30 January 2025
EMA/68123/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Capvaxive

Common name: Pneumococcal polysaccharide conjugate vaccine (21-valent)

Procedure No. EMEA/H/C/006267/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ABCs	Active Bacterial Core Surveillance System
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AOM	Acute Otitis Media
APaT	All Participants as Treated
CAP	Community-Acquired Pneumonia
CD4	Cluster Of Differentiation 4
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CSR	Clinical Study Report
ECL	Electrochemiluminescence
EEA	European Economic Area
EMEA	European Medicines Evaluation Agency
EU	European Union
eVRC	Electronic Vaccination Report Card
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease
iSAP	Integrated Statistical Analysis Plan
MOPA	Multiplexed Opsonophagocytic Assay
NIP	National Immunization Program
NITAG	National Immunization Technical Advisory Group
OPA	Opsonophagocytic Activity
PCV	Pneumococcal Conjugate Vaccine
PCV7	Pneumococcal 7-Valent Conjugate Vaccine (Prevnar™)
PCV10	Pneumococcal 10-Valent Conjugate Vaccine (Synflorix™)

PCV13	Pneumococcal 13-Valent Conjugate Vaccine (Prevnar 13™ / Prevenar 13™)
PCV15	Pneumococcal 15-Valent Conjugate Vaccine (VAXNEUVANCE™)
PCV20	Pneumococcal 20-Valent Conjugate Vaccine (Prevnar 20™ / APEXXNAR™)
Pn ECL	Pneumococcal Electrochemiluminescence
PnPs	Pneumococcal Polysaccharide
PPSV	Pneumococcal Polysaccharide Vaccine
PPSV23	Pneumococcal Vaccine, Polyvalent (23-Valent) (PNEUMOVAX™23)
RNA	Ribonucleic Acid
QIV	Quadrivalent Influenza Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
siDMC	standing internal Data Monitoring Committee
SOC	System Organ Class
US	United States
V116	Pneumococcal 21-Valent Conjugate Vaccine
VWP	Vaccines Working Party
WHO	World Health Organization
WOCBP	Women of child bearing potential

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 6 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Capvaxive, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 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 tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0485/2022 on the agreement of a paediatric investigation plan (PIP) and P/0510/2023 on the modification of the PIP.

At the time of submission of the application, the PIP P/0510/2023 was not yet completed as some measures were deferred.

The PDCO issued an opinion on partial compliance for the PIP P/0510/2023.

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. New active substance status

The applicant requested the active substances pneumococcal polysaccharide serotype 9N, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B conjugated to CRM_{197} contained in Capvaxive (pneumococcal polysaccharide conjugate vaccine (21-valent)) to be considered as new active substances, as the applicant claims that they are not constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
17 October 2019	EMEA/H/SA/4272/1/2019/III	*Filip Josephson, Mair Powell*
24 February 2022	EMA/SA/0000074352	*Andreas Kirisits, Jens Reinhardt*

The scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- *Drug Substance (DS) Process Performance Qualification (PPQ) Strategy.*
- *Nonclinical toxicology program.*
- *Plans and timing for the Developmental and Reproductive Toxicology (DART) study.*
- *Agreement with the design of the Phase 1/2 trial to evaluate safety, tolerability and immunogenicity of V116 compared to PNEUMOVAX 23 (PPSV23) in adults 18-49 years of age (Phase 1), and in adults 50 years of age and older (Phase 2).*
- *Appropriateness of the phase 3 clinical program, in particular dose, comparator, endpoints and study population.*

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	6 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 June 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 July 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 October 2024
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	18 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to	28 November 2024

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 December 2024
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	15 January 2025
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 Capvaxive on	30 January 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substances pneumococcal polysaccharide serotype 9N, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B conjugated to CRM_{197} contained in Capvaxive (see Appendix on NAS)	30 January 2025

2. Scientific discussion

2.1. Problem statement

Capvaxive (V116) is a protein conjugated polysaccharide vaccine intended for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) 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 can lead to meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis. The non-invasive disease can present as, e.g. otitis media, sinusitis and non-bacteraemic pneumonia.

2.1.2. Epidemiology

Invasive Pneumococcal Disease

In the EU, the notification rate of IPD in adults ≥65 years of age was 16.1 cases per 100,000 in 2019. The overall case fatality rate of IPD was 15% in the EU in 2017. The case fatality rate increased with age: 3% in children <15 years of age, 6% in 15 to 44-year-olds, 11% in 45 to 64-year-olds, and 22% in adults ≥65 years of age. The case fatality rate was as high as 10% to 30% among patients with pneumococcal meningitis.

