
9V	GMT	Day 1	589	265.6	(239.1, 295.0)	587	274.8	(247.4, 305.1)
		Day 30	587	1799.9	(1610.4, 2011.7)	583	2239.3	(2008.1, 2497.2)
	GMFR	Day 1 to Day 30	578	5.3	(4.8, 6.0)	573	6.3	(5.6, 7.1)
	% ≥ 4-fold rise	Day 1 to Day 30	578	54.0% (312/578)	(49.8, 58.1)	573	60.0% (344/573)	(55.9, 64.1)
14	GMT	Day 1	592	273.8	(238.5, 314.4)	593	241.3	(208.8, 278.9)
		Day 30	585	2036.1	(1794.8, 2309.7)	581	2605.1	(2299.3, 2951.5)
	GMFR	Day 1 to Day 30	579	6.2	(5.4, 7.2)	576	8.7	(7.5, 10.0)
	% ≥ 4-fold rise	Day 1 to Day 30	579	52.2% (302/579)	(48.0, 56.3)	576	60.8% (350/576)	(56.6, 64.8)
18C	GMT	Day 1	591	177.7	(160.0, 197.3)	596	185.6	(166.4, 207.0)
		Day 30	585	2736.9	(2432.0, 3080.0)	581	2581.1	(2287.2, 2912.7)
	GMFR	Day 1 to Day 30	578	11.3	(10.0, 12.9)	579	10.4	(9.1, 11.8)
	% ≥ 4-fold rise	Day 1 to Day 30	578	71.3% (412/578)	(67.4, 74.9)	579	69.1% (400/579)	(65.1, 72.8)
19A	GMT	Day 1	594	257.4	(224.5, 295.2)	591	277.1	(241.1, 318.6)
		Day 30	585	3169.9	(2861.1, 3511.9)	582	4003.2	(3594.7, 4458.2)

19A	GMFR	Day 1 to Day 30	581	10.9	(9.5, 12.5)	575	13.1	(11.4, 15.1)
	% ≥ 4-fold rise	Day 1 to Day 30	581	70.6% (410/581)	(66.7, 74.2)	575	71.1% (409/575)	(67.2, 74.8)
19F	GMT	Day 1	591	193.2	(173.9, 214.5)	593	197.5	(177.8, 219.3)
		Day 30	586	1688.1	(1513.2, 1883.3)	581	1918.1	(1724.3, 2133.7)
	GMFR	Day 1 to Day 30	579	6.6	(5.9, 7.5)	576	7.4	(6.6, 8.3)
	% ≥ 4-fold rise	Day 1 to Day 30	579	62.0% (359/579)	(57.9, 66.0)	576	65.1% (375/576)	(61.1, 69.0)
23F	GMT	Day 1	571	85.6	(74.8, 98.1)	572	91.7	(79.5, 105.9)
		Day 30	582	2027.5	(1760.3, 2335.3)	581	1748.5	(1493.0, 2047.7)
	GMFR	Day 1 to Day 30	555	16.2	(14.0, 18.9)	555	13.5	(11.5, 15.9)
	% ≥ 4-fold rise	Day 1 to Day 30	555	75.0% (416/555)	(71.1, 78.5)	555	71.4% (396/555)	(67.4, 75.1)
2 Serotypes Unique to V114								
22F	GMT	Day 1	538	54.7	(44.6, 67.1)	548	63.8	(51.9, 78.5)
		Day 30	580	2328.7	(2036.5, 2662.9)	536	73.8	(59.7, 91.2)
	GMFR	Day 1 to Day 30	524	28.3	(22.8, 35.1)	498	1.2	(1.0, 1.4)
	% ≥ 4-fold rise	Day 1 to Day 30	524	71.4% (374/524)	(67.3, 75.2)	498	14.3% (71/498)	(11.3, 17.6)
33F	GMT	Day 1	589	1044.5	(910.4, 1198.3)	586	1089.2	(948.1, 1251.3)
		Day 30	587	7876.9	(7009.6, 8851.5)	571	1142.9	(994.4, 1313.5)
	GMFR	Day 1 to Day 30	578	7.4	(6.4, 8.6)	560	1.0	(1.0, 1.2)
33F	% ≥ 4-fold rise	Day 1 to Day 30	578	56.7% (328/578)	(52.6, 60.8)	560	6.3% (35/560)	(4.4, 8.6)

† 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 subjects randomized and vaccinated; n=Number of subjects 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; GMFR=geometric mean fold-rise; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

V114-017

Primary Immunogenicity endpoints

Both V114 and PCV 13 elicited an immune response in immunocompetent adults with or without risk factors for pneumococcal disease as assessed by OPA GMTs 30 days postvaccination for all serotypes contained in each vaccine, see Table 10.

Serotype-specific OPA GMTs at 30 days postvaccination in the FAS population were consistent with those observed in the PP population in each intervention group.

Table 10 Summary of OPA GMTs at Day 30 – PP population V114-017

Pneumococcal Serotype	V114 (N = 1133)			Prevnar 13™ (N = 379)		
	n	Observed GMT	95% CI[†]	n	Observed GMT	95% CI[†]
13 Shared Serotypes						
1	1019	268.6	(243.7, 296.0)	341	267.2	(220.4, 323.9)
3	1004	199.3	(184.6, 215.2)	340	150.6	(130.6, 173.8)
4	1016	1416.0	(1308.9, 1531.8)	342	2576.1	(2278.0, 2913.2)
5	1018	564.8	(512.7, 622.2)	343	731.1	(613.6, 871.0)
6A	1006	12928.8	(11923.4, 14019.0)	335	11282.4	(9718.8, 13097.5)
6B	1014	10336.9	(9649.4, 11073.4)	342	6995.7	(6024.7, 8123.2)
7F	1019	5756.4	(5410.4, 6124.6)	342	7588.9	(6775.3, 8500.2)
9V	1015	3355.1	(3135.4, 3590.1)	343	3983.7	(3557.8, 4460.7)
14	1016	5228.9	(4847.6, 5640.2)	343	5889.8	(5218.2, 6647.8)
18C	1014	5709.0	(5331.1, 6113.6)	343	3063.2	(2699.8, 3475.5)
19A	1015	5369.9	(5017.7, 5746.8)	343	5888.0	(5228.2, 6631.0)
19F	1018	3266.3	(3064.4, 3481.4)	343	3272.7	(2948.2, 3632.9)
23F	1016	4853.5	(4469.8, 5270.2)	340	3887.3	(3335.8, 4530.0)
2 Serotypes Unique to V114						
22F	1005	3926.5	(3645.9, 4228.7)	320	291.6	(221.8, 383.6)
33F	1014	11627.8	(10824.6, 12490.7)	338	2180.6	(1828.7, 2600.2)

[†] 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 subjects randomized and vaccinated; n=Number of subjects contributing to the analysis.

Note: Per protocol, Day 30 is 30 days following vaccination with PCV.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity;

PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Secondary Immunogenicity endpoints

Serotype-specific OPA GMTs were lower at Month 6, prior to vaccination with PPV23, than Day 30 but remained above baseline levels for all the serotypes contained in the either V114 or PCV13 groups, see Table 11 for 3 by the assessor chosen examples.

PPV23 vaccination at Month 6 following vaccination with either V114 or PCV13 was immunogenic for all 15 serotypes, including 22F and 33F, as assessed by serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 7), see Table 11 for 3 by the assessor chosen for examples. The magnitude of serotype-specific OPA GMFRs and proportions of participants with a ≥4-fold rise in OPA titres varied by serotype from Month 6 to Month 7; however, the GMFRs and proportions of participants with a ≥4-fold rise in OPA titres were higher between Day 1 and Day 30 (following vaccination with V114 or PCV13) than levels observed between Month 6 and Month 7 (following PPV23 vaccination).

Table 11 Summary of OPA responses over time – PP population V114-017

Serotype	End-point	Timepoint	V114			PCV13		
			N	Response	95% CI	N	Response	95% CI
1	GMT	D 1	1100	7.0	(6.6, 7.5)	368	7.5	(6.7, 8.3)
		D 30	1019	268.6	(246.7, 296.0)	341	267.2	(220.4, 323.9)
		Mo 6	946	79.5	(71.7, 88.3)	315	95.8	(78.6, 116.7)
		Mo 7	841	266.6	(243.6, 291.8)	281	214.4	(180.7, 254.5)
	GMFR	D 1 to D 30	1001	22.8	(20.6, 25.1)	334	21.9	(18.4, 26.2)
		D 1 to Mo 7	826	22.6	(20.6, 24.8)	276	17.4	(14.8, 20.5)
		Mo 6 to Mo 7	839	3.2	(2.9, 3.5)	280	2.0	(1.7, 2.2)
	% ≥4-fold rise	D 1 to D 30	1001	83.9%	(81.5, 86.1)	344	81.4%	(76.8, 85.5)
		D 1 to Mo 7	826	87.7%	(85.2, 89.8)	276	83.7%	(78.8, 87.9)
		Mo 6 to Mo 7	839	40.2%	(36.8, 43.6)	280	21.4%	(16.8, 26.7)
14	GMT	D 1	1073	537.1	(483.9, 596.1)	363	573.0	(481.7, 681.5)
		D 30	1016	5228.9	(4847.6, 5640.2)	343	5889.8	(5218.2, 6647.8)
		Mo 6	946	2929.5	(2718.3, 3157.0)	314	3560.1	(3123.3, 4057.9)
		Mo 7	843	5644.9	(5262.5, 6055.2)	283	5317.6	(4686.1, 6034.1)
	GMFR	D 1 to D 30	973	8.2	(7.4, 9.2)	331	8.7	(7.2, 10.6)
		D 1 to Mo 7	809	9.2	(8.2, 10.3)	275	8.0	(6.6, 9.7)
		Mo 6 to Mo 7	841	2.0	(1.8, 2.1)	280	1.5	(1.3, 1.6)
	% ≥4-fold rise	D 1 to D 30	973	59.8%	(56.7, 62.9)	331	60.4	(54.9, 65.7)
		D 1 to Mo 7	809	64.9%	(61.5, 68.2)	275	58.9%	(52.8, 64.8)
		Mo 6 to Mo 7	841	17.8%	(15.3, 20.6)	280	8.6%	(5.6, 12.5)
22F	GMT	D 1	985	227.0	(194.4, 265.0)	341	190.9	(145.5, 250.4)
		D 30	1005	3926.5	(3645.9, 4228.7)	320	291.6	(221.8, 383.6)
		Mo 6	932	2054.4	(1909.0, 2210.8)	286	335.6	(250.9, 449.1)
		Mo 7	837	3624.0	(3384.5, 3880.3)	280	4060.2	(3358.6, 4908.4)
	GMFR	D 1 to D 30	885	13.9	(11.8, 16.3)	290	1.3	(1.1, 1.6)
		D 1 to Mo 7	742	12.1	(10.4, 14.3)	254	16.6	(12.2, 22.6)
		Mo 6 to Mo 7	822	1.8	(1.7, 1.9)	253	9.6	(7.1, 13.0)
	% ≥4-fold rise	D 1 to D 30	885	58.9%	(55.5, 62.1)	290	15.5%	(11.5, 20.2)
		D 1 to Mo 7	742	59.0%	(55.4, 62.6)	254	65.4%	(59.2, 71.2)
		Mo 6 to Mo 7	822	16.7%	(14.2, 19.4)	253	52.6%	(46.2, 58.9)

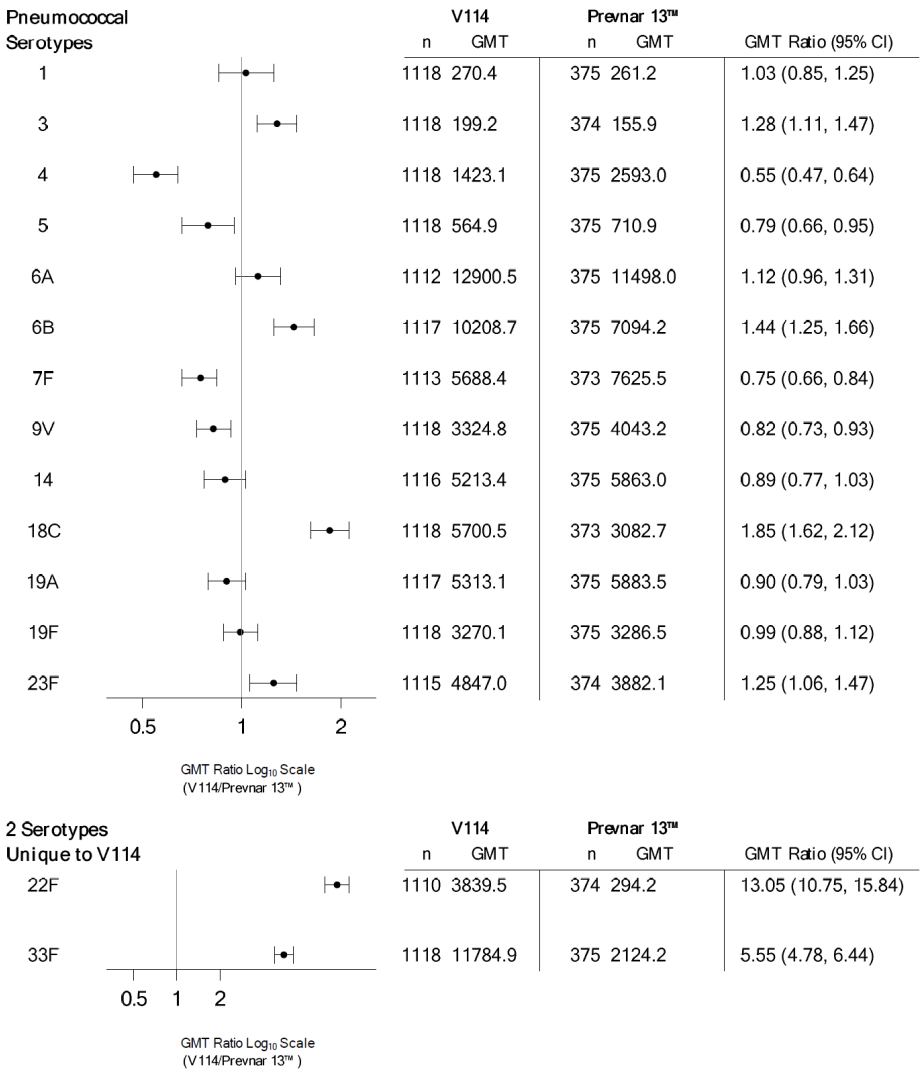
D=Day; GMT=geometric mean titer; GMFR=geometric mean fold rise; Mo= month; PCV13=Prevenar 13^{TM}

Trends observed for serotype-specific IgG GMCs were consistent with the primary analysis of OPA GMTs, with V114 and PCV13 being immunogenic and inducing an antibody response that remained for at least 6 months postvaccination.

Exploratory Immunogenicity endpoints

Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination were generally comparable across intervention groups for the 13 shared serotypes between V114 and PCV13 and higher in the V114 group for the 2 unique serotypes, see Figure 2.

Figure 2 Forest plot of OPA GMT ratios at Day 30 – PP population V114-017



Following PPV23 vaccination at Month 6, serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination, i.e. at Month 7, were generally comparable across intervention groups for all 15 serotypes.

- **Ancillary analyses**

Age

V114-019

V114 was immunogenic within each age subgroup (50 to 64 years of age, 65 to 74 years of age and ≥75 years of age) as assessed by OPA GMTs for all 15 serotypes 30 days postvaccination. A trend towards lower immunogenicity was seen in the older age groups (65 to 74 years of age and ≥75 years of age) compared with the younger age group (50 to 64 years of age), see Table 12.

V114-017

V114 was immunogenic within each age subgroup (18 to 29, 30 to 39 and 40 to 49 years of age) as assessed by OPA GMTs, see Table 13. As expected, a trend towards lower immunogenicity was seen in the older age group (40 to 49 years of age) compared with the younger age group (18 to 29 years of age).

Table 12 Analysis of OPA GMTs at Day 30 per age group – PP population V114-019

	Subjects 50 to 64 years of age				Subjects 65 to 74 years of age				Subjects ≥75 years of age			
	V114 (N=186)		PCV13 (N= 186)		V114 (N=346)		PCV13 (N= 346)		V114 (N=68)		PCV13 (N= 67)	
Serotype	n	GMT	n	GMT	n	GMT	n	GMT	n	GMT	n	GMT
1	186	329.8	186	475.8	344	241.4	345	279.3	68	174.8	67	233.4
3	186	203.1	186	150.0	344	215.9	345	130.6	68	255.7	67	121.5
4	186	1255.5	186	2216.8	344	1061.0	345	1411.3	68	1153.4	67	1698.9
5	186	528.5	186	792.5	344	410.1	345	434.4	68	427.1	67	857.0
6A	186	7048.9	186	7716.6	344	4915.7	345	4454.8	68	4336.0	67	5466.0
6B	186	5112.9	186	4778.7	344	3702.5	345	2571.1	68	3026.0	67	3927.1
7F	185	5590.2	186	7518.0	342	4316.7	345	5037.8	68	3856.1	67	6599.1
9V	186	2156.8	186	3056.3	344	1668.5	344	1901.2	68	1736.8	67	2151.7
14	186	2513.5	186	4529.6	344	1854.7	345	2086.6	68	1567.0	67	2088.0
18C	186	3379.7	186	3090.3	344	2683.3	345	2259.9	68	1816.7	67	3138.5
19A	186	3810.7	186	4706.7	344	2987.6	345	3559.3	68	2789.8	67	4389.2
19F	186	1966.0	186	2312.3	344	1614.4	345	1754.9	68	1440.0	67	1809.5
23F	186	2327.9	186	2432.6	344	1891.5	345	1465.6	68	2294.7	67	1554.2
22F	186	2537.1	181	99.8	340	2356.3	338	64.7	68	2132.2	67	68.9
33F	186	9291.5	186	1416.0	344	7550.3	344	1019.3	68	6996.5	67	1001.8

PCV13=Prevenar 13™

Table 13 Summary of OPA GMTs at Day 30 per age group – PP population V114-017

	18 to 29 years of age				30 to 39 years of age				40 to 49 years of age			
	V114 (N=329)		PCV13 (N=105)		V114 (N=351)		PCV13 (N=112)		V114 (N=453)		PCV13 (N=162)	
Serotype	n	GMT	n	GMT	n	GMT	n	GMT	n	GMT	n	GMT
1	290	337.2	91	240.6	318	255.6	102	252.7	411	237.7	148	296.2
3	288	184.1	90	144.0	316	182.5	102	160.6	400	226.3	148	148.1
4	289	1563.8	92	3133.5	317	1384.2	103	2661.0	410	1343.6	147	2227.7
5	289	692.4	92	803.7	318	543.5	103	743.3	411	504.1	148	687.2
6A	284	21579.1	90	16905.6	314	13586.0	100	11059.1	408	8712.4	145	8899.7
6B	288	14439.8	92	11108.2	315	11639.5	103	7507.1	411	7467.2	147	4985.2
7F	290	6732.6	91	8969.8	318	5600.4	103	8017.1	411	5264.9	148	6590.9
9V	289	4160.0	92	5261.7	317	3387.4	103	3554.0	409	2860.8	148	3628.0
14	288	7896.1	92	9842.2	317	5312.5	103	5734.3	411	3869.6	148	4359.1
18C	287	7347.7	92	3364.1	316	5537.4	103	2730.7	411	4900.3	148	3130.4
19A	289	6785.9	92	7159.9	318	5850.6	103	5959.3	408	4255.4	148	5170.4
19F	290	4416.4	92	4303.0	318	3440.0	103	3489.9	410	2534.7	148	2639.9
23F	288	7258.1	92	7162.2	317	4997.1	101	3671.4	411	3579.5	147	2758.1
22F	288	4616.5	87	416.9	317	3947.7	96	345.1	400	3479.5	137	206.6
33F	287	13835.1	92	3418.2	317	12801.7	103	1888.3	410	9558.0	143	1811.3

PCV13=Prevenar 13™

Data Source: Modified from Mod5.3.5.1/p017v114/Tab14.2-9, 14.2-10 and 14.2-11

Sex, Race and Ethnicity

V114-019

V114 was immunogenic in both male and female participants as assessed by OPA GMTs for all 15 serotypes contained in the vaccine 30 days postvaccination. The ratio of OPA GMTs between male and female participants for all serotypes ranged from 0.56 to 0.86. A similar range was observed for PCV13.

Similar results were observed when comparing race subgroups and both ethnic subgroups, with V114 being immunogenic and resulting in OPA GMT ratios between V114 and PCV13 at 30 days postvaccination that are generally consistent with the OPA GMT ratios between V114 and PCV13 observed for the overall population.