In the US, the incidence of IPD in adults ≥65 years of age was 23.6 cases per 100,000 in 2019 while in Canada, the incidence of IPD in adults ≥65 years of age was 23.2 per 100,000 in 2019. Case fatality

rate of bacteraemic pneumococcal pneumonia, the most common presentation of IPD in adults, ranged from 5% to 7%, being higher in elderly persons. The overall case fatality rate of IPD was approximately 11% in the US in 2019. Mortality is highest among adults ≥50 years of age, ranging from 15% to 25%, with higher mortality observed in adults >85 years of age. In adults 50 to 64 years of age, 67% of IPD cases are in adults with underlying medical conditions. Among adults, the incidence rates of IPD are 2- to 8-fold higher in persons with chronic illnesses (eg, alcoholism, chronic heart disease, chronic lung disease, diabetes, cancer, and HIV) than in healthy individuals, and rates increase with the number of concurrent chronic illnesses present. The risk of IPD is increased further in individuals considered high-risk or immunocompromised.

Pneumococcal Pneumonia

Pneumococcal pneumonia consists of bacteraemic pneumococcal pneumonia and nonbacteraemic pneumococcal pneumonia and remains one of the most important causes of death from infection in many regions. The incidence of nonbacteraemic pneumococcal pneumonia is difficult to estimate due to the lack of diagnostic testing in routine outpatient clinical practice. Clinically defined cases of pneumonia, chest x-ray confirmed pneumonia, and hospitalizations due to pneumonia have been used as surrogates to estimate the incidence. In adults 50 to 64 years of age, 71% of pneumococcal pneumonia cases occurred in individuals with underlying medical conditions in the US between 2013 and 2015. CAP has a high incidence in the general population and is an important cause of death from infection.

The pathogen causing CAP is only identified in 12% to 34% of all CAP cases, which primarily reflects data from hospitalized patients. However, when microbiologic results are available, *S. pneumoniae* is the most commonly identified bacterial pathogen. The WHO estimates that about 11% of CAP in North America is caused by *S. pneumoniae*. Recent studies have found that *S. pneumoniae* causes 10% to 37% of CAP requiring hospitalization in adults in the EU and the US. In 2017, pneumococcal pneumonia contributed an estimated 103,000 hospitalizations in the US.

2.1.3. Aetiology and pathogenesis

Streptococcus pneumoniae is a gram-positive encapsulated diplococcus, which lives in the human nasopharynx. Usually, pneumococci are carried asymptomatically before being cleared. 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 capsular polysaccharide on the cell surface of the pneumococci is the most important virulence factor. 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.

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.

PNEUMOVAX 23 (pneumococcal vaccine polyvalent; PPSV23) was first licensed in the US in 1983. 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.

The 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 (PCV7) 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 the original PCV7 was replaced by these. Until 2021, PCV13 was the only PCV licensed for use in adults. In 2021, Vaxneuvance (PCV15) and Prevenar 20 (PCV20) were licensed for use in adults in the US and EU.

Unmet medical need

Pneumococcal 21-Valent Conjugate Vaccine (V116) is being developed to provide significantly broader pneumococcal disease coverage in adults compared with currently licensed pneumococcal vaccines.

V116 specifically targets residual disease in adults with the inclusion of key serotypes common to licensed vaccines and 8 unique serotypes not contained in any currently licensed vaccine.

V116 Serotypes Contained in Currently Licensed Pneumococcal Vaccines

PCV13	3	6A	7F	19A																
PCV15	3	6A	7F	19A	22F	33F														
PCV20	3	6A	7F	19A	22F	33F	8		10A	11A	12F									
PPSV23	3		7F	19A	22F	33F	8	9N	10A	11A	12F	17F	20							
V116	3	6A	7F	19A	22F	33F	8	9N	10A	11A	12F	17F	20A	15A	15C	16F	23A	23B	24F	31	35B

PCV13=pneumococcal 13-valent conjugate vaccine; PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Note: Advances in serotyping methods have led to further characterization of the serotype 20 included in PPSV23 as 20A [Ref. 5.4: 08B5C0]. The composition for V116 specifies serotype 20A.

Note: Serotype 15C represents the immune response to the deOAc15B polysaccharide as the molecular structure for deOAc15B and 15C are similar.

Comparison of IPD Distribution due to Serotypes in V116 Compared With Licensed Pneumococcal Vaccines in Adults in Countries With an Established Pediatric Pneumococcal Vaccination Program

Vaccines	**US (2019)**	**Canada (2019)**	**UK (2019)**	**Germany (2018/19)**	**France (2017)**	**Japan (2017)**	**Australia (2019)**
	≥65 year	≥65 years	≥65 years	≥60 years	≥65 years	≥65 years	≥65 years
PCV7	4.2%	7.7%	2.9%	4.2%	6.6%	7.3%	10.3%
PCV13	25.0%	26.6%	21.4%	28.7%	30.8%	29.1%	32.8%
PCV15	40.30	41.9%	33.2%	38.7%	41.2%	36.0%	44.6%
PCV20	52.9%	54.3%	61.4%	61.3%	64.8%	66.1%	53.3%
PPSV23	60.2%	64.1%	71.6%	68.0%	73.7%	66.4%	60.0%
V116	84.8%	80.7%	86.4%	82.7%	81.0%	82.0%	71.1%
V116 (Unique Serotypes)	30.2%	25.2%	18.9%	19.6%	15%	not available	22.9%

IPD=invasive pneumococcal disease; PCV7=pneumococcal 7-valent conjugate vaccine; PCV13=pneumococcal 13-valent conjugate vaccine; PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); UK=United Kingdom; US=United States.

Sources: Centers for Disease Control and Prevention, IPD serotype data 2019, as compiled from data provided through Active Bacterial Core surveillance (ABCs); [Ref. 5.4: 08CNXR, 06FY94, 08499F, 06FY9H, 06FYM4, 06FHG4, 08CSMD].

2.2. About the product

Capvaxive is a pneumococcal conjugate vaccine (PCV) that contains 21 distinct pneumococcal capsular polysaccharides, each individually conjugated to the CRM_{197} carrier protein originating from *Corynebacterium diphtheriae* C7.

Capvaxive contains conjugated polysaccharides of *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. Eight of these serotypes are unique (15A, deOAc15B, 16F, 23A, 23B, 24F, 31, 35B) and are not currently

part of any other licensed vaccine. Serotype 9N, 17F and 20A are present in non-conjugated pneumococcal vaccine but has not part of any approved vaccine in their conjugated form.

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, Capvaxive elicits a T-cell dependent immune response that induces antibodies which enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. Capvaxive may not prevent disease caused by *Streptococcus pneumoniae* serotypes that are not contained in the vaccine.

The proposed indication was:

Capvaxive 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.

The recommended dosing regimen for Capvaxive is a single dose of 0.5mL.

2.3. Type of application and aspects on development

Development programme

The clinical development program for V116 (Pneumococcal 21-Valent Conjugate Vaccine) to support licensure in adults consists of 6 Phase 3 studies, V116-003, V116-004, V116-005, V116-006, V116-007, V116-010 and the Phase 1/2 dose-finding study V116-001.

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

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

Scientific advice

During the course of development, the sponsor sought regulatory and scientific advice from EMA's Committee for Medicinal Products for Human Use (CHMP) on several occasions between 2019 and 2024.

The selection of comparator(s) should be based on the following two aspects: (1) the level/availability of evidence supporting vaccine efficacy (including for immunobridging purposes) and (2) the overlap in serotypes between candidate vaccine and comparator(s) (WHO Technical Report Series No. 977, 2013, EMA guidance (EMEA/CHMP/VWP/164653/2005, EMEA/CHMP/VWP/164653/05 Rev.01)).

Serotype Composition																																
PCV7	4	6B	9V	14	18C	19F	23F																									
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A																			
PCV15	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F																	
PCV20	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F		8		10A	11A	12F	15B										
PPSV23	4	6B	9V	14	18C	19F	23F	1	3	5		7F	19A	22F	33F	2	8	9N	10A	11A	12F	15B	17F	20								
V116									3		6A	7F	19A	22F	33F		8	9N	10A	11A	12F		17F	20	15A	15C*	16F	23A	23B	24F	31	35B

* Note that 15C represents the immune response to deOAc15B as the molecular structure of deOAc15B and 15C are similar.

The comparators for the pivotal immunobridging studies were PCV20 (study 003) and PPSV23 (study 010), not PCV13 followed by 23-valent unconjugated vaccine at least 30 days apart as recommended by CHMP. This can challenge the immunobridging approach:

- PPSV23 is not recommended as first vaccine in naive adults and vaccine efficacy is not considered

established for pneumonia for this vaccine. Of note: In Europe the pneumococcal vaccinations differ between countries: Vaccine Scheduler | ECDC (europa.eu)

- In a bridge-to-bridge scenario (which is the case if PCV20 is used as a comparator) the proposed 0.5 NI margin is not conservative enough.

An additional observation is made on study 006 in primed subjects ≥50 years of age. An unvaccinated cohort was not added as recommended in the letter. This might have implications on the interpretation of immunogenicity data since the comparison with naive population will be based on cross study assessment.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) Capvaxive (V116) is presented as a solution for injection in pre-filled syringe containing 21 distinct pneumococcal capsular polysaccharides (serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B, all individually conjugated to the carrier protein cross-reactive material 197 (CRM_{197}) originating from *Corynebacterium diphtheriae* C7. The content expressed as polysaccharide per serotype is 4 µg / 0.5 ml dose for each serotype.