V114-017

V114 was immunogenic in both male and female participants, as assessed by OPA GMTs between male and female participants for all 15 serotypes contained in the vaccine 30 days postvaccination. Immunogenicity was comparable, as the ratio of OPA GMTs between male and female participants for all serotypes ranged from 0.87 to 1.18, except for serotype 1, which was 1.51.

Slight differences in immune response could be observed between the subgroups in race and ethnicity, however no clear trends were observed as assessed by OPA GMTs for all 15 serotypes contained in the vaccine 30 days postvaccination.

Risk factors

V114-017

V114 was immunogenic in participants with no, a single and 2 or more risk factors as assessed by OPA GMTs for all 15 serotypes in the vaccine 30 days postvaccination, see Table 14. Similar results were seen for IgG GMCs. PPV23 vaccination following either V114 or PCV13, was immunogenic in participants with no, a single and 2 or more risk factors as assessed by OPA GMTs for all 15 serotypes tested 30 days postvaccination (data not shown).

Table 14 Summary of OPA GMTs at Day 30 by number of risk factors – PP population V114-017

Serotype	No risk factors				1 risk factor				2 or more risk factors			
	V114 (N=285)		PCV13 (N=96)		V114 (N=620)		PCV13 (N=207)		V114 (N=228)		PCV13 (N=76)	
	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)
13 shared serotypes												
1	266	166.9 (137.2, 202.9)	87	122.7 (79.6, 189.0)	552	327.7 (287.8, 373.1)	185	367.1 (286.3, 470.9)	201	292.0 (237.5, 359.1)	69	304.2 (214.9, 430.5)
3	263	160.2 (137.4, 186.8)	87	155.0 (113.3, 212.1)	544	208.8 (189.1, 230.6)	184	157.4 (131.6, 188.2)	197	234.5 (194.1, 283.4)	69	129.2 (91.1, 183.2)
4	265	1066.5 (918.3, 1238.7)	88	2196.6 (1678.8, 2874.2)	550	1594.1 (1434.1, 1772.1)	185	2831.8 (2418.7, 3315.4)	201	1487.6 (1239.0, 1786.0)	69	2449.2 (1845.4, 3250.5)
5	265	456.8 (371.2, 562.0)	88	695.3 (494.7, 977.1)	552	618.5 (545.4, 701.4)	186	813.9 (643.0, 1030.1)	201	582.2 (469.5, 722.0)	69	583.6 (382.9, 889.5)
6A	263	14092.5 (11948.5, 16621.2)	86	9977.4 (7437.1, 13385.6)	544	12773.3 (11487.3, 14203.2)	182	12514.6 (10248.3, 15282.0)	199	11924.9 (9847.1, 14441.2)	67	9968.8 (6971.9, 14254.0)
6B	265	11847.9 (10368.0, 13569.1)	88	8406.3 (6254.4, 11298.6)	548	10159.2 (9270.5, 11133.1)	185	6990.7 (5688.9, 8590.5)	201	9053.1 (7673.5, 10680.9)	69	5545.2 (4001.0, 7685.3)
7F	266	5186.3 (4651.9, 5782.1)	88	7593.1 (6184.8, 9322.1)	552	5824.1 (5333.2, 6360.3)	185	7574.3 (6544.0, 8766.7)	201	6399.7 (5561.5, 7364.1)	69	7622.9 (5546.4, 10476.9)
9V	264	3013.3 (2639.1, 3440.5)	88	3657.5 (2871.6, 4658.5)	552	3455.9 (3149.4, 3792.4)	186	4279.4 (3681.6, 4973.4)	199	3563.8 (3069.6, 4137.5)	69	3663.4 (2859.4, 4693.4)
14	266	6300.5 (5433.0, 7306.5)	88	6061.1 (4720.7, 7782.2)	549	5120.4 (4628.1, 5665.1)	186	5893.2 (5014.8, 6925.5)	201	4326.5 (3625.3, 5163.3)	69	5669.1 (4281.5, 7506.4)
18C	266	5357.5 (4692.4, 6116.9)	88	3155.5 (2494.2, 3992.0)	549	5840.7, (5322.5, 6409.3)	186	3215.0 (2696.2, 3833.6)	199	5836.2 (4976.9, 6843.9)	69	2588.9 (1934.4, 3464.8)
19A	263	5362.3 (4729.5, 6079.7)	88	5453.4 (4438.6, 6700.2)	551	5508.5 (5022.7, 6041.4)	186	6354.1 (5340.4, 7560.3)	201	5016.7 (4257.1, 5911.9)	69	5287.3 (4097.2, 6823.1)
19F	266	3387.7 (3007.3, 3816.3)	88	3674.6 (2993.7, 4510.4)	552	3327.9 (3045.9, 3636.1)	186	3328.0 (2889.5, 3833.0)	200	2954.9 (2555.6, 3416.6)	69	2698.5 (2119.0, 3436.5)
23F	265	5076.5 (4422.7, 5826.9)	87	4901.8 (3812.3, 6302.6)	550	4911.5 (4372.5, 5516.8)	184	3731.5 (3017.3, 4614.9)	201	4428.2 (3624.7, 5409.9)	69	3236.3 (2189.5, 4783.6)
2 unique serotypes												
22F	265	3140.6 (2773.4, 3556.3)	84	549.7 (346.9, 871.0)	543	4498.2 (4049.2, 4996.9)	171	210.0 (142.5, 309.4)	197	3645.7 (3069.2, 4330.5)	65	305.0 (160.2, 580.9)
33F	263	11701.9 (10227.7, 13388.6)	88	3380.1 (2550.1, 4480.2)	550	12608.2 (11462.0, 13881.1)	183	1874.0 (1473.0, 2384.3)	201	9240.5 (7778.9, 10976.8)	67	1854.6 (1165.9, 2949.9)

GMT= geometric mean titre; OPA=Opsonophagocytic activity; PCV13=Prevenar 13^{TM}; PP=Per protocol
Data Source: Mod5.3.5.1/p017v114/Tab14.2-22, 14.2-24 and 14.2-36

- **Summary of main efficacy results**

There is no clinical efficacy data available in the dossier. OPA GMT results are used as surrogate markers for protection. The following tables summarise the immunogenicity results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

Table 15 Summary of immunogenicity for trial V114-019

Title: A Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-AGE)			
Study identifier	Protocol Number: P019V114 IND: 14977 EudraCT: 2018-004316-22		
Design	multicentre, randomised, active-controlled, parallel-group, double-blind study to evaluate the safety, tolerability, and immunogenicity of V114 in adults 50 years of age or older		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First participant, first visit: 13-06-2019 Last participant, last visit: 30-03-2020 9.5 Months not applicable not applicable
Hypothesis	Non-inferiority and Superiority		
Treatments groups	V114		Single 0.5 mL IM dose at visit 1 (Day 1) 604 participants randomised 602 participants vaccinated (99.7%) 596 participants completed the study (98.7%) 8 participants discontinued (1.3%)
	PCV13		Single 0.5 mL IM dose at visit 1 (Day 1) 601 participants randomised 600 participants vaccinated (99.8%) 594 participants completed the study (98.8%) 7 participants discontinued (1.2%)
Endpoints and definitions	Primary Endpoints	Immunogenicity	• Serotype-specific OPA GMTs for the 15 serotypes in V114 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) at Day 30. • Serotype-specific OPA responses for the 2 unique serotypes in V114 (serotypes 22F and 33F) at Day 1 and Day 30.
	Secondary Endpoints	Immunogenicity	• OPA responses for serotype 3 at Day 30. • OPA responses for serotype 3 at Day 1 and 30. • Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30. • Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and 30.
Database lock	31 July 2020		

Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	PP population: all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Participants were included in vaccination group to which they were randomised. Time point: Day 30 (30 days postvaccination)
Results	**Serotype-specific OPA Responses at 30 Days Postvaccination** V114 met non-inferiority criteria for the 13 shared serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination. The lower bound of the 95% CI of the estimated OPA GMT ratio (V114/PCV13) was >0.5 for all shared serotypes. V114 met superiority criteria for the 2 serotypes unique to V114 as assessed by serotype-specific OPA GMTs at 30 days postvaccination. The lower bound of the 95% CI of the estimated OPA GMT ratio (V114/ PCV13) was >2.0 for both unique serotypes. V114 met superiority criteria for the 2 serotypes unique to V114 as assessed by the proportions of participants with a ≥4-fold rise from prevaccination to 30 days postvaccination for serotype-specific OPA responses. The lower bound of the 2-sided 95% CI of the difference in percentages [V114- PCV13] was >10 percentage points for both unique serotypes.
Notes	The clinical impact of meeting the non-inferiority or superiority margin is unknown. Results for OPA responses are presented in Figure 1 OPA GMTs at Day 30 postvaccination were lower for 7 of the 13 shared serotypes in the V114 group compared to the PCV13 group, with serotype 1, 4, 5, 7F, 9V, 14 and 19F having a upper bound of the 2-sided 95% CI that did not contain 1.00. Serotypes 3 and 6B had OPA GMTs that were higher in the V114 group compared to the PCV13 group, with a lower bound of the 2-sided 95% CI that was higher than 1.00.
Analysis description	**Secondary analysis**
Analysis population and time point description	PP population: all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Participants were included in vaccination group to which they were randomised. Time point: Day 30 (30 days postvaccination)
Results	**Serotype 3 OPA Responses at 30 Days Postvaccination** V114 met the superiority criterion for serotype 3 as assessed by the OPA GMTs at 30 days postvaccination. The lower bound of the 95% CI of the OPA GMT ratio (V114/ PCV13) was >1.2. V114 met the superiority criterion for serotype 3 as assessed by the proportions of participants with a ≥4-fold rise from prevaccination to 30 days postvaccination for OPA responses. The lower bound of the 2-sided 95% CI of the difference in percentages [V114- PCV13] was >0 percentage points. **Serotype-specific IgG responses at 30 Days Postvaccination** Between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the primary analysis of OPA GMTs.
Notes	The clinical impact of meeting the superiority margin is unknown. Results for proportion of participants achieving ≥4-fold rise in OPA GMT are presented in Table 7.

Table 16 Summary of immunogenicity for trial V114-017

Title: A Phase 3, multicentre, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 followed by administration of PNEUMOVAX™23 six months later in immunocompetent adults between 18 and 49 years of age at increased risk for pneumococcal disease			
Study identifier	Protocol Number: P017V114 IND: 14977 EudraCT: 2017-004915-38		
Design	multicentre, randomised, double-blind, active-comparator controlled study to evaluate the safety, tolerability, and immunogenicity of V114 followed by administration of PPV23 six months later in immunocompetent adults between 18 and 49 years of age at increased risk for pneumococcal disease (PNEU-DAY)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First participant, first visit: 16-07-2018 Last participant, last visit: 20-01-2020 18 Months not applicable not applicable
Hypothesis	Not applicable		
Treatments groups	V114		Single dose V114 IM at visit 1 (Day 1) Single dose PPV23 IM at visit 4 (Month 6) 1135 participants randomised 1133 participants vaccinated with V114 (99.8%) 1035 participants vaccinated with PPV23 (91.2%) 1038 participants completed the study (91.5%) 97 participants discontinued (8.5%)
	PCV13		Single dose PCV13 IM at visit 1 (Day 1) Single dose PPV23 IM at visit 4 (Month 6) 380 participants randomised 379 participants vaccinated with PCV13 (99.5%) 346 participants vaccinated with PPV23 (91.1%) 350 participants completed the study (92.1%) 30 participants discontinued (7.9%)
	Primary Endpoints	Immunogenicity	• Serotype-specific OPA GMTs for the 15 serotypes in V114 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) at Day 30.
	Secondary Endpoints	Immunogenicity	• Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30. • Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and 30. • Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1, 30, Month 6 and Month 7.
Database lock	31 July 2020		

Results and Analysis.	
Analysis description	**Primary Analysis**
Analysis population and time point description	PP population: all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Participants were included in vaccination group to which they were randomised. Time point: Day 30 (30 days postvaccination)
Results	**Serotype-specific OPA Responses at 30 Days Postvaccination** V114 was immunogenic in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease as assessed by OPA GMTs at 30 days postvaccination for all 15 serotypes contained in the vaccine. PCV13 was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine.
Notes	Results for OPA GMTs are shown in Table 10. Both V114 and PCV13 elicited an immune response in immunocompetent adults with or without risk factors for pneumococcal disease. For 4 of the 13 shared serotypes response in V114 group was lower compared to the PCV13 group, serotypes 4, 5, 7F and 9V. For 3 of the 13 shared serotypes, response in the V114 group was higher compared to the PCV13 group, serotypes 3, 6B and 18C.
Analysis description	**Secondary analysis**
Analysis population and time point description	PP population: all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Participants were included in vaccination group to which they were randomised. Time points: Day 1 (prevaccination) Day 30 (30 days postvaccination) Month 6 (prevaccination PPV23) Month 7 (30 days postvaccination PPV23)
Results	As observed for OPA GMTs, V114 was immunogenic as assessed by IgG GMCs at 30 days postvaccination for all 15 serotypes contained in the vaccine. PCV13 was immunogenic as assessed by IgG responses at 30 days postvaccination for all 13 serotypes contained in the vaccine. V114 or PCV13 followed by PPV23 was immunogenic for all 15 serotypes as assessed by serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23. PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the PCV13 group. V114 was immunogenic for all 15 serotypes contained in the vaccine as assessed by serotype-specific OPA GMFRs and IgG GMFRs and the proportions of participants with a ≥4-fold rise in OPA titres and IgG concentrations from prevaccination with PCV to 30 days postvaccination.
Notes	Results for OPA antibody responses are shown in Table 10. For pneumococcal vaccines it is known that GMTs after the second dose are generally lower than after the first dose (Greenberg et al. Vaccine 2014).

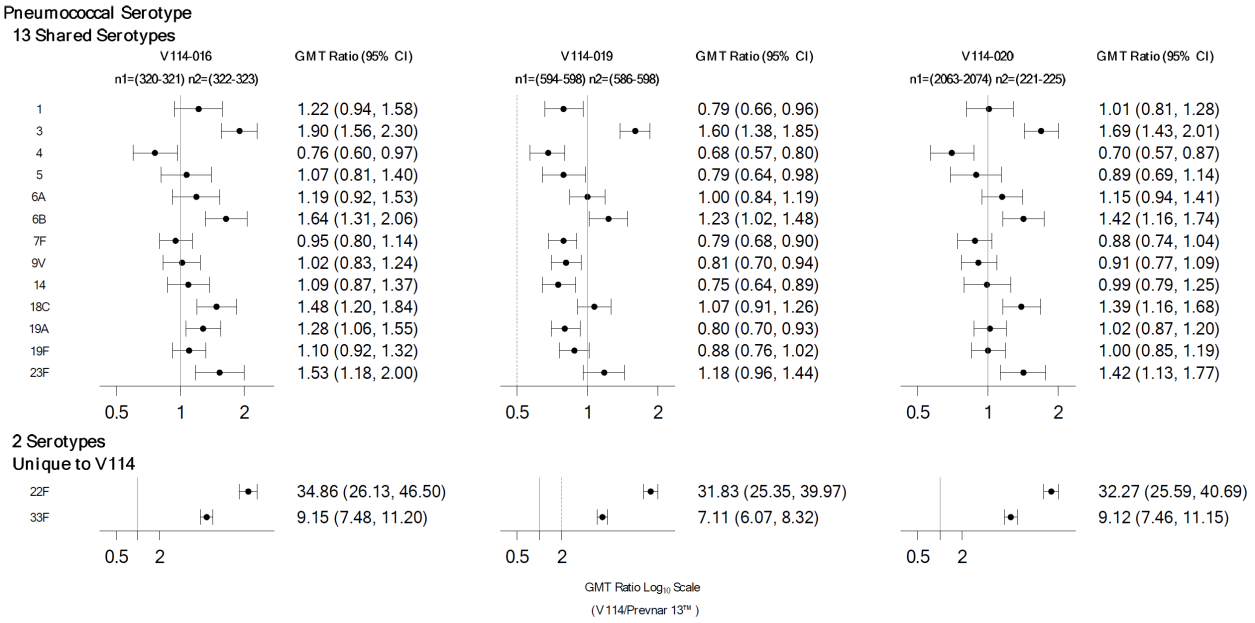
2.5.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

V114-016, V114-019 and V114-020 enrolled pneumococcal vaccine-naïve adults ≥50 years of age, and the results from these studies were directly compared. Demographic characteristics were generally comparable across the intervention groups: median age ranging from 64.5 to 67.0 years old, and the majority of participants were female, white, and not of Hispanic or Latino ethnicity. Randomization was stratified by age group (50 to 64 years of age, 65 to 74 years of age and ≥75 years of age) to ensure balance across intervention groups with respect to age.

A consistent immune response was observed across studies in pneumococcal vaccine-naïve adults ≥50 years of age, as assessed by OPA GMTs (see Figure 3), IgG GMCs, OPA and IgG GMFRs, and proportions of participants with a ≥4-fold rise in OPA and IgG responses from pre-vaccination to 30 days post-vaccination with PCV.

A trend toward lower serotype-specific OPA GMTs in the older age groups (65 to 74 years of age and ≥75 years of age) compared with the younger age group (50 to 64 years of age) was seen (data presented in clinical AR).

Figure 3 Forest plot of OPA GMT ratios by study at Day 30 – PP population (≥50 years of age)



n1=Number of subjects contributing to the analysis from V114 across all 15 serotypes;
n2=Number of subjects contributing to the analysis from Prevnar 13™ across all 15 serotypes.

Immunogenicity responses in adults 18-49 years of age compared to adults ≥50 years of age (V114-017, V114-019)

For all 15 serotypes in V114, OPA GMTs at 30 days post-vaccination in V114-017 (adults 18 to 49 years of age) following vaccination with V114 were generally comparable to or higher than OPA GMTs in study V114-019 (adults ≥50 years of age) in both intervention groups. In addition, trends observed for OPA GMTs in study V114-017 were generally consistent with the results of study V114-019, which demonstrated non-inferiority of V114 to PCV13 for the shared serotypes in V114 and superiority of V114 to PCV13 for serotypes 3, 22F, and 33F at 30 days post-vaccination with PCV. Similar trends were observed for OPA GMFRs and proportions of participants with a ≥4-fold rise in OPA responses from pre-vaccination to 30 days post-vaccination with PCV.

Table 17 Immunogenicity OPA GMT responses in adults 18-49 years of age (study V114-017) compared to adults ≥50 years of age V114-019

	V114-017 adults 18 to 49 years of age						V114-019 adults ≥50 years of age					
Sero type	V114 (N=1133)			Prevnar 13™ (N=379)			V114 (N=602)			Prevnar 13™ (N=600)		
	n	GMT	(95% CI)	n	GMT	(95% CI)	n	GMT	(95% CI)	n	GMT	(95% CI)
13 shared serotypes												
1	1019	268.6	(243.7, 296.0)	341	267.2	(220.4, 323.9)	588	259.2	(225.4, 298.1)	577	319.7	(276.1, 370.2)
3	1004	199.3	(184.6, 215.2)	340	150.6	(130.6, 173.8)	582	219.4	(197.4, 243.8)	581	132.9	(119.1, 148.3)
4	1016	1416.0	(1308.9, 1531.8)	342	2576.1	(2278.0, 2913.2)	587	1106.7	(975.5, 1255.4)	582	1672.3	(1487.6, 1880.0)
5	1018	564.8	(512.7, 622.2)	343	731.1	(613.6, 871.0)	588	444.8	(379.7, 521.1)	584	561.7	(481.2, 655.6)
6A	1006	12928.8	(11923.4, 14019.0)	335	11282.4	(9718.8, 13097.5)	575	5469.4	(4824.9, 6200.0)	576	5284.2	(4614.4, 6051.3)
6B	1014	10336.9	(9649.4, 11073.4)	342	6995.7	(6024.7, 8123.2)	587	4001.0	(3493.7, 4581.9)	582	3237.5	(2806.3, 3735.0)
7F	1019	5756.4	(5410.4, 6124.6)	342	7588.9	(6775.3, 8500.2)	586	4601.1	(4168.4, 5078.8)	584	5891.4	(5336.2, 6504.4)
9V	1015	3355.1	(3135.4, 3590.1)	343	3983.7	(3557.8, 4460.7)	587	1799.9	(1610.4, 2011.7)	583	2239.3	(2008.1, 2497.2)
14	1016	5228.9	(4847.6, 5640.2)	343	5889.8	(5218.2, 6647.8)	585	2036.1	(1794.8, 2309.7)	581	2605.1	(2299.3, 2951.5)
18C	1014	5709.0	(5331.1, 6113.6)	343	3063.2	(2699.8, 3475.5)	585	2736.9	(2432.0, 3080.0)	581	2581.1	(2287.2, 2912.7)
19A	1015	5369.9	(5017.7, 5746.8)	343	5888.0	(5228.2, 6631.0)	585	3169.9	(2861.1, 3511.9)	582	4003.2	(3594.7, 4458.2)
19F	1018	3266.3	(3064.4, 3481.4)	343	3272.7	(2948.2, 3632.9)	586	1688.1	(1513.2, 1883.3)	581	1918.1	(1724.3, 2133.7)
23F	1016	4853.5	(4469.8, 5270.2)	340	3887.3	(3335.8, 4530.0)	582	2027.5	(1760.3, 2335.3)	581	1748.5	(1493.0, 2047.7)
2 Serotypes Unique to V114												
22F	1005	3926.5	(3645.9, 4228.7)	320	291.6	(221.8, 383.6)	580	2328.7	(2036.5, 2662.9)	536	73.8	(59.7, 91.2)
33F	1014	11627.8	(10824.6, 12490.7)	338	2180.6	(1828.7, 2600.2)	587	7876.9	(7009.6, 8851.5)	571	1142.9	(994.4, 1313.5)

2.5.5.4. Clinical studies in special populations

HIV-1 infected subjects

Study V114-018 was a randomised, double-blind, active comparator-controlled study. Participants were randomised 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.