Other ingredients are: sodium chloride, histidine, polysorbate 20, hydrochloric acid for pH adjustment and water for injections.

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

2.4.2. Active substance

The active substance is manufactured by conjugation of CRM_{197} to the pneumococcal capsular polysaccharides which are defined as intermediates in the process. Therefore, the information on these intermediates (polysaccharides (PnP) and CRM_{197}) and active substance (monovalent bulk conjugate (MBC)) are included as separate sections in the report below.

The applicant requested New active substance (NAS) status for 9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31, 35B and De-O-acetylated serotype 15B individually conjugated to carrier protein CRM_{197} which was acceptable. Further details are included in the dedicated assessment on the NAS claim.

Of note, the following designations V110 and V114 are also used in this report. V110 equals Pneumovax, the 23-valent non-conjugated pneumococcal vaccine by Merck, Sharp & Dohme, and V114 equals Vaxneuvance, the 15 valent conjugated pneumococcal vaccine from the same manufacturer.

2.4.3. Pneumococcal polysaccharide (PnP) - AS intermediate

2.4.3.1. General information

The V116 polysaccharides are the purified PnPs from 21 serotypes of *Streptococcus pneumoniae*. The serotype designations using the Danish naming system are 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B.

Each of the PnPs types has a unique monomeric repeat unit structure. O-Acetate is a component of the PnPs repeating unit structure for nine of the V116 polysaccharides.

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 V116) 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.

2.4.3.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

All relevant manufacturing sites for the active substance intermediates, PnPs powders, have valid manufacturing authorisations or hold valid GMP certificates or/and are covered by qualified person (QP) declarations as appropriate.

Each of the 21 PnPs serotypes is manufactured independently using a common manufacturing platform with some variations to accommodate differences in strains, process stream properties, and manufacturing-scale and facility. Of the 21 PnPs serotypes, 14 are shared with the applicant's Pneumovax23 (the approved 23 valent non-conjugated pneumococcal vaccine (V110) and/or Vaxneuvance (the EU approved 15 valent pneumococcal conjugate vaccine; V114) and are referred to as legacy serotypes.

The remaining PnPs serotypes 15A, 16F, 23A, 23B, 24F, 31, and 35B developed for V116 are referred to as novel serotypes.

Appropriate GMP compliance documentation has been submitted for all relevant manufacturing sites for the polysaccharides.

The manufacturing process for the PnPs intermediates consists of the following process modules: fermentation, inactivation, clarification, membrane ultrafiltration (UF), polishing, and product recovery.

The process modules are grouped into two main manufacturing stages: upstream fermentation and inactivation modules which produce the inactivated pneumococcal bacteria, and downstream purification module which consists of clarification, UF, polishing and recovery modules to produce purified PnPs.

One or more Working cell bank (WCB) vials are thawed and expanded in a fermentor/bottle until reaching a target cell density. The culture of the fermentor/bottle 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. 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.

In the platform purification process used for all 21 PnPs serotypes, phenol inactivated broth (PIB) containing PnPs is first flocculated, and then clarified using continuous centrifugation and depth filtration. The clarified broth is then concentrated, and buffer exchanged by UF. The volume-reduced batch is then further purified by phenol and alcohol precipitations followed by polishing filtration. The

purified polysaccharide product is finally recovered using a second alcohol precipitation, harvest centrifugation, trituration, powder washing, powder drying, powder equilibration, and powder harvest.

Due to the unique physicochemical properties of each PnPs, the specific operational conditions for some of the platform process unit operations are adjusted for, or to optimize, serotype-specific performance. For example, in the alcohol fractionation steps, the percentages of alcohol used for the low cut and the high cut are tailored for each serotype to optimize purity and recovery. Likewise, to achieve the desired clarification after the first in- line filtration step, filter grades differ.

The purified polysaccharide powder (AS intermediate) is stored. 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 great detail including also controls of critical steps and intermediates.

Manufacturing process development

All legacy PnPs serotypes in V116 were produced using the commercial process for these serotypes. The manufacturing process for the novel serotypes was developed based on the general process used for the legacy serotypes, which has remained essentially unchanged since its first approval in 2004. The Phase 3 clinical batches were manufactured in the commercial facility for the novel serotypes. The Phase 1/2 and Phase 3 novel serotype processes both utilized the same unit operations and process flow at the same scale for production of the PnPs bulk intermediates for all novel serotypes. Minor process differences for the novel serotypes have accounted for facility fit, process robustness, and serotype-specific sensitivities. The process changes from Phase 1/2 and Phase 3 clinical manufacturing to commercial manufacturing do not impact the quality and safety of PnPs batches.