In total, 302 subjects were enrolled, of which 152 participants were vaccinated with V114, and 150 participants were vaccinated with PCV13. In total, 10 participants discontinued the study, 7 (4.6%) in the V114 group and 3 (2.0%) in the PCV13 group.

Demographics and baseline characteristics were comparable between the intervention groups. The median age was 41.0 years, ranging from 21 to 74 years. The majority of participants were male (78.8%) and not Hispanic or Latino (68.2%). In total, 4 (1.3%) participants had a CD4+ T-cell count of ≥50 to <200 cells/µL, 152 (50.3%) participants had a CD4+ T-cell count of ≥200 to <500 cells/µL, and 146 (48.3%) participants had a CD4+ T-cell count of ≥500 cells/µL. All participants received antiretroviral therapy (ART) prior to study entry.

Both V114 and PCV13 were immunogenic in pneumococcal vaccine-naïve adults infected with HIV-1 as assessed by OPA GMTs, see Table 18, and IgG GMCs at 30 days postvaccination for all serotypes contained in the vaccines. Similar results were observed in both CD4+ T-cell count subgroups (≥200 to <500 cells/µL and ≥500 cells/µL) (data are not shown). In both intervention groups, there was a trend toward higher serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination in participants with CD4+ T-cell count ≥500 cells/µL compared with participants with CD4+ T-cell count ≥200 to <500 cells/µL.

Table 18 Summary of OPA GMTs at Day 30 – PP population v114-018

Pneumococcal Serotype	V114 (N = 152)			Prevnar 13™ (N = 150)		
	n	Observed GMT	95% CI†	n	Observed GMT	95% CI†
13 Shared Serotypes						
1	131	238.8	(173.1, 329.3)	131	200.9	(142.7, 282.7)
3	131	116.8	(94.9, 143.7)	130	72.3	(58.6, 89.2)
4	130	824.0	(618.8, 1097.2)	131	1465.5	(1154.5, 1860.3)
5	131	336.7	(242.4, 467.7)	130	276.7	(197.9, 386.7)
6A	126	6421.0	(4890.4, 8430.7)	128	5645.1	(4278.9, 7447.4)
6B	129	4772.9	(3628.3, 6278.7)	130	3554.0	(2751.0, 4591.4)
7F	131	6085.8	(4871.6, 7602.8)	131	6144.3	(4982.8, 7576.6)
9V	129	2836.3	(2311.5, 3480.4)	128	2133.9	(1721.8, 2644.5)
14	131	3508.7	(2730.6, 4508.5)	130	3000.3	(2350.0, 3830.5)
18C	129	3002.2	(2435.5, 3700.8)	129	1560.3	(1213.8, 2005.6)
19A	131	4240.7	(3415.4, 5265.3)	131	3715.9	(2949.2, 4681.8)
19F	131	2438.6	(1972.7, 3014.6)	131	2042.0	(1618.9, 2575.5)
23F	129	1757.4	(1276.1, 2420.2)	127	1787.0	(1309.9, 2437.9)
2 Serotypes Unique to V114						
22F	128	3943.7	(3049.2, 5100.5)	116	109.3	(66.2, 180.3)
33F	131	11342.4	(9184.3, 14007.6)	129	1807.6	(1357.3, 2407.3)

† 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 subjects randomized and vaccinated; n=Number of subjects contributing to the analysis.

Note: Per protocol, Day 30 is 30 days following vaccination with PCV.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Serotype-specific OPA GMTs at Day 30 postvaccination with PPV23 (Week 12) were generally comparable with those observed at 30 days postvaccination with either V114 or PCV13 (data presented in clinical AR). Similar results were observed for IgG GMCs at 30 days postvaccination with PPV23.

2.5.5.5. Supportive studies

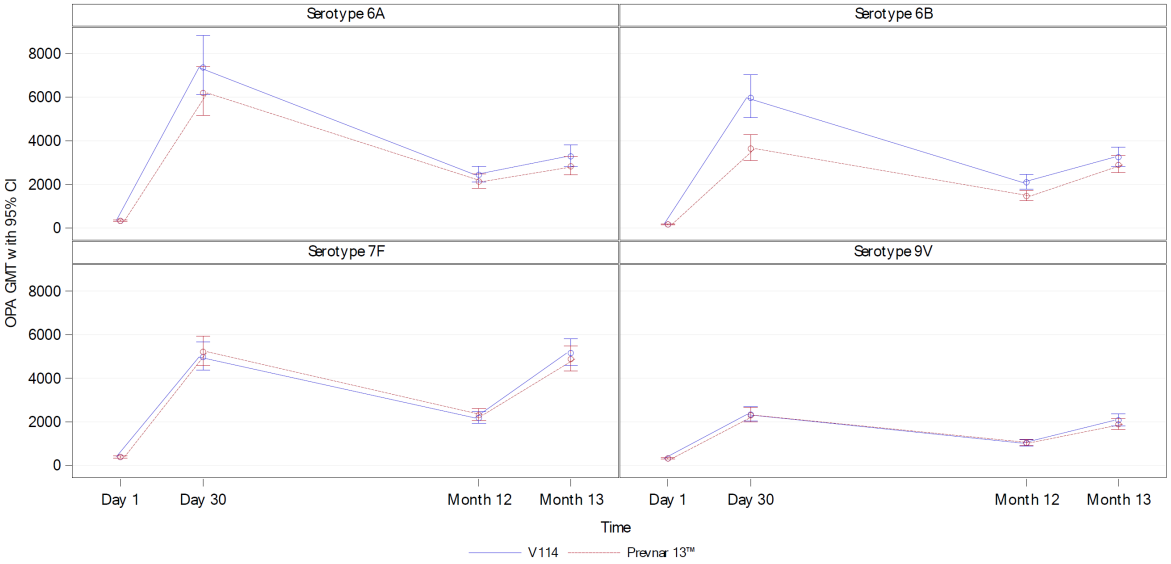
The supportive studies, V114-007, V114-016, V114-020 and V114-021, showed results that are in line with the results achieved with the pivotal studies. V114-016 and V114-020 were included in the analysis across studies.

Study **V114-007** was designed to compare the safety, tolerability and immunogenicity of V114 and PCV13 in healthy adults aged ≥65 years who were vaccinated previously with PPV23 at least 1 year prior to study entry. The results showed that serotype-specific IgG GMCs at 30 days postvaccination were generally comparable in the V114 and PCV13 groups for the shared serotypes and higher in V114 recipients for the unique serotypes. Trends observed for OPA GMTs at 30 days postvaccination were generally consistent with the primary analysis results for the IgG GMCs. For both interventions, the response is lower compared to the response seen in pneumococcal vaccine naïve subjects, as shown by the proportion of patients with a ≥ 4-fold rise in GMT at Day 30. For pneumococcal vaccines, it is known that GMTs after the second dose are generally lower than after the first dose (Greenberg et al. Vaccine 2014), however, an immune response is still elicited.

Study **V114-016** was designed to evaluate the safety, tolerability and immunogenicity of V114 followed by PPV23 1 year later in healthy adults aged ≥50 years. The results showed that OPA GMTs at 30 days postvaccination with V114 or PCV13 were generally comparable for the 13 shared serotypes, with the exception of serotype 3, which was higher in the V114 group compared with the PCV13 group (see Figure 3). OPA GMTs at 30 days postvaccination for the 2 unique serotypes were higher in the V114 group compared with those observed in the PCV13 group.

Both V114 and PCV13 elicit immune responses that persist for at least 12 months postvaccination. Serotype-specific OPA GMTs at Month 12 postvaccination were lower than at Day 30, but higher than the OPA GMTs at baseline (Day 1), as represented by serotype 6A, 6B, 7F and 9V in Figure 4. At 30 days postvaccination with PPV23, serotype-specific OPA GMTs were comparable between participants administered a sequential regimen of V114 followed by PPV23 or PCV13 followed by PPV23 for all 15 serotypes in V114, represented by serotype 6A, 6B, 7F and 9V in Figure 4. Similar results were seen for serotype-specific IgG GMCs.

Figure 4 Longitudinal OPA GMTs at Day 1, Day 30, Month 12 and Month 13 - PP population V114-016

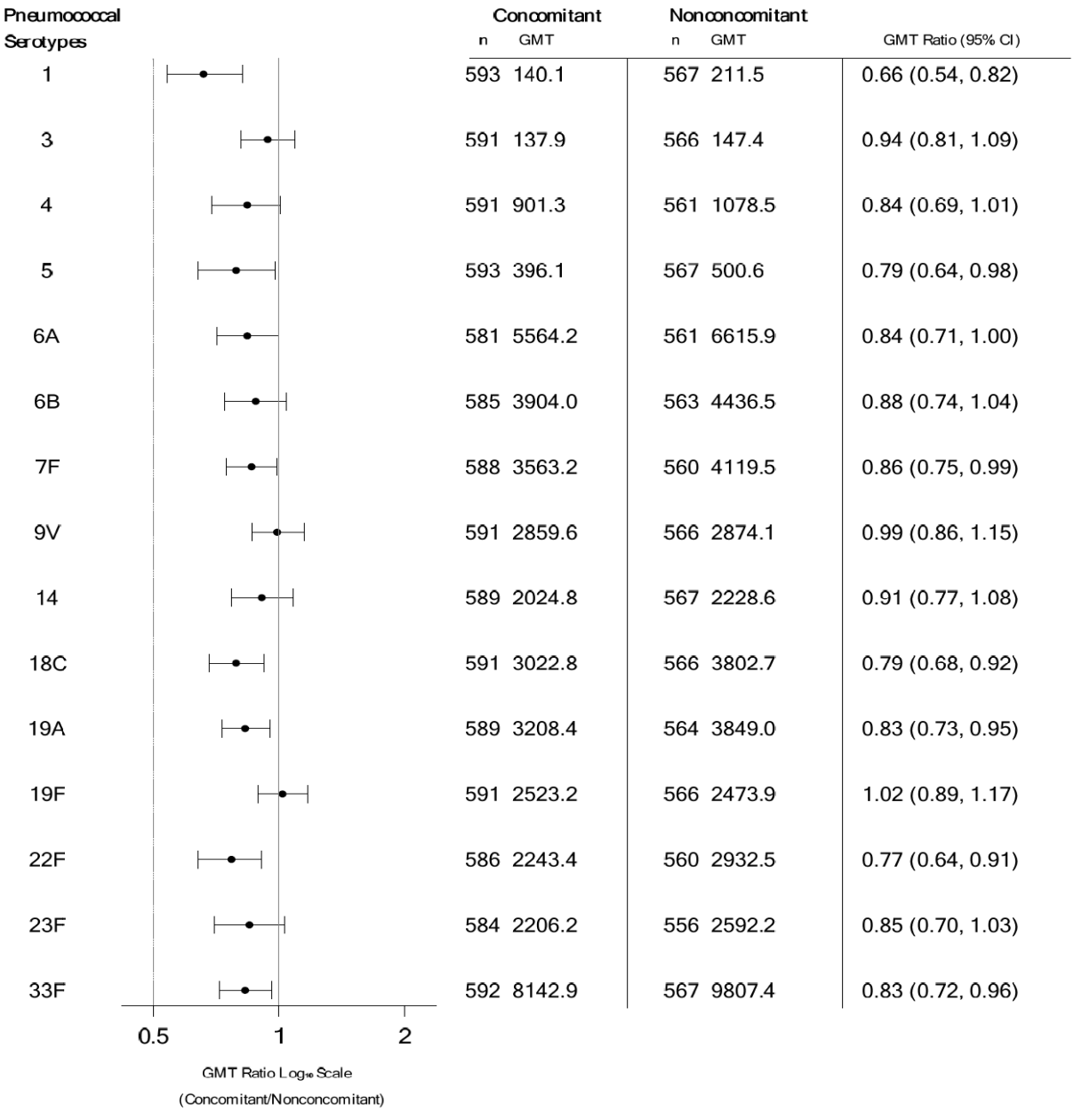


Data Source: Mod5.3.5.1/p016v114/Fig 14.2-4

Study **V114-020** was a lot-to-lot consistency study to evaluate the safety, tolerability and immunogenicity of V114 in healthy adults 50 years of age or older. V114 elicited an immune response to all 15 serotypes that was consistent across 3 lots of V114 as measured by OPA GMTs and IgG GMCs at 30 days postvaccination.

Study **V114-021** was designed to evaluate the safety, tolerability and immunogenicity of V114 when administered concomitantly with the influenza vaccine in healthy adults 50 years of age or older. V114 administered concomitantly with QIV was non-inferior to V114 administered non-concomitantly with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V114, see Figure 5. QIV administered concomitantly with V114 was non-inferior to QIV administered non-concomitantly with V114 as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV (data presented in Clinical Assessment report). OPA GMTs and HAI GMTs at 30 days postvaccination in the FAS population were generally consistent with those observed in the PP population.

Figure 5 Forest plot of postvaccination OPA GMT ratios – PP population V114-021



Serotype-specific OPA GMT ratios and strain-specific HAI GMT ratios for the concomitant versus non-concomitant group at 30 days post-vaccination were generally consistent with the ratios observed in the overall population in subgroups based on age, sex, race, ethnicity and history of PNEUMOVAX23. Nevertheless, there was a trend toward lower serotype-specific OPA GMTs and H1N1 HAI GMTs in the older age groups (65 to 74 and ≥75 years of age) compared with the younger age group (50 to 64 years of age). In addition, subjects with a history of PPV23 administration showed lower OPA GMTs compared to PPV23 naïve subjects. This was also observed with H1N1 HAI GMTs but less pronounced.

2.5.6. Discussion on clinical efficacy

The sought indication for V114 is active immunisation for the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by *Streptococcus pneumoniae* in adults 18 years of age and older. 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 Prevenar 13™ (PCV13), plus 2 additional serotypes (22F and 33F) that are not included in any currently licensed PCV.

This application is based on immunogenicity data from 6 phase 3 studies (V114-016, -017, -018, -019, -020 and -021) and 1 phase 2 study (V114-007). Immunogenicity data obtained from study V114-017 and V114-019 were considered by the Assessor to provide the main evidence. The objective of both studies was to determine the immunogenicity and safety of V114. The applicant put forward V114-019 as pivotal, as the main use of V114 will be in elderly subjects, and this study included healthy adults ≥50 years of age. However, the indication states the use in adults 18 years of age and older. Study V114-017 included adults ≥18 years of age with and without risk factors for pneumococcal disease. Risk factors included underlying comorbidities (i.e., diabetes mellitus, chronic liver disease, chronic lung disease including asthma, chronic heart disease) and behavioural factors (current smoker, increased alcohol use). Combined, these two studies represent the entire target population for this vaccine. The objective of the other studies was to determine the immunogenicity of sequential vaccinations (Pneumovax 23 [PPV] followed by PCV in V114-007 or PCV followed by PPV in V114-016), lot-to-lot consistency (V114-020), immunogenicity and safety of V114 in HIV-positive participants (V114-018) and the effect of concomitant vaccination with an influenza vaccine (V114-021).

No efficacy or effectiveness data is available, which is accepted since efficacy trials were not feasible. There is no correlate of protection known for IPD or pneumonia caused by *Streptococcus pneumoniae* in adults. The opsonophagocytic assay reflects in vivo protection by the vaccine-induced antibodies and has been found to correlate with protection against disease (Song et al. J. Infect Chemother. 2013). Therefore, opsonophagocytic activity (OPA) geometric mean titres (GMTs) are considered surrogate markers for vaccine efficacy. The objective of the clinical development programme was to support immunobridging of V114 to PCV13 for the 13 shared serotypes. Since PCV13 is the only licensed pneumococcal conjugate vaccine licensed for adults in the EU and based on its similar composition, its use as a comparator is supported. This has also been previously agreed in a scientific advice.

The development programme has been formally discussed with CHMP at various moments throughout development, and an agreement was reached regarding the key elements of the clinical development plan.

Dose selection

No dose-selection studies were submitted. For each of the 13 shared serotypes, a similar dosage as in the licensed PCV13 was maintained, i.e. 2 µg/serotype/dose and 4 µg/dose for serotype 6B. For the 2 unique serotypes, 22F and 33F, not present in PCV13 a dose of 2 µg/serotype/dose was selected. The V114 clinical programme was designed to demonstrate that the 0.5 mL IM dose is both safe and immunologically similar to the licensed PCV13 for the 13 shared serotypes and superior for the 2 unique serotypes, which is agreed with.

Design and conduct of clinical studies

All 7 clinical studies included in the application were randomised, double-blind, placebo/ active comparator PCV13-controlled, multicentre studies. This study design is considered adequate. In all studies, vaccination with V114 consisted of a single IM dose of 0.5 mL, which is the posology recommended in the applicant's SmPC. The posology of PCV13, the comparator, was in line with the approved regimen for PCV13. Immunogenicity was evaluated immediately before and 30 days after vaccination. In three studies, immunogenicity of sequential vaccination of V114/PCV13 followed by PPV23 was evaluated, also covering different time intervals between vaccinations (8 weeks, 6 months and 12 months), which is in line with several national vaccination recommendations. Due to the evaluation of the sequential vaccination also long-term data on immune persistence of V114 is available for 6 months (946 subjects) and 12 months (321 subjects). The studies were conducted globally, with countries in Europe, North America, South America, Asia, and Oceania.

In the main studies, the primary immunogenicity objective was to assess serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with V114 and PCV13. This objective is considered to provide pivotal immunogenicity information for the MA application as OPAs are used as surrogate markers for protection against disease. There is no correlate of protection for pneumococcal disease in adults. Secondary immunogenicity objectives included the evaluation of the serotype-specific IgG geometric mean concentrations (GMCs), the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and PCV13. These objectives are considered acceptable for this clinical development programme, as IgG GMCs, GMFRs and the proportion of patients with a ≥4-fold rise after vaccination will provide information on the consistency and robustness of the immune response and insight into the proportion of responders. Immunogenicity endpoints seem appropriately chosen and in line with the vaccine guideline (EMA/CHMP/VWP/164653/05 Rev.1). The presented serological assays are overall considered appropriate and fit for purpose.

Study V114-019 was designed to demonstrate non-inferiority (for 13 shared serotypes) and superiority (for 2 serotypes unique to V114) of V114 compared to PCV13. Of note, the observed OPA GMTs at each timepoint were calculated based on participants with an available OPA titer measurement at that specific timepoint. OPA GMFR from Day 1 to Day 30 was calculated among participants who have OPA titer measurements at both Day 1 and Day 30. This resulted in a slightly different population included, however, the difference between the ratio of Day 30 GMT to Day 1 GMT is nearly identical to the value of the GMFR, and thus this slight difference does not impact the overall conclusion.

Study V114-017 was a descriptive study and not designed to test a statistical hypothesis. The main driver was to substantially contribute to the overall safety database, which is acceptable.

The randomisation and blinding procedures seem overall acceptable for both studies.

Few protocol amendments and changes have been made, which are mainly acceptable.

Analyses were performed on the PP population, defined as all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analysis. The main reason for excluding the immunogenicity analysis in both studies was missing serology results for all 15 serotypes and blood draw out of window. For study V114-017, not being vaccinated with PPV23 was also a main reason for exclusion. Safety analyses were based on the all participants as treated population (APaT) population. The analysis sets and the statistical analysis of the primary and secondary endpoints are generally considered adequate. Multiplicity was controlled by testing each of the co-primary hypotheses at a 1-sided 0.025 level of significance and predicating study success on all co-primary immunogenicity hypotheses having been met. The addition of two superiority hypotheses during the conduct of the study is considered acceptable, considering the corresponding decision was taken independent of (preliminary) immunogenicity data.

Immunogenicity data and additional analyses

During the main studies, the participant flow was comparable between the treatment groups. Low numbers of participants discontinued the studies. In study V114-019, one protocol deviation led to discontinuation of the study. Baseline characteristics were balanced across treatment groups in both studies. Study V114-019 included healthy adults with a median age of 66 years (range: 50 to 92), of which 830 participants (69%) were ≥65 years of age. Of the participants, 57.3% were male, 67.7% were white, and 78.0% were not Hispanic or Latino. Study V114-017 included adults 18 to 49 years of age, with a median age of 36.0 years (range: 18 to 49). Of the participants, 48.3% were male, 51.0% were white, and 87.2% were not Hispanic or Latino. Randomization was stratified based on the presence and number of risk factors for pneumococcal disease. Differences between planned versus actual strata occurred at a low frequency. These were mainly due to mis-stratifications and are not considered to have impacted the overall study results.

V114 was immunogenic in all studies and subgroups tested, as OPA GMTs at 30 days postvaccination were always higher compared to the OPA GMTs pre-vaccination. The non-inferiority margin of the lower bound of the 95% CI for the serotype-specific OPA GMT ratio [V114/PCV13] >0.5 was met for all 13 shared serotypes as assessed by the serotype-specific OPA GMTs at 30 days postvaccination. In addition, in all studies, the superiority margin of the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V114/ PCV13] to be greater than 2.0 was met for the 2 unique serotypes. The clinical relevance of meeting or not meeting both the non-inferiority margin or the superiority margin is unknown. Due to the lack of an established threshold value associated with clinical benefit, interpretation of the outcome is difficult. Nevertheless, a comparison to the main study for the authorization of PCV13 provides further reassurance. Titres induced by PCV13 showed a nearly 2-fold difference compared to PPV23, indicating that meeting the 0.5 NI margin employed for the comparison V114/PCV13 places V114 between two vaccines with known efficacy. Although uncertainties concerning the magnitude of the protective effect remain, the explanation is considered reassuring and additional data concerning (lack of) vaccine efficacy including break through disease will be collected post-marketing.

<u>Healthy adults aged ≥50 years and older</u>

Three studies included healthy adults aged ≥50 years and older: the pivotal study V114-019 and the supportive studies V114-016 and V114-020. In these three studies, similar trends were observed for OPA GMT ratios of V114/PCV13 at 30 days postvaccination, indicating that the effect of V114 is robust, leading to consistent immune responses to the different serotypes across studies in similar populations. This was also reflected by the fact that trends seen for OPA GMTs are also seen for IgG GMCs.

It is noteworthy that for the pivotal study V114-019, although non-inferiority was met for all shared serotypes, the GMT ratios [V114/PCV13] appear to be shifted to the left, indicating a somewhat reduced immune response to V114 compared to PCV13 in this study. For study V114-019, the upper bound of the 2-sided 95% CI of the GMT ratio did not contain 1.00 for 7 of the shared serotypes, while this was the case for only 1 serotype in both studies V114-016 and V114-020. The applicant discussed the apparent reduced immune response in the pivotal study V114-019 compared to the responses seen in the supportive studies V114-016 and V114-020. The applicant did not identify any particular factor to explain these differences. Differences may be due to study-to-study variability as a result of slightly different enrolled populations, variability of the clinical assays, and/or observed variability in antibody titres between individuals. However, considering all the immunogenicity information obtained during study V114-019, the immune response elicited by V114 was still substantial with the majority of participants having a ≥4-fold rise in OPA GMT, with proportions being 52.2% to 81.2% in the V114 group compared to 58.7% to 84.8% in the PCV13 group for 13 shared serotypes. In addition, the change from baseline in immunogenicity response is largely comparable between the studies. Finally, reverse cumulative distribution curves (RCDC) also show similar distributions.

A reduction in response to serotype 4 in the V114 group compared to the PCV13 group and an increased response to serotype 3 and 6B was seen during the pivotal study V114-019 in healthy adults aged ≥50 years and older. Similar observations were made during studies V114-016 and V114-020. The reduction in serotype 4 response is considered not clinically relevant, as the percentage of participants with a ≥4-fold rise in OPA GMTs was still substantial (≥79%), and the difference in the percentage of responders (≥4-fold rise) in the V114 and PCV13 group was relatively small, <10%, in all three studies. In addition, RCDC for serotype 4 showed that the distribution is similar between V114 and PCV13.

Both V114 and PCV13 were immunogenic in the different age groups of 50 to 64 years of age, 65 to 74 years of age and ≥75 years of age. In general, as expected, trends toward lower serotype-specific OPA GMTs at Day 30 postvaccination can be seen with increasing age. During study V114-019, the ≥75-year-old subgroup in the PCV13 treatment arm seems to have a stronger immune response compared to the 65 to 74-year-old group, which is most probably due to the low number of subjects in the ≥75-year-old group (n=67) compared to the 65 to 74-year-old group (n=344).

For the 2 unique serotypes not present in PCV13, the OPA GMTs at Day 30, GMFR and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from Day 1 to Day 30 were higher in the V114 group compared to the PCV13 group. This also holds true for the different age groups. These results indicate that 2 µg/dose is sufficient to elicit an immune response for the 2 unique serotypes in healthy adults ≥50 years of age.

Adults aged 18 to 49 years with or without risk factors for pneumococcal disease

In adults aged 18 to 49 years with or without risk factors for pneumococcal disease, the immune response elicited by V114 is robust as indicated by serotype-specific OPA GMT results being consistent with serotype-specific IgG GMC results and the analysis performed using the FAS population providing similar results to the analysis performed on the PP population.

Both V114 and PCV13 elicited an immune response in immunocompetent adults with or without risk factors for pneumococcal disease. However, for 4 of the shared serotypes, serotype 4, 5, 7F and 9V, the response seems lower in the V114 group compared to the PCV13 group. For both serotype 4 and 5 ≥79.0% of subjects achieved a 4-fold rise in OPA GMT in the V114 group, indicating that the response to V114 is still robust, with the majority of participants achieving a 4-fold rise in GMT. For serotype 7F and 9V in both treatment groups, the proportion of subjects achieving a 4-fold rise in OPA GMT was lower, ≥51.5% in the V114 group vs ≥ 55.4% in the PCV13 group. OPA GMTs at Day 30 were high in the V114 group for these serotypes, with 5756.4 for serotype 7F and 3355.1 for serotype 9V. This is

lower than the response against these serotypes in the PCV13 group (GMT 7588.9 and 3983.7 for serotype 7F and 9V, respectively). In conclusion, considering all the immunogenicity information, even though the OPA GMT ratio was slightly lower for 4 of the 13 shared serotypes, the immune response elicited by V114 was still substantial, with the majority of participants having a ≥4-fold rise in OPA GMT and RCDC curves that show similar distributions.

For 3 serotypes, serotype 3, 6B and 18C, the response in the V114 group was higher compared to PCV13 group. This is especially noteworthy for serotype 3, as the response to serotype 3 is low in the PCV13 group, with OPA GMTs at 30 days postvaccination of 155.9 compared to 199.2 in the V114 group, and serotype 3 still being one of the most common serotypes causing disease in adults. The OPA GMTs generated using PCV13 in these studies are comparable to the OPA GMTs generated during the studies included in the MA application for PCV13 [EPAR]. In addition, for the 2 unique serotypes, the OPA GMT ratios were, as expected, higher in the V114 group compared to the PCV13 group.

Overall, V114 is shown to be immunogenic in participants without risk factors for pneumococcal disease, in participants with a single risk factor and participants with 2 or more risk factors.

Persistence of Immune Response

Serotype-specific OPA GMTs declined over time from Day 30 to Month 6/12 (depending on the study) but remained above baseline levels for all the serotypes contained in either V114 or PCV13. IgG GMCs show a similar trend. As OPA GMTs are generally comparable between V114 and PCV13 at Month 6 or Month 12, these results indicate that the persistence of the response after vaccination with either V114 or PCV13 is comparable. Long-term persistence of the immune response has, however, not been investigated; thus, there is no information on long-term protection by V114. In addition, no data is available concerning a potential booster vaccination of V114. The lack of information on long-term protection/immunogenicity and the need for a booster dose are reflected in the SmPC.

Subsequent Vaccination

The PPV23 vaccination at Month 6, following either vaccination with V114 or PCV13 at Day 1, was able to elicit an immune response for all 15 serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 7). Vaccination with PPV23 at 6 months after vaccination with either V114 or PCV13 induced serotype-specific OPA GMTs at Month 7 comparable in both treatment groups. Similar results were obtained when vaccinating with PPV23 at 12 months after vaccination with either V114 or PCV13: PPV23 elicited an immune response for all 15 serotypes comparable in both treatment groups.

GMFRs and proportions of participants with a ≥4-fold rise in OPA titres were higher between Day 1 and Day 30 than the levels observed after the second vaccination, which is partly due to the fact that the levels of OPA GMTs are higher at Month 6 or Month 12 compared to Day 1. For pneumococcal vaccines it is known that GMTs after the second dose are generally lower than after the first dose (Greenberg *et al.* Vaccine 2014). This phenomenon was also observed in adults previously vaccinated with PPV23 (included in study V114-007 and V114-021). Overall, the results in participants previously vaccinated with PPV23 were comparable between V114 and PCV13 for the shared serotypes included in study V114-007 and V114-021, however, they are lower compared to the results obtained in vaccine naïve subjects studied in study V114-019.

HIV-infected subjects

In total, 302 HIV-infected subjects received a single dose of either V114 or PCV13 on Day 1, followed by a single dose of PPV23 at Week 8. The median age was 41.0 years (range: 21-74). The participants included in the study all received antiretroviral therapy, and the majority did not have a detectable viral load and had a CD4 count >200 cells/µL. As already stated in the scientific advice, patients with

HIV and a CD4+ T-cell count >200 cannot be considered as severely immunocompromised. This should be accurately reflected in the SmPC.

Both interventions, V114 and PCV13, were immunogenic, and the induced immune responses were generally comparable between the intervention groups. A stronger response for serotype 3 and 18C was seen in the V114 group compared to the PCV13 group, while the immune response for serotype 4 was lower. As expected, responses for the 2 unique serotypes were higher in the V114 group. Similar results were observed when looking at the IgG GMCs. No notable differences were observed between CD4+ T-cell count subgroups (≥200 to <500 cells/µL, ≥500 cells/µL) in either OPA GMTs or IgG GMCs 30 days postvaccination. The results are generally lower compared to study V114-017, including adults aged 18 to 49 years old.

Following vaccination with PPV23, an immune response was elicited as measured by OPA GMTs and IgG GMCs at Week 12.

Previously vaccinated subjects

Overall, during Study V114-007 performed in adults previously vaccinated with PPV23, immune response was comparable between both treatment arms for the 13 shared serotypes and higher for both unique serotypes in the V114 arm. Although the results were comparable between V114 and PCV13, they are lower compared to vaccine naïve subjects studied in study V114-019. This was also observed in subgroup analyses in the supportive study V114-021. Since this is also observed for PCV13 in both studies and it is a known phenomenon for pneumococcal vaccinations, no concerns are raised.

Subgroup analyses

Slight differences in immune response could be observed between the subgroups in sex, race and ethnicity; however, no clear trends were observed.

All in all, the differences observed between subgroups are small and considered not to impact the use of V114 in these subpopulations.

Concomitant administration of influenza vaccine

Regarding co-administration of an inactivated quadrivalent influenza vaccine (QIV), the data suggest that concomitant administration of V114 does not affect the immunogenicity of the influenza vaccine, as strain-specific HAI GMTs at 30 days postvaccination with QIV were comparable in groups where QIV was administered concomitantly and non-concomitantly with V114. However, the immune response induced by V114 was generally reduced when both vaccines were administered concomitantly. Interaction between influenza vaccines and pneumococcal vaccines are a known phenomenon (Schwartz et al. 2011). Consistently lower immune responses were observed in several studies after concomitant administration of PCV13 with inactivated influenza vaccine compared to PCV13 administered alone. However, the proportion of OPA responders after PCV13 and TIV co-administration was similar to that observed after PCV13 alone for all serotypes evaluated (Schwarz *et al.*, Vaccine 2013). This is in line with the results of study V114-021. Serotype specific GMFRs and proportions of participants with a ≥4-fold rise from prevaccination to 30 days postvaccination for OPA responses were generally comparable between the 2 groups. In addition, effectiveness studies of the concomitant use of PPV23 and the influenza vaccine support the coadministration of both vaccines to prevent pneumonia, death, and hospitalizations during the influenza season. Together these results indicate that although no firm conclusion can be drawn on the impact of the observed reduction in V114-induced immune response after concomitant QIV administration on the efficacy of V114, it seems unlikely that efficacy will be reduced. No data is available for the concomitant vaccination of V114 with adjuvanted and high dose quadrivalent influenza vaccines.

Overall, as the immunological response to V114 is comparable to the immunological response to PCV13, it is considered reasonable to conclude that V114 could protect against pneumococcal disease. Some differences, such as the lower response to serotype 4, between the V114 and PCV13 induced immune responses have been observed. However, it is unknown to what extent these differences may impact on the protection against invasive pneumococcal disease, as clinical efficacy has not been demonstrated for V114. For the two unique serotypes contained in the V114 vaccine, no efficacy has been shown and immunogenicity cannot be bridged to PCV13, even though V114 was shown to induce a robust immune response towards these additional serotypes. In a Phase 2 study (Ermlich *et al.,* Vaccine 2018), using an earlier formulation, V114 induced OPA and IgG responses against 22F and 33F that were generally higher or comparable to those induced by PPVS23 with proven efficacy. Epidemiological surveillance will be necessary to ensure early detection of breakthrough disease caused by potential vaccine failure or reduced vaccine effectiveness. In addition, next to breakthrough disease, serotype replacement should be included in surveillance studies. The applicant commits to discuss these topics in the yearly PSURs within the context of routine pharmacovigilance. The information provided will include: post-marketing spontaneous reports on breakthrough disease/vaccine failure, efficacy/effectiveness studies and publications on V114 use in adults and new data for serotype distribution from IPD surveillance from countries (US and EU) where V114 is used in adults as these data become available.

2.5.7. Conclusions on the clinical efficacy

Overall, the results indicate that V114 is immunogenic in all subgroups tested, with the immune response being consistent across studies. Of note, and similar to other pneumococcal vaccines, no correlate of protection has been identified for pneumococcal disease, and immunogenicity observed cannot be directly translated to efficacy.

As expected, a trend towards a lower immune response is seen with increasing age. In general, the immune response to V114 is similar compared to the immune response generated by PCV13.

2.5.8. Clinical safety

The discussion of clinical safety is based on available safety data from 7 clinical studies: 1 Phase 2 study (V114-007) and 6 Phase 3 studies (V114-016, -017, -018, -019, -020 and -021).

Safety data were integrated across 3 Phase 3 studies in pneumococcal vaccine-naïve adults ≥50 years of age (V114-016, V114-019, and V114-020), with the aim to increase precision for characterizing the safety profile of V114 among healthy pneumococcal vaccine-naïve adults 50 years of age or older. In addition, safety data collected in immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease (V114-017) is presented.

The section on special populations describes the following special populations: immunocompromised adults ≥18 years of age infected with HIV-1 (V114-018), adults ≥65 years of age who previously received PPV23 (V114-007), and adults ≥50 years of age administered PCV concomitantly with an inactivated quadrivalent influenza vaccine (V114-021).

Approximately 3,000 participants for the V114 group and approximately 1,100 participants for the PCV13 group are included in the integrated summary of safety (ISS).

Summaries of pooled data include point estimates based on the "naïve pooling" (the total number of participants with a certain event across the 3 studies as the numerator and the total number of participants in the population across the 3 studies as the denominator) and between group comparisons (risk differences and associated 95% confidence intervals for pre-specified endpoints)

calculated via weighted risk differences i.e. stratified Miettinen and Nurminen (M&N) method using Cochran-Mantel-Haenszel (CMH) weights. The justification for the weighted approach for risk differences is to maintain the balance afforded by the randomization within each study for the purpose of between group comparisons. The naïve pooling approach for between group comparisons would be subject to Simpson's Paradox, a bias that causes over- or under-estimates of the vaccination effect (or even a complete reversal of the direction of the effect). Simpson's Paradox can be particularly impactful when the randomization ratios across integrated studies is vastly different. Given that the randomization ratio for V114-020 (9:1) differs from that of the other studies (1:1), a weighted approach is preferable in this setting to the naïve pooling approach. The naïve pooling analyses were however submitted in parallel to the weighted analyses within the 'Integrated Summary of Safety' for completeness.

2.5.8.1. Patient exposure

The 7 studies contributing to the evaluation of safety, enrolled a diverse population of over 7,400 adults across more than 260 clinical study sites in 18 countries. V114 is given as a single IM dose.

In total, 5,630 adults received V114 in these studies, and 1,808 received an active comparator (PCV13). The extent of exposure in the different studies is presented in Table 19. Out of 2,666 participants 65 to 74 years of age, 1999 received V114. Out of 646 participants 75 years of age and older, 479 participants received V114, see Table 20.

Table 19 Number of participants who received V114 or PCV13 in Studies V114-007, V114-016, V114-017, V114-018, V114-019, V114-020 and V11-021

Population	Study Number	Number of Vaccinated Participants	
		V114	Prevnar 13™
Pneumococcal vaccine-naïve adults ≥50 years of age (Integrated population)	V114-016†	327	324
	V114-019	602	600
	V114-020†	2103	230
	Total:	3032	1154
Pneumococcal vaccine-naïve adults 18 to 49 years of age	V114-017†	1134	378
Special populations	V114-007	127	126
	V114-018	152	150
	V114-021‡	1185	NA
Overall population	**Total:**	5630	1808

NA=not applicable.

† Participants were included in the intervention group according to the intervention they actually received. One participant randomized to the Prevnar 13™ group inadvertently received V114 in each of the following studies: V114-016, V114-017, and V114-020 (Lot 1).

‡ One participant in Study V114-021 in the nonconcomitant group who received V114 at both vaccination timepoints was excluded from the safety population and is therefore not represented in this table.

Source: [Ref. 5.3.5.1: P007V114: Table 12-1] [Ref. 5.3.5.1: P016V114: Table 12-1] [Ref. 5.3.5.1: P017V114: Table 12-1] [Ref. 5.3.5.1: P018V114: Table 12-1] [Ref. 5.3.5.1: P019V114: Table 12-1] [Ref. 5.3.5.1: P020V114: Table 12-1] [Ref. 5.3.5.1: P021V114: Table 10-1]

Table 20 Number of participants by age in studies V114-007, V114-016, V114-017, V114-018, V114-019, V114-020 and V11-021 - APaT

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials Receiving either V114 or PCV13	2,666/7,438 (35.8%)	595/7,438 (8.0%)	51/7,438 (0.7%)
Controlled Trials Receiving V114	1,999/5,630 (35.5%)	442/5,630 (7.9%)	37/5,630 (0.7%)
Non Controlled trials	0 (0%)	0 (0%)	0 (0%)
[a] Includes total number of participants in 7 studies included in the original submission.			

2.5.8.2. Adverse events

Clinical safety profile evaluation

Solicited injection site AEs were injection site erythema, injection site pain and injection site swelling.

*Solicited systemic AE*s were arthralgia, fatigue, headache and myalgia.

The methods used for safety evaluation were consistent across all studies in the V114 clinical programme. The evaluation of safety included both (1) AEs assessed by the investigator and (2) complaints reported directly by the participant. The primary mechanism for reporting adverse events was an electronic Vaccination Report Card (eVRC). Complaints were reported by participants on the eVRC and later reviewed by the investigator via telephone contact 14 days later. The study investigator reviewed the data with the participant and reported events meeting the protocol-specified AE definition in the clinical database. Investigators also assessed the causal relationship to the study vaccine, intensity, toxicity, and seriousness of each identified AE. Differences between complaints reported on the eVRC/VRC and AEs reported in the clinical database could occur for a variety of reasons (complaint that is a symptom of a documented pre-existing condition that did not worsen following vaccination, complaint was a sign or symptom of a separate event or diagnosis, the complaint could be more accurately characterised as a different AE upon investigator review (e.g., a solicited complaint of 'muscle pain' may be assessed by the investigator as 'injection site pain' and not 'myalgia' due to proximity to the injection site). These reasons were not pre-specified, however.