Legacy scale up and development of the final process as well as Phase 1/2 to Phase 3 Process improvements for novel serotypes have been described in sufficient detail including parameter and attribute classification. The additional novel serotypes resemble to a high degree, the other serotypes and appropriate data have been submitted to verify the feasibility of the manufacturing process. Some changes to the classification of criticality for certain parameters and attributes have been made and these have been appropriately justified.

The differences in the testing of PnPs of the legacy serotypes and the novel serotypes are acceptably justified. A comparison of the methods used to test Phase 1/2, Phase 3/PPQ, and commercial batches have been provided for the PnPs legacy and novel serotypes. All methods for each release and stability attribute were verified, qualified, or validated as appropriate at each PnPs testing site.

Control of materials

Original wild-type isolates for Capvaxive serotypes 3, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F were received. Information on the source of the original wild-type isolates for the *S. pneumoniae* serotypes have been provided.

Master cell banks (MCBs) and WCBs for serotypes 6A, 15A, 16F, 23A, 23B, 24F, 31 and 35B were generated via a similar process. The starting materials for the clonal isolation were obtained either as cryopreserved, frozen cell banks or lyophilized cell banks. Serotypes 6A and 35B underwent a series of additional passaging to prepare the pre-master isolates. The establishment of the MCB and WCB have been adequately addressed.

PnPs process raw materials have been listed, and the composition of the buffers and solutions have been presented. All buffers and prepared solutions are prepared using water for injections (WFI). All

raw materials used are tested or verified against the appropriate acceptance criteria for their intended use.

No animal-derived products were used in the production of the current MCBs and WCBs for all serotypes. The raw materials are the same as already approved for V110 and V114. The applicant certifies that all raw materials used in production of V116 conform to the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01, current version).

Process validation

Out of the 21 PnPs contained in Capvaxive, 13 of the serotypes are also used in the currently licensed 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23) and one (6A) is included in V114.

The general manufacturing process enabled the establishment of a universal set of critical process parameters (CPPs) and critical quality attributes (CQAs), with only minor variation in specification ranges for the different serotypes. The general process was successfully validated for V110 and V114. The consistency and reproducibility of the PnPs general manufacturing process was successfully demonstrated during process performance qualification (PPQ) for the legacy serotypes. The commercial process is routinely monitored through the continuous process verification (CPV) program to ensure that the process continues to operate in a controlled, validated state.

The PPQ of the seven novel PnPs serotypes 15A, 16F, 23A, 23B, 24F, 31, and 35B contained in Capvaxive is described below. The consistency and reproducibility of the general manufacturing process for novel PnPs serotypes was successfully demonstrated by meeting predefined PPQ acceptance criteria for three batches of each serotype.

Commercial-scale batches of each serotype were manufactured to qualify the production process. Successful manufacture of several batches was determined to be appropriate due to the following:

• The qualified process was transferred where there is extensive experience with process development and clinical batch manufacturing.

• The equipment is similar and appropriately scaled.

• Developmental batches were completed successfully prior to initiation of the PPQ series.

The validation data provided show that the production is consistent, controlled and robust.

Characterisation

The chemical structures of the repeating units of the PnPs are well established. The repeating unit structures contain between two and seven 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 thirteen of the serotypes contain either backbone (serotypes 6A, 10A, 17F, 19A, 20 and 35B) or sidechain (serotypes 11A, 15A, 15B, 16F, 23A, 23B and 24F) phosphate groups.

Serotypes 7F, 11A, 15B, 16F, 17F, 20, 22F, 31, 33F and 35B repeating units contain potentially labile O-Acetate functional groups. Serotype 15B is de-O-acetylated during the MBC process such that 15B in final finished product does not contain O-Acetate.

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 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 V116 serotypes (7F, 11A, 15B, 16F, 17F, 20, 22F, 31, 33F and 35B). 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 of each PnPs bulk powder batch is 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. The 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 has shown that the NMR assay applied in routine testing would replace the tests mentioned. 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.

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

The PnPs release and stability specifications were provided. Overall, the tests (appearance and description, identification, impurities, and microbiological quality) are considered adequate.

PnP specifications are in compliance with Ph. Eur. 0996 and Ph Eur. 2150. For the legacy serotypes, specifications acceptance criteria are leveraged from the currently approved 15-valent conjugated pneumococcal polysaccharide vaccine. This is acceptable as the manufacturing process of V116 is similar to the manufacturing process of the 15-valent conjugated pneumococcal polysaccharide vaccine.

Analytical methods

The methods have been accurately described and appropriately validated. Validation of analytical methods is partially leveraged from the currently approved 15-valent conjugated pneumococcal polysaccharide vaccine for those methods which are not serotype specific. For serotype specific analytical methods, additional method validation/verification was performed in line with ICH for the novel serotypes. This is considered acceptable.

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

Batch analysis

Batch data have been shown from several batches of the different serotypes. All batches fulfil the acceptance criteria. The results show good reproducibility within batches and are in most cases far from the outer boundaries of the acceptance criteria.

Container closure

The PnPs active substance intermediates are stored in bottles compliant with ISO 10993. Data has been provided to ensure that this material also meets the requirement of Ph. Eur. 3.1 and 3.2.

An extractables study was conducted. Based on the results of the extractables studies, the risk of carryover of potential leachables into the final finished product is negligible.

2.4.3.4. Stability

The shelf-life claim is based on completed or ongoing primary stability programs together with stability data.

Attributes tested are characteristics and molecular mass. No atypical results have been reported for characteristics through the test period. All batches meet the proposed commercial molecular acceptance criteria through the proposed shelf-life periods. No downward trends were observed in the stability for PnPs stored at the long-term storage condition.

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

2.4.4. Cross-Reactive Material 197 CRM197 - AS intermediate, (carrier protein)

2.4.4.1. General Information

Cross-Reactive Material 197 (CRM_{197}) protein is an intermediate used in the manufacture of the Pneumococcal polysaccharide conjugate vaccine (21-valent) 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}) 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.

2.4.4.2. Manufacture, process controls and characterisation

Manufacturer and process controls

Satisfactory GMP compliance for the intermediate CRM_{197} manufacturers has been demonstrated.

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, several sequential chromatographic steps, ultrafiltration, membrane chromatography and a bioburden reduction filtration prior to CRM_{197} final bulk intermediate (FBI) filling.

The manufacturing process of CRM_{197} is adequately described. Manufacturing process flow diagrams have been provided, stating process intermediates and in-process controls (IPCs), as well as CPPs and CQAs for each step. Details about operating parameters, CQA and process attributes are provided in the dossier which are acceptable, with corresponding acceptable criteria.

Manufacturing process development

PPQ and commercial manufacture were initiated to support clinical trials as well as routine commercial supply for V114. During the transfer of the CRM_{197} manufacturing process, changes and modifications were made to the process to accommodate an increased scale and other facility fit related requirements. All changes were supported by laboratory studies and experience accumulated during commercial-scale manufacturing.

Equivalency of the CRM_{197} process between the two manufacturing sites was previously established in V114, and is supported by the intentionally aligned manufacturing processes, as well as by the extensive analytical characterisation data. Both sources of CRM_{197} have been successfully used in the manufacture of AS clinical batches. The information provided on manufacturing process development is adequate.

Control of materials

Sufficient information on the raw materials used during the manufacture of CRM_{197} has been provided. All materials are adequately tested and meet the quality standards for its intended use.

Process validation and/or evaluation

Data from several PPQ batches of CRM_{197} have been presented. Relevant validation results provided for all steps and all validation criteria were met. The process validation was found acceptable.

Hold times were validated for process intermediates. A summary of the chromatography resins, the associated process step, and number of currently validated re-use cycles has been presented. Resin sanitization validation results have also been provided. In addition, an optional refiltration step that can be performed once in the event of a filter integrity test failure was acceptably validated i.e. validation of CRM_{197} FBI refiltration at commercial-scale and supportive small-scale studies demonstrates that the optional refiltration step is consistently capable of producing a product meeting its predetermined specifications and quality attributes.

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 and receptor-binding domains. 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 CRM_{197} PPQ batches manufactured at commercial-scale were used for the characterisation analyses.

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 adenosine diphosphate-ribosylation (ADP-ribosylation) activity analysis. The PPQ batches data supports the consistent lack of toxicity in commercial-scale CRM_{197} batches.

The levels of each process-related impurity were demonstrably cleared, with concentrations at an acceptable level. The information provided is adequate.

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

The specification for CRM_{197} includes analysis of identity, pH, protein content, bioburden and bacterial endotoxins. Culture Purity testing is performed on the fermentation harvest. All other tests are performed on CRM_{197} FBI.

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 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.

Analytical procedures

Detailed descriptions of the non-compendial analytical procedures included in the specifications are provided. 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.

Batch analysis

Batch analyses data for CRM_{197} FBI presented include PPQ batches, stability batches, supportive commercial batches for post-PPQ changes, batches used as MBC PPQ inputs, and batches used as MBC clinical material inputs.