All safety analyses were performed in the APaT population, defined as all randomised participants who received study intervention (vaccination with V114 or PCV13). The analyses were based on the study intervention that participants actually received.

Pneumococcal vaccine-naïve adults ≥50 years of age (V114-016, V114-019 and V114-020)

In both intervention groups, the majority of participants experienced 1 or more AEs, and 1 or more vaccine-related AE, see Table 21.

Table 21 Analysis of adverse event summary in adults ≥ 50 years – APaT population

	V114		Prevnar 13™		Difference in % vs Prevnar 13™†
	n	(%)†	n	(%)†	Estimate (95% CI)†
Subjects in population	3,032		1,154		
with one or more adverse events	2,302	(72.3)	705	(62.2)	10.1 (6.6, 13.7)
injection-site	2,050	(63.7)	582	(51.4)	
systemic	1,484	(45.1)	434	(39.1)	
with no adverse event	730	(27.7)	449	(37.8)	
with vaccine-related‡ adverse events	2,192	(68.0)	655	(57.7)	10.3 (6.6, 13.9)
injection-site	2,050	(63.7)	582	(51.4)	
systemic	1,196	(34.6)	321	(29.2)	
with serious adverse events	59	(2.1)	25	(2.2)	-0.0 (-1.2, 1.0)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.4, 0.2)
who died	4	(0.1)	1	(0.1)	0.0 (-0.4, 0.4)

† Percentages, differences and confidence intervals are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights. Differences and confidence intervals are provided in accordance with the integrated statistical analysis plan.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Month 6.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Data source: Mod 2.7.4 / Tab 6

Between-group comparisons were generally consistent between participant-recorded solicited complaints and investigator-assessed AEs, some systemic events (e.g., myalgia) were reported more frequently by the participant than assessed as AEs by the investigator.

Pneumococcal vaccine-naïve adults 18-49 years of age with and without risk factors (V114-017)

In both intervention groups, the majority of participants experienced 1 or more AEs, and 1 or more vaccine-related AE, see Table 22.

Table 22 Summary of adverse events adults 18-49 years old – APaT population

	V114			Prevnar 13™		
	n	(%)	(95% CI)†	n	(%)	(95% CI)†
Subjects in population	1134			378		
with one or more adverse events	960	(84.7)	(82.4, 86.7)	312	(82.5)	(78.3, 86.2)
injection-site	893	(78.7)		272	(72.0)	
systemic	707	(62.3)		238	(63.0)	
with no adverse event	174	(15.3)		66	(17.5)	
with vaccine-related‡ adverse events	925	(81.6)	(79.2, 83.8)	293	(77.5)	(73.0, 81.6)
injection-site	893	(78.7)		272	(72.0)	
systemic	555	(48.9)		176	(46.6)	
with serious adverse events	49	(4.3)	(3.2, 5.7)	12	(3.2)	(1.7, 5.5)
with serious vaccine-related adverse events	0	(0.0)	(0.0, 0.3)	0	(0.0)	(0.0, 0.8)
who died	3	(0.3)	(0.1, 0.8)	2	(0.5)	(0.1, 1.9)
discontinued vaccine due to an adverse event	3	(0.3)	(0.1, 0.8)	0	(0.0)	(0.0, 0.8)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)		0	(0.0)	
discontinued vaccine due to a serious adverse event	3	(0.3)		0	(0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)		0	(0.0)	

† 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.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Month 6.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Data source: Mod 2.7.4 / Tab 13

Pooled analysis across all 7 studies

Results from pooled analyses across the 7 studies included in the Summary of Clinical Safety (V114-007, V114-016, V114-017, V114-018, V114-019, V114-020, and V114-021), referred to as the 7-study pool, support the safety conclusions of the separate analyses.

In both intervention groups, the majority of participants experienced 1 or more AEs, and 1 or more vaccine-related AE, see Table 23.

Table 23 Summary of adverse events 7-study pool – ApaT population

	V114		Prevenar 13™	
	n	(%)†	n	(%)†
Subjects in population	5,030		1,808	
with one or more adverse events	3,902	(76.0)	1,192	(66.8)
injection-site	3,528	(68.5)	1,000	(56.3)
systemic	2,545	(48.6)	776	(44.3)
with no adverse event	1,128	(24.0)	616	(33.2)
with vaccine-related‡ adverse events	3,724	(72.0)	1,108	(62.2)
injection-site	3,528	(68.5)	1,000	(56.3)
systemic	1,984	(36.5)	568	(32.7)
with serious adverse events	123	(2.6)	38	(2.2)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)
who died	7	(0.1)	3	(0.2)

† Percentages are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring from Day 1 through 6 months with the exception of studies V114-007 and V114-018, in which the safety follow up period post PCV was 30 days and 8 weeks, respectively.

For study V114-021, only participants in the nonconcomitant group are included; participant who inadvertently received more than 1 dose of V114 was excluded.

PCV=pneumococcal conjugate vaccine (V114 or Prevenar 13™).

Solicited adverse events

Pneumococcal vaccine-naïve adults ≥50 years of age (V114-016, V114-019 and V114-020)

In both intervention groups, the majority of participants experienced 1 or more solicited AEs, see Table 24. Injection site pain was the most frequently reported solicited AE, followed by fatigue and myalgia.

A higher proportion of participants with solicited AEs was observed in the V114 group compared with the PCV13 group, which was mainly due to a higher proportion of participants with solicited AEs of injection site pain (difference >10%).

Of the participants with solicited AEs, the majority had events mild in intensity, with toxicity of Grade 1 and a size ≤2.4 cm. Of participants with solicited events, the majority had events of short duration (≤3 days). The proportions of participants with solicited AEs by maximum intensity, toxicity, size and duration were low and generally comparable across intervention groups.

Table 24 Analysis of subjects with solicited adverse events in adults ≥50 years – APaT population

	V114		Prevnar 13™		Difference in % vs Prevnar 13™†
	n	(%)†	n	(%)†	Estimate (95% CI)†
Subjects in population	3,032		1,154		
with one or more solicited adverse events	2,220	(68.9)	659	(58.2)	
with no solicited adverse events	812	(31.1)	495	(41.8)	
Solicited injection site adverse events	**2,023**	**(62.6)**	**561**	**(49.8)**	
Injection site erythema	315	(9.8)	108	(9.4)	0.4 (-1.9, 2.6)
Injection site pain	1,910	(58.2)	508	(45.1)	13.1 (9.3, 16.8)
Injection site swelling	451	(14.3)	137	(12.2)	2.1 (-0.5, 4.5)
Solicited systemic adverse events	**1,305**	**(38.8)**	**369**	**(33.5)**	
Arthralgia	214	(6.3)	63	(5.5)	0.8 (-1.0, 2.6)
Fatigue	634	(20.2)	200	(18.0)	2.2 (-0.8, 5.1)
Headache	513	(14.5)	162	(14.7)	-0.2 (-2.9, 2.4)
Myalgia	717	(19.5)	158	(14.8)	4.8 (1.9, 7.5)

† Percentages, differences and confidence intervals are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights. Differences and confidence intervals are provided in accordance with the integrated statistical analysis plan.

Every subject is counted a single time for each applicable row and column.

Injection site erythema, injection site pain, and injection site swelling were solicited from Day 1 to Day 5 following vaccination. Arthralgia, fatigue, headache, and myalgia were solicited from Day 1 to Day 14 following vaccination.

Adverse event terms are reported using MedDRA version 23.0.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Data source: Mod 2.7.4 / Tab 8

Pneumococcal vaccine-naïve adults 18-49 years of age with and without risk factors (V114-017)

In both intervention groups, the majority of participants experienced 1 or more solicited AE, see Table 25. Injection site pain was the most frequently reported solicited AE, followed by fatigue and myalgia. The proportions of participants with solicited AEs were generally comparable across intervention groups.

Table 25 Summary of subjects with solicited AEs in adults 18-49 years – APaT population

	V114			Prevnar 13™		
	n	(%)	(95% CI)†	n	(%)	(95% CI)†
Subjects in population	1134			378		
with one or more solicited adverse events	934	(82.4)		298	(78.8)	
with no solicited adverse events	200	(17.6)		80	(21.2)	
Solicited injection site adverse events	**889**	**(78.4)**		**272**	**(72.0)**	
Injection site erythema	171	(15.1)	(13.0, 17.3)	53	(14.0)	(10.7, 17.9)
Injection site pain	860	(75.8)	(73.2, 78.3)	260	(68.8)	(63.8, 73.4)
Injection site swelling	246	(21.7)	(19.3, 24.2)	84	(22.2)	(18.1, 26.8)
Solicited systemic adverse events	**627**	**(55.3)**		**208**	**(55.0)**	
Arthralgia	144	(12.7)	(10.8, 14.8)	44	(11.6)	(8.6, 15.3)
Fatigue	389	(34.3)	(31.5, 37.1)	139	(36.8)	(31.9, 41.9)
Headache	300	(26.5)	(23.9, 29.1)	94	(24.9)	(20.6, 29.5)
Myalgia	327	(28.8)	(26.2, 31.6)	100	(26.5)	(22.1, 31.2)

† 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.

Every subject is counted a single time for each applicable row and column.

Injection site erythema, injection site pain, and injection site swelling were solicited from Day 1 to Day 5 following vaccination. Arthralgia, fatigue, headache, and myalgia were solicited from Day 1 to Day 14 following vaccination.

MedDRA version 23.0 was used in the reporting of this study.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Of the participants with solicited AEs, the majority had events that were mild in intensity, with toxicity of Grade 1 and a size ≤5.0 cm. Of participants with solicited events, the majority had events of short duration (≤3 days). The proportions of participants with solicited AEs by maximum intensity, toxicity, size and duration were low and generally comparable across intervention groups.

Pooled analysis across all 7 studies

Results from pooled analyses across the 7 studies included in the Summary of Clinical Safety (V114-007, V114-016, V114-017, V114-018, V114-019, V114-020, and V114-021), support the safety conclusions of the separate analyses.

Solicited injection site and systemic AEs (independent of investigator-determined causality) are presented graphically in Figure 6 and Figure 7, respectively for each of the individual studies. V114-021 is not included in these plots as this study did not include a PCV13 intervention group. In general, V114 is slightly more reactogenic compared to PCV13. In addition, higher incidence of injection site pain and myalgia related to the study vaccine was consistently observed with V114 throughout the studies.

Figure 6 Solicited injection site AEs by study - APaT

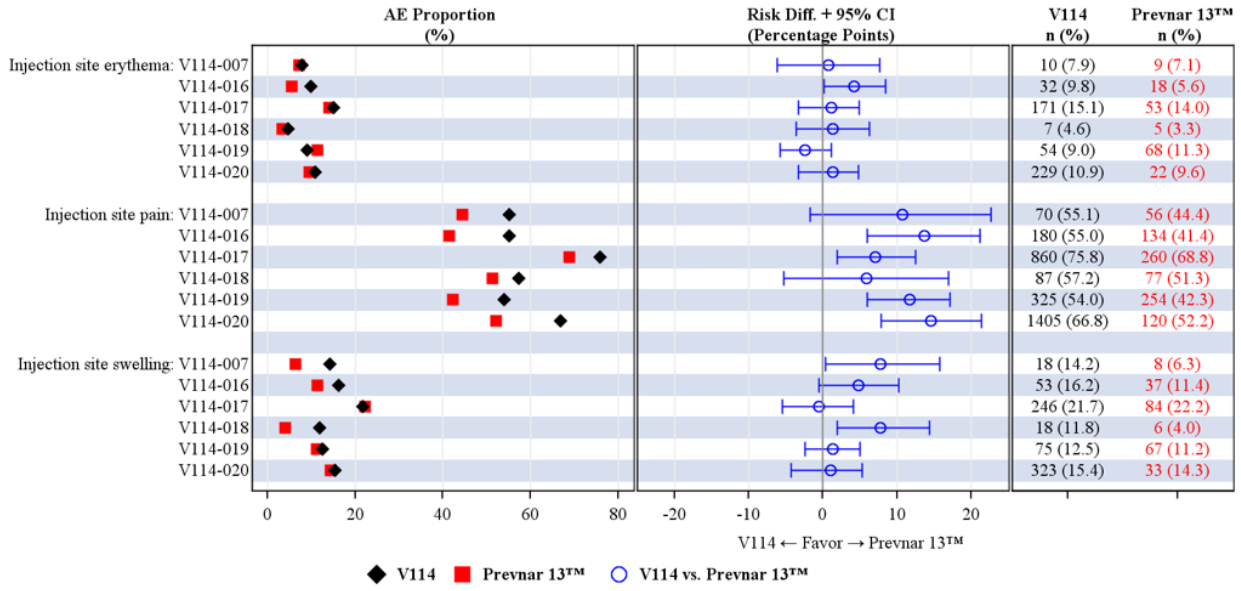
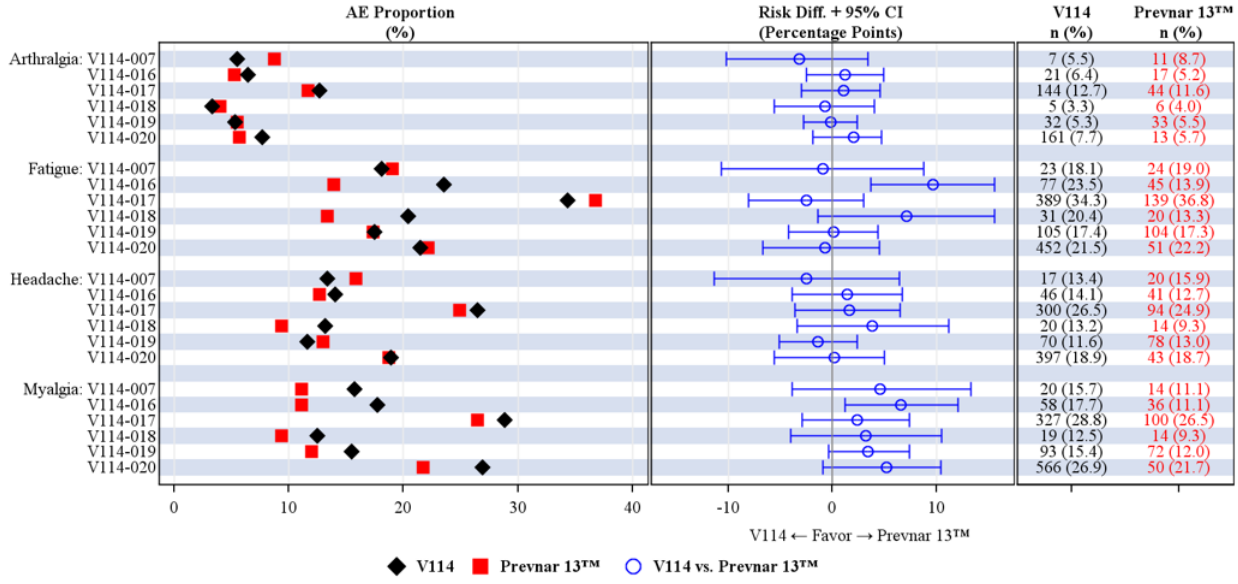


Figure 7 Solicited systemic AEs by study - APaT



Unsolicited adverse events

Unsolicited events were collected during 14 days after vaccination.

Pneumococcal vaccine-naïve adults ≥50 years of age (V114-016, V114-019 and V114-020)

Table 26 contains all AEs by system organ class (SOC), both solicited and unsolicited. PTs were added for any AE present in ≥1% in either treatment group.

Pneumococcal vaccine-naïve adults 18-49 years of age with and without risk factors (V114-017)

Table 27 contains all AEs by system organ class (SOC), both solicited and unsolicited. PTs were added for any AE present in ≥1% in either treatment group.

Table 26 All AEs (solicited and unsolicited) by SOC in adults ≥50 years – APaT population

	V114 (N = 3032)	**PCV13 (N = 1154)**
Participants with 1 or more AE	2302 (72.3%)	705 (62.2%)
Participants with no AE	730 (27.7%)	449 (37.8%)
Blood and lymphatic system disorders	3 (0.0%)	2 (0.1%)
Cardiac disorders	13 (0.4%)	3 (0.3%)
Ear and labyrinth disorders	9 (0.3%)	1 (0.1%)
Eye disorders	10 (0.4%)	2 (0.1%)
Gastrointestinal disorders	82 (2.3%)	27 (2.5%)
General disorders and administration site conditions	2148 (67.0%)	625 (55.2%)
Fatigue[a]	634 (20.2%)	200 (18.0%)
Injection site erythema[a]	351 (11.1%)	121 (10.4%)
Injection site pain[a]	1918 (58.5%)	516 (45.9%)
Injection site pruritus	43 (1.5%)	26 (2.2%)
Injection site swelling[a]	462 (14.5%)	147 (13.0%)
Injection site warmth	22 (0.7%)	12 (1.0%)
Pyrexia	29 (0.7%)	12 (1.0%)
Hepatobiliary disorders	2 (0.0%)	1 (0.1%)
Immune system disorders	1 (0.0%)	1 (0.1%)
Infections and infestations	107 (2.8%)	41 (4.0%)
Nasopharyngitis	33 (1.0%)	12 (1.3%)
Injury, poisoning and procedural complications	19 (0.7%)	9 (0.9%)
Investigations	4 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	5 (0.1%)	2 (0.1%)
Musculoskeletal and connective tissue disorders	845 (24.4%)	206 (18.8%)
Arthralgia[a]	214 (6.3%)	63 (5.5%)
Myalgia[a]	717 (19.5%)	158 (14.8%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	11 (0.3%)	9 (0.8%)
Nervous system disorders	536 (15.2%)	167 (15.1%)
Headache[a]	513 (14.5%)	162 (14.7%)
Psychiatric disorders	12 (0.4%)	1 (0.1%)
Renal and urinary disorders	4 (0.1%)	1 (0.1%)
Reproductive system and breast disorders	5 (0.2%)	3 (0.3%)
Respiratory, thoracic and mediastinal disorders	86 (2.6%)	18 (1.6%)
Skin and subcutaneous tissue disorders	46 (1.5%)	12 (1.0%)
Vascular disorders	10 (0.5%)	4 (0.4%)

Data source: Mod 5.3.5.3.3/Tab 13

[a] Solicited AEs

Table 27 All AEs (solicited and unsolicited) by SOC in adults 18-49 years old – APaT population

	V114 (N = 1134)	**PCV13 (N = 378)**
Participants with 1 or more AE	960 (84.7%)	312 (82.5%)
Participants with no AE	174 (15.3%)	66 (17.5%)
Blood and lymphatic system disorders	1 (0.1%)	1 (0.3%)
Cardiac disorders	2 (0.2%)	2 (0.5%)
Ear and labyrinth disorders	8 (0.7%)	8 (2.1%)
Endocrine disorders	3 (0.3%)	2 (0.5%)
Eye disorders	4 (0.4%)	5 (1.3%)
Gastrointestinal disorders	68 (6.0%)	13 (3.4%)
Diarrhoea	13 (1.1%)	3 (0.8%)
Nausea	28 (2.5%)	4 (1.1%)
Vomiting	7 (0.6%)	4 (1.1%)
General disorders and administration site conditions	917 (80.9%)	284 (75.1%)
Chills	11 (1.0%)	1 (0.3%)
Fatigue [a]	389 (34.3%)	139 (36.8%)
Injection site erythema [a]	174 (15.3%)	56 (14.8%)
Injection site pain [a]	865 (76.3%)	260 (68.8%)
Injection site pruritus	17 (1.5%)	5 (1.3%)
Injection site swelling [a]	251 (22.1%)	84 (22.2%)
Injection site warmth	12 (1.1%)	0 (0.0%)
Pyrexia	23 (2.0%)	6 (1.6%)
Hepatobiliary disorders	3 (0.3%)	2 (0.5%)
Immune system disorders	2 (0.2%)	1 (0.3%)
Infections and infestations	64 (5.6%)	32 (8.5%)
Nasopharyngitis	15 (1.3%)	5 (1.3%)
Upper respiratory tract infection	11 (1.0%)	4 (1.1%)
Injury, poisoning and procedural complications	14 (1.2%)	5 (1.2%)
Investigations	2 (0.2%)	2 (0.5%)
Metabolism and nutrition disorders	6 (0.5%)	4 (1.1%)
Musculoskeletal and connective tissue disorders	396 (34.9%)	119 (31.5%)
Arthralgia [a]	144 (12.7%)	44 (11.6%)
Myalgia [a]	327 (28.8%)	100 (26.5%)
Pain in extremity	14 (1.2%)	7 (1.9%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.4%)	0 (0.0%)
Nervous system disorders	315 (27.8%)	99 (26.2%)
Headache [a]	300 (26.5%)	94 (24.9%)
Psychiatric disorders	7 (0.6%)	4 (1.1%)
Renal and urinary disorders	4 (0.4%)	3 (0.8%)
Reproductive system and breast disorders	9 (0.8%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	47 (4.1%)	18 (4.8%)
Oropharyngeal pain	13 (1.1%)	8 (2.1%)
Skin and subcutaneous tissue disorders	17 (1.5%)	7 (1.9%)
Social circumstances	1 (0.1%)	0 (0.0%)
Vascular disorders	4 (0.4%)	3 (0.8%)

Data source: Mod5.3.5.1/p017v114/Tab14.3-6

[a] Solicited AEs

Related adverse events

Pneumococcal vaccine-naïve adults ≥50 years of age (V114-016, V114-019 and V114-020)

The incidence of vaccine-related AEs was 68.0% in the V114 group and 57.7% in the PCV13 group (Table 21).

All injection site AEs were considered vaccine-related and occurred in 2,050 participants (63.7%) in the V114 group and 582 (51.4%) in the PCV13 group. The most frequently reported (≥1%) injection site AEs following V114 vaccination were injection site pain, injection site swelling, injection site erythema, and injection site pruritus.

Vaccine-related systemic AEs were experienced by 1196 (34.6%) of participants in the V114 group and 321 (29.2%) of participants in the PCV13 group. The most frequently reported (≥1%) vaccine-related systemic AEs were the 4 solicited systemic AEs, myalgia, fatigue, headache, arthralgia, in both intervention groups.

Pneumococcal vaccine-naïve adults 18-49 years of age with and without risk factors (V114-017)

The incidence of vaccine-related AEs was 81.6% in the V114 group and 77.5% in the PCV13 group (Table 22).

All injection site AEs were considered vaccine-related and occurred in 893 participants (78.7%) in the V114 group and 272 (72.0%) in the PCV13 group. The most frequently reported (≥1%) injection site AEs following V114 vaccination were injection site pain, injection site swelling, injection site erythema, injection site pruritus and injection site warmth.

Vaccine-related systemic AEs were experienced by 555 (48.9%) of participants in the V114 group and 176 (46.6%) of participants in the PCV13 group. The most frequently reported (≥1%) vaccine-related systemic AEs following V114 vaccination were fatigue, myalgia, headache, arthralgia, nausea and pyrexia. This was similar in the PCV13 group, except for nausea which occurred in 0.8% of participants.

2.5.8.3. Serious adverse event/deaths/other significant events

In each of the 7 studies in the V114 clinical programme to support licensure, the proportion of participants with SAEs following PCV vaccination was low and comparable across intervention groups, see Table 28. None of the SAEs were considered by the investigator to be related to V114 and the SAEs experienced were in line with expectation considering the elderly population enrolled. The SAEs occurred in similar SOCs in both intervention groups, with the most commonly reported SAEs being experienced in the SOCs of infections and infestations (33 subjects (0.6%) in the V114 group and 9 (0.5%) in the PCV13 group), cardiac disorders (20 subjects (0.4%) in the V114 group and 6 (0.4%) in the PCV13 group) and neoplasms benign, malignant and unspecified (18 subjects (0.3%) in the V114 group and 10 (0.6%) in the PCV13 group). More information is presented in the clinical assessment report.

Table 28 SAEs per study following PCV vaccination

Study	All SAEs		Vaccine-related SAE	
	V114	**PCV13**	**V114**	**PCV13**
V114-007	0/127 (0.0%)	2/126 (1.6%)	0/127 (0.0%)	0/126 (0.0%)
V114-016	17/327 (5.2%)	19/324 (5.9%)	0/327 (0.0%)	0/324 (0.0%)
V114-017	49/1134 (4.3%)	12/378 (3.2%)	0/1134 (0.0%)	0/378 (0.0%)
V114-018	3/152 (2.0%)	0/150 (0.0%)	0/152 (0.0%)	0/150 (0.0%)
V114-019	9/602 (1.5%)	13/600 (2.2%)	0/602 (0.0%)	0/600 (0.0%)
V114-020	38/2103 (1.8%)	5/230 (2.2%)	0/2103 (0.0%)	0/230 (0.0%)
V114-021[a]	36/1196 (3.0%)		0/1196 (0.0%)	

[a] 2 intervention groups: V114 concomitant with QIV or non-concomitant

In total, 11 participants died during the safety follow-up period across the 7 studies. An additional 2 participants died outside of the protocol-specified reporting period (studies -017 and -021), both following vaccination with V114. All deaths occurred more than 40 days following vaccination with PCV. None of the deaths were considered by the investigator to be related to the study vaccine. More information is presented in the clinical assessment report.

2.5.8.4. Laboratory findings

Laboratory safety tests were not collected, except in the study 018 conducted in the HIV patients, where CD4+ T-cell count was measured.

Mean change in CD4+ T-cell count

The mean change from baseline (at screening) in CD4+ T-cell count at Day 30 and Week 12 was small (<15 cells/µL) in both intervention groups.

Table 29 Mean change in CD4⁺ T-cell count from baseline over time (all participant as Treated Population)

	V114 (N=152)			Prevnar 13™ (N=150)		
Visit	N	Baseline Mean	Mean Change (SD)	N	Baseline Mean	Mean Change (SD)
CD4+ T-cell Count (cells/mm3)						
Screening	151	563.2		148	551.2	
Day 30	141	567.8	3.0 (139.0)	138	556.7	-2.2 (126.0)
Week 12	133	554.2	4.1 (145.8)	138	559.3	14.2 (133.2)
SD=standard deviation. N=Number of subjects with baseline and at least one postbaseline test result in the specified analysis window.						

The proportion of participants with undetectable plasma HIV RNA (i.e., <20 copies/mL [LLOD] using a real time PCR) was similar (approximately 80%) at screening, Day 30, and Week 12 within each intervention group.

Table 30 Proportion of participants with undetectable HIV RNA viral load over time (all participant as Treated Population)

Visit	V114 (N=152)		Prevnar 13™ (N=150)	
	n/N	% (95% CI)	n/N	% (95% CI)
Screening	123/151	81.5 (74.3, 87.3)	113/148	76.4 (68.7, 82.9)
Day 30	111/136	81.6 (74.1, 87.7)	108/134	80.6 (72.9, 86.9)
Week 12	106/132	80.3 (72.5, 86.7)	116/138	84.1 (76.9, 89.7)

The 95% CIs are provided based on Clopper Pearson method.
HIV viral load results of <20 copies/mL and negative are categorized as undetectable because the low limit of detection of HIV viral load assay is 20 copies/mL.
n=Number of subjects with undetectable HIV RNA viral load at each visit.
N=Number of subjects with HIV RNA viral load result at each visit.

Source: [P018V114: adam-adsl; admb]

No clinically meaningful change in CD4+ T-cell count or plasma HIV RNA was observed from baseline to postvaccination and no AEs associated with these parameters were reported. No concern arises based on the review of the laboratory data collected in study -018.

Vital Signs, Physical Examinations and Other Observations Related to Safety

With the exception of solicited body temperature measurements, no vital signs or physical assessments were documented in the clinical database during the studies.

Solicited Body Temperature Measurements

Among participants ≥50 years of age (V114-016, V114-019, V114-020) nearly all reported a maximum body temperature of <100.4°F (38.0°C) in both intervention groups. The proportions of participants with maximum body temperature measurements based on the Brighton Collaboration cut points were generally comparable across the intervention groups. Temperatures ≥105.8°F (41.0°C) after PCV vaccination were reported by 4 participants (3 of whom in the V114 group and 1 in the PCV13 group). These measurements were suspected by the investigator to be erroneous based on review of additional clinical information and that no AEs of body temperature increased or pyrexia were reported for these participants. In each case, the elevated temperature was reported once via an eVRC, with all remaining postvaccination temperatures considered to be within the normal range (except for 1 participant who did not report any other postvaccination temperatures).

During study V114-017, only a low number of subjects reported increased body temperatures with no notable differences between vaccine groups. Following V114 vaccination 2 subjects showed a body temperature between 39.5 and 40.0°C. Following PPV23 vaccination, 2 participants in the V114 group and 1 participant in the PCV13 group showed a body temperature between 39.0 and 40.5°C.

2.5.8.5. Safety in special populations

Age

The safety profile observed for each age subgroup (50 to 64, 65 to 74, and ≥75 years of age) for all (see Table 31) and solicited AEs were generally consistent with those observed in the overall population, see Table 21. In both intervention groups, the majority of participants experienced 1 or more AEs. In all age groups, injection site pain was the most frequently reported solicited AE, followed by fatigue and myalgia.

Reactogenicity decreased with age regardless of the intervention group.

Table 31 Summary of AEs in adults ≥50 years by age group – APaT population

	50 to 64 Years				65 to 74 Years				75 Years and Older			
	V114		Prevnar 13™		V114		Prevnar 13™		V114		Prevnar 13™	
	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†
Subjects in population	1,282		449		1,435		575		315		130	
with one or more adverse events	1,062	(79.3)	296	(67.0)	1,044	(69.4)	338	(60.1)	196	(60.4)	71	(54.3)
injection-site	974	(72.3)	260	(58.7)	915	(59.9)	271	(48.3)	161	(49.4)	51	(39.2)
systemic	725	(53.0)	192	(44.2)	641	(40.5)	196	(36.0)	118	(36.8)	46	(34.8)
with no adverse event	220	(20.7)	153	(33.0)	391	(30.6)	237	(39.9)	119	(39.6)	59	(45.7)
with vaccine-related‡ adverse events	1,028	(76.1)	283	(64.0)	980	(63.9)	311	(55.1)	184	(57.2)	61	(47.0)
injection-site	974	(72.3)	260	(58.7)	915	(59.9)	271	(48.3)	161	(49.4)	51	(39.2)
systemic	616	(44.2)	152	(35.0)	489	(28.7)	139	(25.8)	91	(26.9)	30	(23.4)
with serious adverse events	20	(1.3)	11	(2.5)	34	(2.8)	10	(1.8)	5	(1.7)	4	(2.7)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	0	(0.0)	1	(0.7)

† Percentages are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights.
‡ Determined by the investigator to be related to the vaccine.
Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Month 6.
PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

Data source: Mod 2.7.4/Tab 16

A separate analysis was performed to subdivide types of AE per age category, see Table 32. In general, older adults reported fewer AEs than younger adults regardless of the intervention group. It was not possible to draw meaningful conclusions for the ≥85 years of age category due to the small number of participants.

In Study V114-016, 3 participants discontinued study intervention (i.e., did not receive PPV23 at Month 12) due to AEs. Two of the participants (64 year old, 75 year old) were in the V114 group and both discontinued study vaccine due to nonserious, vaccine-related AEs, and 1 participant (57 year old) was in the PCV13 group and discontinued study vaccine due to a serious, nonvaccine-related AE. No new safety concerns were identified.

Table 32 AEs per age category – ApaT (V114-016, V114-019 and V114-020)

MedDRA Terms	50-64 Years		65-74 Years		75-84 Years		85 Years and Older	
	V114 n (%)†	Prevenar 13™ n (%)†	V114 n (%)†	Prevenar 13™ n (%)†	V114 n (%)†	Prevenar 13™ n (%)†	V114 n (%)†	Prevenar 13™ n (%)†
Subject in Population	1,282	449	1,435	575	298	123	17	7
Total AEs – any treatment emergent AEs following PCV	1,062 (79.3)	296 (67.0)	1,044 (69.4)	338 (60.1)	189 (62.6)	67 (53.8)	7 (24.4)	4 (63.0)
Serious AEs – Total	20 (1.3)	11 (2.5)	34 (2.8)	10 (1.8)	4 (1.7)	4 (2.9)	1 (3.5)	0 (0.0)
– Fatal	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
– Hospitalization/prolong existing hospitalization	19 (1.3)	10 (2.2)	27 (2.4)	7 (1.2)	3 (0.9)	4 (2.9)	1 (3.5)	0 (0.0)
– Life-threatening	6 (0.2)	1 (0.3)	8 (0.2)	1 (0.2)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
– Disability/incapacity	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Other (medically significant)	1 (0.0)	2 (0.5)	3 (0.3)	3 (0.6)	0 (0.0)	0 (0.0)	1 (3.5)	0 (0.0)
Psychiatric disorders	5 (0.5)	1 (0.2)	6 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	304 (21.3)	78 (18.0)	195 (10.8)	79 (14.6)	35 (12.6)	9 (6.4)	2 (7.0)	1 (12.3)
Accidents and injuries	5 (0.5)	1 (0.3)	6 (0.4)	3 (0.6)	0 (0.0)	1 (0.7)	1 (3.5)	0 (0.0)
Cardiac disorders	4 (0.3)	2 (0.5)	8 (0.5)	0 (0.0)	1 (0.1)	1 (0.7)	0 (0.0)	0 (0.0)
Vascular disorders	5 (0.6)	1 (0.2)	5 (0.5)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (19.1)
Cerebrovascular disorders	1 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	50 (3.1)	17 (4.4)	50 (3.0)	20 (3.9)	7 (1.5)	3 (2.3)	0 (0.0)	1 (12.3)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.5)	0 (0.0)

† Percentages are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights.

Every subject is counted a single time for each applicable row and column.

For the analysis in the ≥85 years of age group, subjects from V114-016 and V114-019 were combined into one cohort due to the small number of subjects in this age group

in V114-019; weighted percentages were then calculated from this combined cohort and participants ages 85 years and older in V114-020.

Adverse event terms are reported using MedDRA version 23.0.

PCV=pneumococcal conjugate vaccine (V114 or Prevenar 13™).

Psychiatric disorders, Nervous system disorders, Cardiac disorders, Infections and infestations, Vascular disorders were defined by the respective MedDRA System Organ Class (SOC).

Cerebrovascular disorders were defined by the Central nervous system vascular disorders SMQ (narrow).

Anticholinergic syndrome was defined by the Anticholinergic syndrome SMQ (narrow).

Accidents and injuries were defined by the Accidents and injuries SMQ (narrow).

Quality of life decreased was defined by a Custom MedDRA Query (CMQ) and included the following Preferred Terms (PTs): Quality of life decreased, Impaired quality of life.

Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures was defined by a CMQ and included the following PTs: MedDRA High Level Group Term (HLGT) of Fractures plus the MedDRA PTs of Orthostatic hypotension, Blood pressure orthostatic decreased, Presyncope, Syncope, Dizziness, Ataxia, Cerebellar ataxia, Cerebral ataxia, Vestibular ataxia, Fall.

HIV-1 infected subjects

The safety of V114 was evaluated in study V114-018 in which 302 HIV-1 infected subjects received either V114 or PCV13 followed by PPV23 8 weeks later. The participants included in the study all received antiretroviral therapy, and the vast majority did not have a detectable viral load and had a CD4 count ≥200 cells/µL. This indicates that the participants still had a functioning immune system.

In both intervention groups, the majority of participants experienced 1 or more AEs, see Table 33. The majority of participants in both groups experienced solicited injection site AEs, of which injection site pain was most frequently experienced. Fatigue was the most commonly reported systemic AE in both groups. The majority of solicited AEs were of short duration (≤3 days). The most commonly experienced related AEs were solicited AEs in both intervention groups. The majority of AEs were mild with a toxicity of Grade 1 or 2. Of the injection site AEs of erythema and swelling, the majority had events with a size ≤2.4 cm in both intervention groups. Overall, the safety profile in HIV infected individuals is similar to the safety profile in immunocompetent adults, and no new safety signals are observed.

Table 33 Summary of AEs in HIV-infected participants – APaT population

	V114			Prevnar 13™		
	n	(%)	(95% CI)†	n	(%)	(95% CI)†
Subjects in population	152			150		
with one or more adverse events	111	(73.0)	(65.2, 79.9)	94	(62.7)	(54.4, 70.4)
injection-site	97	(63.8)		82	(54.7)	
systemic	65	(42.8)		54	(36.0)	
with no adverse event	41	(27.0)		56	(37.3)	
with vaccine-related‡ adverse events	101	(66.4)	(58.3, 73.9)	88	(58.7)	(50.3, 66.6)
injection-site	97	(63.8)		82	(54.7)	
systemic	40	(26.3)		36	(24.0)	
with serious adverse events	3	(2.0)	(0.4, 5.7)	0	(0.0)	(0.0, 2.4)
with serious vaccine-related adverse events	0	(0.0)	(0.0, 2.4)	0	(0.0)	(0.0, 2.4)
who died	0	(0.0)	(0.0, 2.4)	0	(0.0)	(0.0, 2.4)
discontinued vaccine due to an adverse event	0	(0.0)	(0.0, 2.4)	0	(0.0)	(0.0, 2.4)
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)	

† Based on the exact binomial method proposed by Clopper and Pearson for the percentages. CIs are provided in accordance with the statistical analysis plan.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Week 8.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

V114 was well tolerated in participants with CD4+ T-cell count ≥500 cells/μL and participants with CD4+ T-cell count ≥200 to <500 cells/μL, with safety results that were generally consistent with those observed in the overall population of Study V114-018. Few (n=4) participants had CD4+ T-cell count ≥50 to <200 cells/μL.

No laboratory associated AEs were reported. There were no clinically meaningful changes from baseline in CD4+ T-cell count and plasma HIV RNA 30 days postvaccination with V114.

Prior pneumococcal vaccination

Study V114-007 was performed to compare the safety, tolerability and immunogenicity of V114 and PCV13 in healthy adults aged ≥65 years who were vaccinated previously with PPV23 at least 1 year prior to study entry.

The safety results (see Table 34) were generally consistent with those observed in pneumococcal vaccine-naïve adults ≥50 years of age (see Table 21), with the majority of participants in both intervention groups experiencing 1 or more AEs.

Table 34 Analysis of AE summary in participants with prior exposure to PPV23 – APaT population

	V114		Prevnar 13™		Difference in % vs Prevnar 13™
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	127		126		
with one or more adverse events	87	(68.5)	81	(64.3)	4.2 (-7.4, 15.8)
injection-site	80	(63.0)	64	(50.8)	12.2 (-0.0, 24.1)
systemic	50	(39.4)	51	(40.5)	-1.1 (-13.1, 10.9)
with no adverse event	40	(31.5)	45	(35.7)	-4.2 (-15.8, 7.4)
with vaccine-related‡ adverse events	83	(65.4)	72	(57.1)	8.2 (-3.8, 20.0)
injection-site	80	(63.0)	64	(50.8)	12.2 (-0.0, 24.1)
systemic	37	(29.1)	35	(27.8)	1.4 (-9.8, 12.5)
with serious adverse events	0	(0.0)	2	(1.6)	-1.6 (-5.6, 1.4)
with serious vaccine-related‡ adverse events	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)
who died	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-3.0, 2.9)

† Based on Miettinen & Nurminen method.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Day 30.

CI=confidence interval; PCV=pneumococcal conjugate vaccine (V114 or Prevnar 13™).

As in the pneumococcal naïve elderly population, the proportion of participants with injection site AEs was higher following vaccination of V114 compared with PCV13, which was mainly due to higher proportions of participants with solicited injection site pain in the V114 group. These differences were not considered clinically meaningful, as the majority of the AEs were transient and mild in intensity.

The proportions of participants with solicited systemic AEs were generally comparable across intervention groups.

Overall, the safety profile in the different subgroups of age, sex, race, ethnicity and time since PPV23 receipt was comparable to the safety profile in the entire population and no new safety signals are observed.

Overall, the safety profile in participants with prior exposure to PPV23 was similar to the safety profile in the pneumococcal vaccine naïve population and no new safety signals are observed.

Pregnancy

Pregnant participants were excluded from studies in the clinical development programme. However, a total of 14 participants (10 in the V114 group and 4 in the PCV13 group) reported 15 pregnancies (10 in the V114 group and 5 in the PCV13 group), all in Study V114-017. All participants were vaccinated prior to conception. In the V114 group, 4 of the 10 participants were vaccinated within 6 weeks prior to conception, while for the other 6 conceptions occurred after 6 weeks postvaccination. Pregnancy outcomes included 8 live births, 1 spontaneous abortion, and 1 elective abortion in the V114 group. Of the known infant outcomes, no congenital or other abnormalities were reported.

The effect of V114 on the breastfed infant or on milk production/excretion was not evaluated; no data regarding exposure during breastfeeding are available.