The manufacturing sites, scales, batch numbers and test results for CRM_{197} FBI are provided. Batch release occurred using validated analytical methods and acceptance criteria in place at the time of batch testing. All batches' results conform to specifications in place at the time of manufacturing.

Container closure system

CRM_{197} FBI is filled into single-use, clean sterilized bottles. The bottles meet the requirements for ISO 10993, Ph. Eur. 3.1 and Ph. Eur. 3.2. The components comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01, current version).

The information on the container closure system is found acceptable.

2.4.4.4. Stability

Stability study results generated for the stability samples stored at the long-term storage condition meet the current acceptance criteria through all tested intervals and demonstrate acceptable stability through the proposed expiry period. No atypical results have been reported for the degree of coloration, endotoxin, or bioburden, and all aggregation data were at or below the limit of quantitation.

Stability studies were also performed at the accelerated condition and the stress condition. The accelerated studies support an overall time out of storage (TOS) allowance and the stress studies support further exposure.

In conclusion, based on the stability data the claimed shelf life for the CRM_{197} intermediate is accepted.

2.4.5. Active Substance Monovalent Bulk Conjugate (MBC)

2.4.5.1. General information

The Capvaxive active substances are composed of pneumococcal polysaccharide (PnPs) serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B 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). In preparation for the conjugation, polysaccharides of serotype 15B is de-O-acetylated. This is further discussed below.

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, some polysaccharide repeating units are 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 MBC batch of a single serotype is a polydisperse distribution of heterogeneous conjugate molecules.

The conjugation process is performed. The molecular weight of the MBC is monitored.

2.4.5.2. Manufacture, process controls and characterisation

Description of manufacturing process and controls

The MBC is produced by MSD International GmbH T/A, MSD Ireland, Brinny, Innishannon, Co Cork, Ireland. Appropriate GMP compliance documentation has been provided.

The MBC active substance manufacturing process is a generally similar process across all 21 serotypes with three main processes: polysaccharide preparation, conjugation, and conjugate purification, which each include multiple process steps. In summary, the PnPs powder is dissolved, size reduced to a target molecular mass, de-O-acetylated, chemically activated, and buffer exchanged by ultrafiltration. The activated PnPs powder and CRM_{197} are lyophilized, resuspended separately in DMSO solvent, and combined for the conjugation reaction. The resulting conjugate is purified via ultrafiltration before a final bioburden reduction filtration.

The MBC process is designed to control the PnPs concentration at steps throughout the process and, in conjugated and free form, in each filled MBC container. Due to the unique biochemical and structural properties of each PnPs serotype, there are serotype-specific operating parameters throughout the manufacturing process to ensure the resulting MBC meets all required specifications.

The description of the manufacturing process is given in sufficient detail. No reprocessing steps are claimed.

The lyophilisation cycle of the CRM_{197} and polysaccharides in the DMSO conjugation has been described in sufficient detail.

MBC process parameters were identified through process risk assessment and subsequent small-scale process characterisation (PC) studies. 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.

Manufacturing process development

The platform process for manufacturing of MBC has been optimised over the V116 development lifecycle but has remained essentially unchanged. Minimal process updates and optimisations were made within the general process. The rationale for process updates across development phases and an assessment of the potential product quality impact has been provided.

A very comprehensive program has been provided for development of the manufacturing process including process characterisation strategy, studies of the container closure system, process optimisations, IPC strategies, comparability, conjugation PnPs concentration targets, processing time studies.

Control of materials

Sufficient information on the raw materials used during the manufacture of the MBC active substance together with a summary of the composition of the buffers and solutions used in the conjugation process have been provided.

All materials are adequately tested and meet the quality standards for its intended use.

Process validation and/or evaluation

The consistency and reproducibility of the MBC manufacturing process was successfully demonstrated by meeting predefined process validation acceptance criteria for the required number of batches of each serotype. Several successful PPQ batches were manufactured over 21 MBC serotypes. Successful use of multiple active substance intermediate PnPs input batches was demonstrated.

PPQ strategy

Given the large number of serotypes and the manufacturing platform, an algorithm was developed to demonstrate manufacturing consistency and control. All valid PPQ batches complied with the predefined acceptance criteria of in-process controls and AS specification.

The MBCs are produced via a low-bioburden process and are bioburden-reduced AS. All process filtrations are classified as either bioburden-reduction or clarification steps. Vendor validation packages were reviewed and leveraged for all process filters. The review determined all filters have acceptable results. All study results met the pre-defined acceptance criteria, demonstrating the suitability of the membrane preparation procedures.