Sex, Race and Ethnicity

Safety results observed in the integrated population in the different subgroups were generally consistent with those observed in the overall population. Male participants generally reported fewer AEs than female participants regardless of the intervention group. A trend towards higher reactogenicity in White subjects was observed for both intervention groups. For HIV-infected participants, a trend towards higher reactogenicity was observed among participants who were multiple-race compared with participants who were Asian, Black or African American, or White for both intervention groups. In addition, higher proportions of participants with solicited AEs were observed among participants who were Hispanic or Latino compared with participants who were Not Hispanic or Latino in both intervention groups. These differences were not considered clinically meaningful, as majority of the AEs were transient and mild in intensity.

2.5.8.6. Immunological events

The goal of vaccination is to induce antibodies; which represents the pharmacodynamics effect of the vaccine. Results are presented in the efficacy section.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Concomitant influenza vaccine

V114 was well tolerated when concomitantly administered with QIV in adults ≥50 years of age, with safety results consistent with those of V114 in pneumococcal vaccine-naïve adults ≥50 years of age, see Table 35.

The proportions of participants with AEs, injection site AEs, systemic AEs, and vaccine-related systemic AEs were generally comparable across concomitant and non-concomitant intervention groups. The proportion of participants who experienced SAEs was low, with 6 participants in the concomitant group (1.0%) and 12 participants in the non- concomitant group (2.1%) experiencing SAEs following V114 injection with or without QIV. None of the SAEs were considered to be vaccine-related by the investigator. Over the duration of the study, 1 participant died, and 3 participants discontinued study intervention due to AEs.

A trend toward lower proportions of participants with AEs was observed in older age groups (65 to 74 and ≥75 years of age) compared with the younger age group (50 to 64 years of age) across both intervention groups (concomitant vs. non-concomitant), in particular with regard to injection site reactions. Higher incidences of AEs were observed for female participants in both the concomitant and non-concomitant group. Lower proportions of participants with solicited AEs were observed among participants who were Hispanic or Latino compared with participants who were Not Hispanic or Latino across both intervention groups. The safety profile was generally comparable across intervention groups within each race subgroup and prior PPV23 administration.

Overall, the safety profile in participants who were vaccinated concomitantly with QIV was similar to the safety profile in the non-concomitantly vaccinated participants, and no new safety signals are observed.

Table 35 Analysis of AE summary study V114-021 – APaT population

	Concomitant Group		Nonconcomitant Group		Difference in % vs Nonconcomitant Group†
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population	600		596		
with one or more adverse events	482	(80.3)	488	(81.9)	-1.5 (-6.0, 2.9)
injection-site	430	(71.7)	440	(73.8)	
systemic	341	(56.8)	345	(57.9)	
with no adverse event	118	(19.7)	108	(18.1)	
with vaccine-related‡ adverse events	452	(75.3)	460	(77.2)	-1.8 (-6.7, 3.0)
injection-site	430	(71.7)	440	(73.8)	
systemic	222	(37.0)	227	(38.1)	
with serious adverse events	22	(3.7)	14	(2.3)	1.3 (-0.7, 3.4)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
who died	1	(0.2)	0	(0.0)	0.2 (-0.5, 0.9)
discontinued vaccine due to an adverse event	2	(0.3)	1	(0.2)	0.2 (-0.6, 1.1)
discontinued vaccine due to a vaccine-related adverse event	1	(0.2)	1	(0.2)	
discontinued vaccine due to a serious adverse event	1	(0.2)	0	(0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	

† Estimated differences and CIs are calculated based on Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
‡ Determined by the investigator to be related to the vaccine.
Non-serious adverse events were collected from Day 1 to Day 14 following vaccination. Serious adverse events were reported throughout the duration of the study.
CI=confidence interval.

Sequential PPV vaccine

Study V114-016 evaluated the safety and tolerability of sequential administration of PPV23 administered 12 months following V114 or PCV13. This sequential regimen was well tolerated in adults ≥50 years of age, and the proportions of participants with AEs, injection site AEs, systemic AEs, and vaccine-related systemic AEs were generally comparable across intervention groups, see Table 36. The proportions of participants who experienced SAEs were low and comparable across intervention groups, and none of the SAEs were considered by the investigator to be related to the study vaccine. No participant died during the study.

Table 36: Analysis of AE summary following PPV23 in Study V114-016 – APaT population

	V114		Prevnar 13™		Difference in % vs Prevnar 13™
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population	298		302		
with one or more adverse events	220	(73.8)	213	(70.5)	3.3 (-3.9, 10.5)
injection-site	202	(67.8)	192	(63.6)	
systemic	141	(47.3)	124	(41.1)	
with no adverse event	78	(26.2)	89	(29.5)	
with vaccine-related‡ adverse events	213	(71.5)	203	(67.2)	4.3 (-3.1, 11.6)
injection-site	202	(67.8)	192	(63.6)	
systemic	122	(40.9)	101	(33.4)	
with serious adverse events	1	(0.3)	2	(0.7)	-0.3 (-2.1, 1.3)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
who died	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)

† Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.

‡ Determined by the investigator to be related to the vaccine.

Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Month 12 (Day 1 relative to vaccination with PNEUMOVAX™23) through Month 13.

CI=confidence interval; PPV23=pneumococcal polysaccharide vaccine (PNEUMOVAX™23).

Similar results were obtained in the study V114-017, in which healthy adults 18-49 year with and without risk factors for pneumococcal disease were exposed to PPV23 6 months after primary vaccination with either V114 or PCV13 and in study V114-018, in which HIV-positive participants were exposed to PPV23, 2 months after primary vaccination with either V114 or PCV13.

2.5.8.8. Discontinuation due to adverse events

In total, 9 participants had AEs leading to study vaccine discontinuation during the protocol specified reporting period across V114-016, V114-017, V114-018, and V114-021, 8 of 2799 (0.3%) participants who received V114 across and 1 of 852 (0.1%) participants who received PCV13.

Five of the 9 AEs leading to study discontinuation were serious and non-vaccine related: 1 each for squamous cell carcinoma of the hypopharynx, colon cancer, nephrotic syndrome, rheumatoid arthritis, and cerebrovascular accident.

Four of the 9 AEs leading to study discontinuation were non-serious, but vaccine related. These were vertigo, injection site pain, sinusitis, and a combination of abdominal pain upper, fatigue, nausea, arthralgia, rhinorrhoea, and myalgia.

2.5.8.9. Post marketing experience

No post-marketing experience is available. V114 is not marketed anywhere in the world.

2.5.9. Discussion on clinical safety

The clinical safety of V114 was evaluated in 7 clinical trials in which in total, 5,630 adults received V114 and 1,808 adults received PCV13. The active comparator PCV13 was included in 6 of the 7 studies (V114-007, V114-016, V114-017, V114-018, V114-019 and V114-020), while 1 study compared V114 when given concomitantly or non-concomitantly with the influenza vaccine QIV (V114-021).

The chosen comparator, PCV13, is acceptable from a safety perspective. PCV13 is the only PCV licensed for use in adults. V114 contains the same 13 serotypes included in PCV13 (plus two additional serotypes 22F and 33F) and the same carrier protein diphtheria toxoid CRM197 is used.

One study in hematopoietic stem cell transplantation recipients was ongoing and remained blinded at the time of MA submission (study V114-022). The eDMC continues to monitor the unblinded safety data and have not recommended any changes to study conduct based on their reviews. One vaccine-related SAE occurred so far (immune thrombocytopenia) following the second vaccination.

An integrated safety analysis was performed for 3 studies, including healthy adults ≥50 years of age: V114-016, V114-019 and V114-020. Safety results obtained from the other studies were analysed separately. A weighted approach to the analysis was used due to heterogeneity of event rates and different randomisation ratios across studies, which is acceptable. A higher incidence of AEs was seen in study V114-020, which may be attributable to an increased AE reporting prompted by anticipation of receiving an investigational vaccine as no other factors that would explain heterogeneity in event rates were identified. Of note, the naïve pooling results were also presented by the applicant and assessed in parallel.

Next to the integrated safety analysis presented by the applicant, a pooled safety analysis including all 7 clinical studies, including participants from studies V114-007, -017, -018 as well as those participants from study -021 without concomitant QIV vaccination (following PCV vaccination), was provided. The results of the new analysis confirmed the previous findings, and no new safety signals were identified.

Safety data collection strategy

All participants were observed for at least 30 minutes after administration of study intervention for any immediate reactions. The need for appropriate medical treatment and supervision to be readily available following administration of the vaccine is included in the SmPC.

Reactogenicity was followed for 5 days when concerning local injection site reactions and for 14 days for systemic reactions, which is considered appropriate (see Guideline on clinical evaluation of vaccines). Non-serious, unsolicited AEs were followed for 14 days while SAEs were collected up to 6 months (except for study V114-007 where follow-up was limited to 30 days). This strategy was agreed by CHMP and led to a sufficient period of time to collect information on the outcome of the adverse events.

The primary mechanism for reporting adverse events was an electronic Vaccination Report Card (eVRC). Complaints were reported by participants on the eVRC and later reviewed by the investigator via telephone contact 14 days later. Overall, the safety data collection strategy is considered adequate.

As safety reporting could be influenced by unblinding, as V114 and Prevenar 13 differ in appearance, the applicant was asked to fully describe blinding. The unblinded pharmacist or designee was instructed to ask the participant to turn their head away from the vaccination until the empty syringe and needle were discarded as biohazardous waste in a manner that did not allow them to be seen by any blinded individual.

Exposure

In the overall safety database, 5,630 participants received V114, of which 4,389 were ≥50 years. In total 1,241 participants receiving V114 were 18 to 49-year-old, 377 had previous exposure to a pneumococcal vaccine, 152 were HIV-positive (107 were 18-49 years of age and 45 were ≥50 years), and 1,185 either received V114 concomitantly with QIV or non-concomitantly. 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. Information on rare but serious AEs should be systematically collected post-licensure. However, the exact number of participants exposed to V114 is unclear.

The demographic characteristics of participants in the 7 clinical studies were generally comparable across intervention groups with respect to age and gender. Overall, the population enrolled across all studies is considered sufficiently representative of the target population (adults 18 years of age and older).

Solicited Adverse Events

In healthy adults ≥50 years of age, 68.9% of participants in the V114 group experienced 1 or more solicited AEs compared to 58.2% in the PCV13 group. Injection site solicited AEs were reported in a higher proportion of participants in the V114 group compared to the PCV13 group, 62.6% vs 49.8%. This difference was mainly driven by a difference in injection site pain, which was reported by 58.2% in the V114 group and 45.1% in the PCV13 group. Most AEs were mild in intensity and of short duration. As AEs that were of maximum intensity or duration were comparable between the treatment arms, the above described differences are not considered clinically relevant. The proportion of participants experiencing solicited systemic events was generally comparable between the intervention groups, with 38.8% in the V114 group and 33.5% in the PCV13 group, with fatigue being most commonly reported in both intervention groups.

In subjects 18 to 49 years old, 82.4% of participants in the V114 groups experienced 1 or more solicited AEs compared to 78.8% in the PCV13 group. In the V114 group, the proportion of subjects experiencing a solicited injection site AE was slightly higher than in the PCV13 group, 78.4% vs 72.0%, respectively. As with adults ≥50 years, the most frequently reported solicited injection site AE was injection site pain. The proportion of participants experiencing solicited systemic events were comparable between the intervention groups, with 55.3% in the V114 group and 55.0% in the PCV13 group experiencing a systemic AE. As with adults ≥50 years, the most frequently reported solicited systemic AEs was fatigue, with 34.3% in the V114 group and 36.8% in the PCV13 group.

Overall, only a low number of subjects reported increased body temperatures with no notable differences between vaccine groups. Among participants ≥50 years of age, temperatures ≥41.0°C were reported by 4 participants (3 of whom were in the V114 group and 1 in the PCV13 group). These measurements were suspected by the investigator to be erroneous based on review of additional clinical information and that no AEs of body temperature increased or pyrexia were reported for these participants. In each case, the elevated temperature was reported once via an eVRC, with all remaining postvaccination temperatures considered to be within the normal range (except for 1 participant who did not report any other postvaccination temperatures).

Across studies, observations about AEs were consistent, with the majority of participants experiencing 1 or more solicited AEs, and injection site pain being the most frequently reported solicited AE, followed by fatigue and myalgia. In addition, across all studies, most AEs were mild to moderate in intensity, with toxicity of Grade 1, a size of ≤5.0 cm and of short duration (≤3 days). The safety profile of V114 was generally comparable to PCV13, with slightly more V114-vaccinated subjects reporting solicited AEs (mainly driven by injection site reactions).

Unsolicited Adverse Events

Unsolicited AEs occurring ≥1.0% in both the adults ≥50 years of age and the 18 to 49-year-old population for V114 were injection site pruritus and nasopharyngitis, both occurring in ≤1.5% of participants in both age groups. In the 18 to 49-year-old population, some additional unsolicited AEs were reported by ≥1.0% in the V114 group: diarrhoea, nausea, chills, injection site warmth, pyrexia, upper respiratory tract infection, pain in extremity and oropharyngeal pain, which were all reported in <2.5% of participants. The occurrence of unsolicited AEs mostly appeared balanced between V114 and PCV13.

Related Adverse Events

The applicant considered all injection site AEs related, which is agreed with.

The proportion of participants experiencing vaccine-related AEs was higher in the 18 to 49-year-old group; with 77.5% to 81.6% of participants experiencing vaccine-related AEs in the 18 to 49-year-old population versus 57.7% to 68.0% of participants in the ≥50-year-old population.

There is a substantial (>10% point) difference in the proportion of participants experiencing a vaccine-related AE in the ≥50-year-old population in the V114 group compared to the PCV13 group, with 68.0% of participants experiencing a vaccine-related AE in the V114 group compared to 57.7% of participants in the PCV13 group. As noted above, this difference is mainly due to the proportion of participants experiencing vaccine-related injection site related AEs, which is 63.7% in the V114 group versus 51.4% in the PCV13 group.

In accordance with CHMP's request, the applicant has added 'rash', 'chills', 'vomiting' and 'nausea' as adverse reactions in Section 4.8 of the SmPC, as these are known effects of protein conjugated polysaccharide vaccines and have been observed in the studies included in the application. In addition, the applicant has added 'dizziness', 'injection site bruising/injection site haematoma' (combined in 1 term) and 'injection site warmth' to Section 4.8 of the SmPC in line with the CHMP's request. Three potential Type I hypersensitivity AEs were identified that were vaccine-related according to the investigator. The applicant has included hypersensitivity reactions in section 4.8 of the SmPC, as hypersensitivity is a known risk for vaccines and 3 hypersensitivity reactions were observed across the 7 studies included in the safety analysis. None of the potential autoimmune events were related to the vaccine. The applicant is encouraged to continue to monitor autoimmune disorders via routine pharmacovigilance.

Serious Adverse Events and Death

The proportion of participants with SAEs in the 7 studies was below 6.0% in all studies and comparable between study interventions. The SAEs occurred in similar SOCs in both intervention groups, with the most commonly reported SAEs being experienced in the SOCs of infections and infestations (33 subjects (0.6%) in the V114 group and 9 (0.5%) in the PCV13 group), cardiac disorders (20 subjects (0.4%) in the V114 group and 6 (0.4%) in the PCV13 group) and neoplasms benign, malignant and unspecified (18 subjects (0.3%) in the V114 group and 10 (0.6%) in the PCV13 group). None of the SAEs were related to the study interventions.

Over the course of the 7 studies, 11 participants died. All deaths occurred over 40 days after vaccination with either V114 or PCV13, and none were related to the study interventions.

Safety in special populations

<u>Age</u>

In total 3,032 participants of ≥50 years were included in the V114 group in the studies in the integrated safety analysis (V114-016, V114-019 and V114-020). The V114 group consisted of 1,282

(42.3%) participants in the age of 50 to 64 year, 1435 (47.3%) participants in the age of 65 to 74 year and 315 (10.4%) participants were ≥75 years. As expected, increasing age led to a decrease in reactogenicity. For the solicited AEs this decrease was especially seen for injection site pain. Even though reactogenicity decreased, the profile of AEs in the V114 group remained similar, with the most commonly reported injection site AE being injection site pain (69.4% in the 50 to 64-year-old population, 53.5% in the 65 to 74-year-old population and 39.5% in the ≥75-year-old population) and the most commonly reported systemic AEs being fatigue (25.9% in the 50 to 64-year-old population, 15.9% in the 65 to 74-year-old population and 18.8% in the ≥75-year-old population) and myalgia (24.0% in the 50 to 64-year-old population, 17.1% in the 65 to 74-year-old population and 14.6% in the ≥75-year-old population).

HIV-infected individuals

The safety of V114 was evaluated in HIV-1 infected individuals in study V114-018, in which 302 HIV-1 patients received either V114 or PCV13 followed by PPV23 8 weeks later. The participants included in the study all received antiretroviral therapy, and the majority did not have a detectable viral load and had a CD4 count >200 cells/µL. This indicates that the participants still had a functioning immune system. In both intervention groups, the majority of participants experienced 1 or more AEs, with 73.0% of participants in the V114 group and 62.7% in the PCV13 group. The majority of participants in both groups experienced solicited injection site AEs (61.8% in the V114 group and 53.3% in the PCV13 group), of which injection site pain was most frequently experienced, with 57.8% of participants in the V114 group and 51.3% in the PCV13 group. Fatigue was the most commonly reported systemic AE in both groups (20.4% in the V114 group vs 13.3% in the PCV13 group). The majority of solicited AEs were of short duration (≤3 days). The most commonly experienced related AEs were solicited AEs in both intervention groups. The majority of AEs were mild with a toxicity of Grade 1 or 2 and a size ≤2.4 cm in both intervention groups. The proportions of participants with solicited AEs by maximum intensity, toxicity, size and duration were low and generally comparable across intervention groups.

Overall, the safety profile in HIV-1 infected individuals is similar to the safety profile in immunocompetent adults, and no new safety signals are observed. The slightly more unfavourable safety profile with V114 as was observed in the pivotal studies is consistent with results obtained in this study population.

However, as the vast majority participants still had a functioning immune system no conclusions are possible with regard to V114 administration in severely immunocompromised subjects. Further, this study does not provide any information on subjects infected with HIV that are vaccinated with V114 with prior history of PPV23 vaccination.

Prior pneumococcal vaccination

Overall, the safety profile in participants with prior exposure to PPV23 was similar to the safety profile in the pneumococcal vaccine naïve population and no new safety signals are observed. The most commonly reported AEs in both intervention groups were solicited injection site AEs (59.8% in the V114 group and 46.8% in the PCV13 group) and systemic AEs (33.9% in the V114 group and 31.7% in the PCV13 group), as was seen in the pneumococcal naïve population. In general, the AEs were reported in similar proportions in both intervention groups.

Pregnancy

In total 14 participants in Study V114-017, 10 in the V114 group and 4 in the PCV13 group, got pregnant after vaccination during the follow-up period. Of the known infant outcomes, no congenital or other abnormalities were reported. These data do not indicate an unusual risk or safety concern; however, exposure to the vaccines in all cases was before the pregnancy. Currently, there is no clinical data of the use of these vaccines in women who are pregnant. The applicant commits to provide a

summary of pregnancy outcomes in future PSURs per the 2005 CHMP Guideline on The Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data.

Sex, Race and Ethnicity

Female subjects reported more AEs than male subjects across the several studies. Higher rates of reactogenicity in females have been reported for different vaccines and does not impact the use of the vaccine. Interestingly, the difference in reactogenicity appears to be greater in the PCV13 group compared to the V114 group. A trend towards higher reactogenicity in white subjects was observed for both intervention groups. No clear trends were observed with respect to reactogenicity between ethnic subgroups. Subgroup analyses by age, sex, race, ethnicity, and time since PPV23 receipt were provided and did not raise concerns.

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.

Safety related to drug-drug interactions

Concomitant injection with QIV does not affect the safety profile of V114 to a clinically relevant extent. The majority of the AEs experienced were solicited AEs, mostly mild in intensity and short duration.

Sequential vaccination regimen of V114 followed by PPV23 is well tolerated. The safety profile in both intervention groups were generally comparable, in healthy adults ≥50 years (V114-016), in healthy adults 18 to 49 years old (V114-017) and in HIV-infected subjects ≥18 years (V114-018).

Discontinuation due to AE

As vaccination with V114 only requires a single dose, participants could only discontinue the intervention in studies in which PCV vaccination was followed by PPV23 or the study investigation concomitant vs non-concomitant QIV administration. The number of discontinuations due to AEs is low (9 in total) and comparable between intervention groups: 0.3% in the V114 groups and 0.1% in the PCV13 group. AEs leading to discontinuation were reported across multiple SOCs with no AEs being reported more than once. However, the conclusion that most AEs were non-serious and not considered vaccine-related cannot be agreed, as AEs leading to discontinuation were either serious or vaccine-related.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The safety profile of V114 appears to be similar to the safety profile of PCV13, although slightly more reactogenic. It is a moderately 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 AEs by PT were solicited AEs: injection site pain, injection site swelling, fatigue, headache and myalgia.

As expected, reactogenicity decreased with age. No SAEs or deaths occurred that were considered possibly related to V114.

In conclusion, V114 is well tolerated in adults ≥18 years. However, compared to PCV13, V114 is slightly more reactogenic. This increase in reactogenicity is mainly due to increased injection site pain and has no further clinical implications.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

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

2.6.2. 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 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

2.6.3. Risk minimisation measures

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

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16.07.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

None requested.

2.8.3. Quick Response (QR) code

None.

2.8.4. 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 and additionally contains two new serotypes, 22F and 33F conjugated to a CRM197 carrier, qualified as a new active substances in itself.

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for V114 is *for active immunization for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults 18 years of age and older.*

Streptococcus pneumoniae, which causes pneumococcal disease (PD), remains a leading cause of morbidity and mortality, particularly in older adults (≥65 years of age), adults ≥18 years of age with certain comorbid conditions (e.g., chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma), and immunocompromised adults (e.g., HIV, HSCT patients). Pneumococcal disease is classified as either invasive pneumococcal disease (IPD) or non-invasive disease. IPD can lead to meningitis, bacteremia, sepsis, bacteraemic pneumonia, and septic arthritis. Non-invasive disease can present as, e.g. otitis media, sinusitis and non-bacteraemic pneumonia. IPD incidence is highest in young children (<5 years of age) and in older adults (≥65 years of age).

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, as treatment starts before bacterial culture results are known. Treatment of CAP caused by S. *pneumoniae* requires rapid initiation of appropriate antibiotic therapy and may require additional supportive care such as supplemental oxygen and sufficient fluid intake.

The increasing rate of 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:

Recommendations for pneumococcal vaccination in adults are typically based on age or risk for pneumococcal disease. However national recommendations differ world-wide and also within the EU.

Prevention of PD in adults currently includes vaccination with pneumococcal polysaccharide vaccine (PPV) and/or pneumococcal conjugate vaccine (PCV) and prophylactic use of antibiotics in certain clinical settings. Currently, the PPV vaccine Pneumovax™23 (PPV23) and the PCV vaccine Prevenar 13™ (PCV13) are licensed for use in adults. The mechanism of action of all licensed pneumococcal vaccines is the induction of protective, serotype-specific, anti-capsular antibodies measured by opsonophagocytic assay called OPA antibodies. Pneumococcal vaccines have demonstrated efficacy and effectiveness against invasive diseases caused by the serotypes in vaccines in children and adults. Serotypes currently covered by vaccines are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (PCV13) and 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. (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. The

case-fatality rate of IPD has not decreased over the past 2 decades. 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.

In Europe, the 10 most common serotypes causing pneumococcal disease in 2018 were 8, 3, 19A, 22F, 12F, 9N, 15A, 10A, 23B and 6C (in order of decreasing frequency), which accounts for 70% of typed isolates. Of note, serotype 3 and 19A are included in the currently licensed PCV and PPV vaccines. There was a significant decrease in the disease caused by 19A, as this was the leading cause of pneumococcal disease prior to inclusion in the PCV and PPV vaccines. Serotype 3 still remains a common serotype that causes disease in adults and children.

Next to 22F, 33F also increased in frequency in several regions and countries. In the United States, 22F and 33F were among the top 10 serotypes causing IPD in adults ≥65 year and children ≤5 year in 2017. 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. IPD due to serotypes 22F and 33F have been associated with an increased 30-day mortality in patients ≥5 year, antibiotic resistance and prolonged hospitalization in adults.

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 V114-019 and V114-017. Both studies are randomised, multicentre, double-blind, active comparator controlled (PCV13) studies evaluating the safety, tolerability and immunogenicity of V114.

Study V114-019 enrolled healthy adults ≥50 years of age who were randomised (1:1) to receive either V114 or PCV13. In total, 602 participants received a single dose of V114 IM, and 600 received a single dose of PCV13 IM.

Study V114-017 enrolled adults 18 to 49 year (inclusive) with or without risk factors for pneumococcal disease (diabetes mellitus, chronic liver disease, COPD, asthma, chronic heart disease, current smoker), who were randomised (3:1) to receive either V114 (n=1,133) or PCV13 (n=379) followed by PPV23 6 months later.

The study populations included the main populations expected to benefit from the vaccine: either healthy elderly subjects (study V114-019) or adults 18 to 49 years old with risk factors for pneumococcal disease (study V114-017). In both studies the subjects received one dose of V114 or PCV13 IM, in line with the proposed regimen for V114 and the approved regimen for PCV13.

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 use of serotype-specific opsonophagocytic activity geometric mean titres (OPA GMTs) and IgG geometric mean concentrations (IgG GMCs) for immunogenicity analyses was adequately justified and accepted in the same scientific advice.

3.2. Favourable effects

OPA antibodies. OPA antibodies are considered surrogate markers for vaccine efficacy. OPA GMTs increased from Day 1 to Day 30 for the 13 serotypes shared between V114 and PCV13 and the 2

unique serotypes 22F and 33F. For the 15 serotypes included in V114 the percentage of participants who had a ≥4-fold rise in OPA GMT ranged from 52.2% to 81.2% in the V114 group in Study V114-019 and 51.5% to 87.5% in the V114 group in study V114-017.

Comparability to PCV13. V114 was shown to be non-inferior to PCV13 for the 13 shared serotypes in study V114-019, based on the predefined non-inferiority margin of the lower bound of the 2-sided 95% CI of the OPA GMT ratio (V114/PCV13) being greater than 0.5. 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.

Elderly. V114 was immunogenic in all age categories investigated. Although the immune response declined with age, a notable immune response was still present in participants ≥75 years old.

Durability of response. During study V114-016, it was seen that OPA GMTs were still above baseline 12 months after vaccination, indicating that the immune response persisted for at least 12 months.

Concomitant vaccination with influenza vaccine. The results from study V114-021 indicated that concomitant vaccination of V114 with QIV did not impact immunogenicity of QIV but did result in a somewhat lower response to V114. The prespecified non-inferiority margin (of the lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant/non-concomitant] being greater than 0.5) was however met for all serotypes.

3.3. Uncertainties and limitations about favourable effects

Efficacy/effectiveness data. No efficacy or effectiveness data is available for V114. 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. For the 2 new serotypes, a Phase 2 study (Ermlich *et al.,* Vaccine 2018), using an earlier formulation, showed that V114 induced OPA and IgG responses against 22F and 33F that were generally higher or comparable to those induced by PPV23 with proven efficacy.

Correlate of protection. There is no correlate of protection known for pneumococcal disease. The primary immunogenicity endpoint in the studies was the level of OPA GMT, as measured by the MOPA, but there is no cut-off value known that can be associated with clinical benefit in adults. This hampers the interpretation of the observed vaccine-induced immunogenicity and the clinical relevance of meeting the non-inferiority and superiority margin compared to PCV13.

Reduced response to certain serotypes. Although the prespecified non-inferiority criteria were met, the immunogenicity results obtained during the pivotal study V114-019 seem to indicate a somewhat reduced immune response to V114 compared to PCV13. For study V114-019, the upper bound of the 2-sided 95% CI of the GMT ratio did not contain 1.00 in 7 of the shared serotypes, while this was the case for only 1 serotype (serotype 4) in 2 supportive studies in a similar population, V114-016 and V114-020. In addition, across all studies, the serotype 4 OPA GMTs elicited by V114 were lower compared to the OPA GMTs elicited by PCV13.

Immunocompromised populations. Data in high-risk immunocompromised populations is currently lacking. Study V114-018 included HIV-infected subjects; however, the participants included in the study all received antiretroviral therapy; the majority did not have a detectable viral load and had a CD4 count >200 cells/µL. This indicates that the participants still had a functioning immune system. The population studied is considered sufficiently representative for the population of HIV infected patients in Europe most likely to get vaccinated. Study V114-022 in allo-HSCT recipients is ongoing, and no information is available. Therefore, information on immunogenicity in adult HSCT recipients is

missing, and therefore an important part of the information in immunocompromised individuals is missing.

Durability of response. Data on antibody persistence is currently limited to one year; therefore, there is no information on long-term protection by V114. In addition, no data is available concerning a potential booster vaccination.

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. The most commonly reported AEs were solicited AEs, i.e., injection site reactions (driven by injection site pain) and myalgia, fatigue, arthralgia and headache.

Overall, slightly more participants receiving V114 reported AEs compared to participants receiving PCV13.

In participants ≥50 years of age, 72.3% of participants experienced 1 or more AE, and 68.0% experienced a vaccine-related AE. The most commonly reported AEs were solicited AEs: injection site pain (58.5%), fatigue (20.2%), myalgia (19.5%), headache (14.5%), injection site swelling (14.5%), injection site erythema (11.1%) and arthralgia (6.3%).

In participants 18-49 years of age (inclusive), 84.7% of participants experienced 1 or more AE and 81.6% experienced a vaccine-related AE. The most commonly reported AEs were solicited AEs: injection site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection site swelling (21.7%), injection site erythema (15.1%) and arthralgia (12.7%).

Overall, a slightly more unfavourable safety profile is consistently observed throughout the clinical study programme for V114 compared to PCV13, as shown by the safety results of the 7-study pool. In the pooled analysis, 76.0% of participants in the V114 group experienced 1 or more AE and 72.0% a vaccine-related AE compared to 66.8% and 62.2% of participants in the PCV13 group respectively. This difference was mainly driven by increased incidences of:

- injection site reactions (mostly pain [64.6% in the V114 group and 51.5% in the PCV13 group], but also swelling [16.1% in the V114 group and 14.2% in the PCV13 group] and erythema [11.3% in the V114 group and 11.0% in the PCV13 group])
- myalgia (20.7% in the V114 group and 16.8% in the PCV13 group)
- fatigue (23.4% in the V114 group and 22.2% in the PCV13 group)
- headache (17.3% in the V114 group and 16.7% in the PCV13 group).

V114-vaccinated subjects tended to show more moderate or Grade 2 events compared to PCV13-vaccinated subjects.

As safety data across the 7 studies, including 5030 participants in the V114 group and 1,808 participants in the Prevenar 13 group, is more robust as compared to the individual studies, ADRs presented in the SmPC should reflect frequencies in the 7-study pool.

Concomitant vaccination with QIV was overall well tolerated, although a trend for slightly more subjects reporting systemic vaccine related AEs is observed in comparison to non-concomitant group 33.0% (V114 and QIV), 26.7% (V114 alone), 22.1% (placebo and QIV), and 11.1% (placebo alone).

Discontinuations due to AE. In total 9 participants had AEs leading to study vaccine discontinuation, 8 of 2799 (0.3%) participants who received V114 and 1 of 852 (0.1%) participants who received PCV13.

In both intervention groups, the majority of participants had events which were mild in intensity, with a toxicity of Grade 1, a size ≤5.0 cm and short duration (≤3 days).

3.5. Uncertainties and limitations about unfavourable effects

Missing information. Safety has not been assessed in pregnant women. The applicant commits to provide a summary of pregnancy outcomes in future PSURs per the 2005 CHMP Guideline on The Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data. In addition, the information on safety in immunocompromised patients is very limited. As stated in the scientific advice by the CHMP, HIV-infected patients and HSCT recipients are deemed sufficiently representative of the wide range of medical conditions associated with cellular and/or humoral immune dysfunction. The vast majority of HIV-1-infected patients included in Study V114-018 had a functioning immune system. However, the population studied is considered sufficiently representative for the population of HIV-infected patients in Europe most likely to get vaccinated. A study, including allo-HSCT recipients (V114-022) is ongoing; however, no information on safety in this population is currently available.

Hypersensitivity reactions. Information on hypersensitivity reactions after vaccination with V114 is limited in the dossier. Hypersensitivity reactions are a known risk for vaccines. The applicant will continue to monitor Type 1 hypersensitivity events via routine pharmacovigilance.

Safety database. In total, 5,630 participants received V114, of which 4,389 were ≥50 years. The size of the safety database limits the detection of more rare adverse events. Information on rare but serious AEs should be systematically collected post-licensure.

3.6. Effects Table

There is no clinical efficacy data available in the dossier. OPA GMT results are taken as surrogate markers for protection and support immunobridging of V114 to the licensed PCV13.

Table 37 Effects Table for V114

Effect	Short Description	Unit	V114	PCV13	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Non-inferiority of 13 shared serotypes	OPA GMT ratio	Non-inferiority met for all shared serotypes[1)]			V114-019
	Superiority of 2 serotypes	OPA GMT ratio	Superiority met for both 22F and 33F[2)]			
Unfavourable Effects						
Injection site AE	Injection site pain	%	64.6	51.5	SoE: These were the most commonly reported AEs in participants of ≥50 years of age (Integrated summary of safety including Study V114-016, V114-019 and V114-020) and in participants of 18-49 years of age with and without risk factors for pneumococcal disease.	7-study pool
Systemic AE	Fatigue	%	23.4	22.2		
	Myalgia	%	20.7	16.8		

Abbreviations: PCV13=Prevenar 13™, SoE=Strength of evidence
[1)]V114-019 has met its primary immunogenicity objectives regarding non-inferiority of V114 compared to PCV13 with respect to OPA GMTs for the 13 shared serotypes; lower bound of the 2-sided 95% CI ⩾0.5).
[2)]Furthermore, V114-019 has met its primary immunogenicity objectives regarding superiority of V114 compared to PCV13 with respect to both OPA GMTs and the proportions of participants with ⩾4-fold rises in OPA responses for the 2 unique serotypes; lower bound of the 2-sided 95% CI ⩾2.0) In addition, the superiority of response to serotype 3 of V114 compared to PCV13 was investigated concerning OPA GMTs (lower bound of the 2-sided 95% CI ⩾1.2) and proportions of participants with ⩾4-fold rises in OPA responses (lower bound of the 2-sided 95% CI ⩾0.0). 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

The mechanism of action of all pneumococcal vaccines, including V114, is the induction of protective, serotype-specific, anti-capsular antibodies, measured using an opsonophagocytic assay. The OPA antibodies are considered surrogate markers for efficacy and have been found to correlate with protection against disease (Song et al. J. Infect Chemother. 2013).

V114 elicits the generation of functional OPA antibodies against the 15 serotypes contained in the vaccine in all 7 clinical studies. Overall, the immunogenicity data showed that the immune response to V114 was generally comparable to the response to PCV13. V114 was shown to be non-inferior to PCV13 for the 13 shared serotypes and superior to PCV13 for the 2 unique serotypes. Next to the OPA antibodies, IgG GMCs, GMFR, the proportion of participants with ≥4-fold rise in OPA or IgG titre and RCDC, all indicated that the immune response elicited by V114 was substantial and largely comparable to the immune response generated by PCV13. In the 7 studies submitted in the dossier, the immunogenicity of V114 has been demonstrated in different populations using both OPA GMTs and IgG

GMCs. The trials were conducted in different geographical areas and included adults ≥18 years with a significant portion of elderly participants (44.5% of all vaccinated participants were ≥65 years old).

The fact that there is no correlate of protection, somewhat hampers the interpretation of the clinical relevance of the results. PCV13 has been shown to be protective against invasive pneumococcal disease. To infer a clinical benefit, the applicant has bridged the immunologic response of V114 to the 13 shared serotypes of V114 to PCV13, which is considered acceptable. As the immunological response to V114 is comparable to the immunological response to PCV13, it is considered reasonable to conclude that V114 could provide protection against pneumococcal disease. It is however unknown to what extent differences between the V114 and PCV13 induced immune responses may have an impact on protection against invasive pneumococcal disease, as clinical efficacy has not been demonstrated for V114. Epidemiological surveillance will be necessary to ensure early detection of breakthrough disease caused by potential vaccine failure or reduced vaccine effectiveness. In addition, next to breakthrough disease, serotype replacement should be included in surveillance studies. The applicant has committed to discuss these topics in the yearly PSURs within the context of routine pharmacovigilance.

In the pivotal studies, a consistently weaker immune response to serotype 4 was seen after vaccination with V114 compared to PCV13. This is most likely not clinically relevant, as the percentage of participants with an ≥4-fold rise in OPA GMTs was still substantial (≥79%), and the difference in the percentage of responders (≥4-fold rise) in the V114 and PCV13 group was relatively small, <10%. In addition, RCDC for serotype 4 showed that the distribution is similar between V114 and PCV13 and that there is a substantial immune response in both intervention groups, as shown by the substantial difference between the baseline curves and the postvaccination curves.

In the pivotal studies, it was observed that the responses to serotype 3 and the 2 unique serotypes were stronger after vaccination with V114 compared to PCV13. This is relevant as serotype 3 still leads to disease even though it is included in PCV13. In addition, 22F and 33F are also among the key non-vaccine serotypes leading to PD. Inclusion of serotypes 22F and 33F and increasing the immune response to serotype 3 might increase protection against disease for these serotypes.

While efficacy could be extrapolated from PCV13 for the 13 shared serotypes, this could not be done for the serotypes unique to V114. However, for both new serotypes a robust immune response is seen, with GMTs of 2,375 and 7,995 being achieved after V114 vaccination during the pivotal study for serotype 22F and 33F respectively. In the V114 arm of study V114-019 71.4% and 56.7% achieved a 4-fold rise in GMT response for serotype 22F and 33F respectively, compared to 14.3% and 6.3% in the PCV13 arm. In addition, in a Phase 2 study (Ermlich *et al.,* Vaccine 2018), using an earlier formulation, V114 induced OPA and IgG responses against 22F and 33F that were generally higher or comparable to those induced by PPV23 with proven efficacy. These results indicate that efficacy could be reasonably assumed, however, as stated previously, post-marketing epidemiological surveillance will be necessary to ensure vaccine effectiveness for these new serotypes.

Currently, antibody persistence has been shown to last for at least 12 months. The immunogenicity data at 12 months is comparable between V114 and PCV13. Due to the lack of any threshold value associated with clinical benefit, it is not possible to establish duration of protection or to advise on when a booster dose should be recommended. The lack of information on long-term protection/immunogenicity and requirement for a booster vaccination is included in the SmPC.

The documented safety exposure is considered sufficient for adequate assessment of the safety profile of V114. However, the size of the safety database limits the detection of more rare but serious adverse events. Information on rare but serious AEs should be systematically collected post-licensure, including hypersensitivity reactions.

The safety profile of V114 was comparable to the safety profile of PCV13. In the 7 studies submitted in the dossier, no new safety signals were observed for V114 compared to PCV13. V114 was slightly more reactogenic, leading to a higher percentage of participants experiencing 1 or more AEs, mainly due to increased incidence of injection site reactions (driven by injection site pain, around 15%-point difference) and solicited systemic AEs (most notably myalgia, around 5% point difference). For both interventions, the majority of participants experienced 1 or more AEs in all studies and the most commonly reported AEs were solicited AEs. V114 is well-tolerated since most of the AEs are mild in intensity, of short duration (≤ 3 days) and the discontinuations due to adverse events are low.

Information on safety and efficacy of V114 in high-risk immunocompromised populations is currently lacking as study V114-022 is currently ongoing. Immunocompromised individuals are at risk of developing pneumococcal disease and are therefore likely to be vaccinated. Information on safety and efficacy/immunogenicity in this population is thus clinically relevant.

3.7.2. Balance of benefits and risks

V114 elicits an immune response to all 15 serotypes contained within the vaccine, as measured by the increase in functional antibodies using the MOPA assay. Based upon bridging of immunological response of V114 to the response to PCV13, for which efficacy has been established, it is considered reasonable to conclude that V114 could provide protection against pneumococcal disease.

The safety profile of V114 is characterised by injection site pain, fatigue and headache and is comparable to the safety profile of PCV13. As the reported AEs are mainly mild in intensity and of short duration, the beneficial effect associated with V114 outweighs the risks.

Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive from a clinical perspective.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit/risk balance of Vaxneuvance is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vaxneuvance is favourable in the following indication(s):

"Vaxneuvance is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.

See sections 4.4. and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Vaxneuvance should be in accordance with official recommendations."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that for Pneumococcal polysaccharide 15 serotypes conjugated to CRM197 (Pneumococcal polysaccharide conjugate vaccine MSD (15-valent, adsorbed), only pneumococcal polysaccharides of serotype 22F and 33F conjugated to a CRM197 carrier are to be qualified as new active substances, as these are not a constituent of a medicinal product previously authorised within the European Union.