The V116 active substance intermediates, PnPs powders and CRM_{197} FBI, and active substances, MBC, are shipped in defined packaging configurations designed and qualified to support the thermal and physical protection of the contents from external conditions and handling anticipated during transportation. The shipping validation supports that the packaging configurations will give sufficient thermal and physical protection.

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.

Results of the characterisation testing performed on these batches indicate that the serotype-specific MBC exhibit the expected properties, and that the conjugation process is well-controlled to produce conjugates with the desired attributes.

The information provided on MCB characterisation is sufficient and acceptable.

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

The MCB specification incudes tests for physicochemical attributes, appearance, identity, assay (polysaccharide and protein content), purity conjugated and free polysaccharide, and microbiological aspects.

The MBC specifications were established based on clinical and process validation experience, as well as regulatory guidelines, Ph. Eur., analytical capability, and nonclinical experience, to provide assurance of the quality, safety, and manufacturing consistency of the MBC.

Analytical methods

The description of the analytical methods and their validations is acceptable. Historical and currently used CRM_{197} reference standards have been sufficiently described (manufacturing, qualification, re-testing and stability testing).

The information provided is sufficient and acceptable.

Batch analysis

Data includes results from several PPQ or commercial batches of each serotype. The PPQ batches all show results well within the applied acceptance criteria and a very good reproducibility between batches. A similar picture is seen for the other supporting data submitted, indicating that the process is robust and under adequate control.

Container closure system

The MBC active substance is filled into clean, sterilized bottles. The incoming bottle assemblies have no functional differences in the assembly configurations and product-contact materials of construction (MOC). All components received must conform to the approved specifications.

Bottle assemblies are received ready-to-use, sterilized by the vendor. The bottle assemblies meet the requirements of Ph. Eur. 3.1 and 3.2 and ICH guidelines and are free of animal-derived ingredients.

The PC container closure system has been found suitable for long-term storage of the MBC. Extractables studies performed with various solvents under extreme conditions found no substance greater than the safety concern threshold.

Container closure integrity studies performed on the bottle assemblies demonstrated the ability to prevent microbial ingress, maintaining safety and quality of the bioburden-reduced active substances.

2.4.5.4. Stability

The stability studies were executed on PnPs manufactured in the commercial-scale production facilities and in the pilot plant and conducted in line with ICH guidelines. In addition to the stability data at the long-term storage condition, supplemental data are included to support intermediate storage in the production facility in stainless steel cans and data to support time out of storage (TOS) events.

Stability studies for the primary stability study (PSS) batches at the long-term condition, the accelerated condition and the stress condition were conducted. The accelerated and stress storage conditions are performed to support distribution and TOS events. Additional studies include a freeze-thaw study, an endothermic transition temperature (ETT) study, and a photostability study.

To date, all stability results at the long-term storage condition remain within the commercial acceptance criteria, and there are no observable trends in the data. The pilot-scale batches are expected to remain within the acceptance criteria applied at the time of manufacture. The storage period varies between serotypes.

The accelerated condition studies were performed on the commercial-scale batches for each serotype.

Long-term stability studies' conclusions

Long-term stability data is provided for batches representative of the commercial process, including data covering the storage period available for several batches per serotype. The available data, together with the structural and chemical properties of the individual serotypes, enables a robust risk analysis which supports the storage period claim.

Based on the information provided, the applicant is proposing to establish the storage period based on the availability of real-time data. Stability studies for several commercial scale batches for each serotype-specific MBC will be continued according to the schedule detailed in the dossier. As additional satisfactory real-time data become available, they will be reported according to an approved protocol and the shelf life will be extended.

The data provided support the claimed shelf life of the different serotype conjugates.

2.4.6. Finished medicinal product

2.4.6.1. Description of the product and pharmaceutical development

The Capvaxive finished product (FP) is presented as a solution for injection in pre-filled syringe (PFS). Each 0.5 mL dose contains a total of 84 µg of the PnPs antigen (4 µg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 µg of CRM_{197}.

The composition of V116 for each 0.5 mL dose has been presented. There are no overages. All the excipients comply with Ph. Eur. requirements and are commonly used in parenteral formulations for biological products. Furthermore, the excipients and the composition used for the V116 presentation are similar to the ones used for the previous vaccine V114. No excipients of human or animal origin and no novel excipients are included in the FP.

The section on description and composition of the finished product is found acceptable.

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

The assembled finished product components consist of:

- Type 1 glass syringe barrel
- Plastic tip cap with rubber closure
- Rubber plunger stopper

The FP is sterile filtered as it is filled into the syringe barrel assembly and stoppered with a plunger stopper to make a PFS. Final device assembly includes the addition of the plunger rod to the PFS. The combination product consists of the syringe barrel assembly, filled, and stoppered, and with plunger rod inserted.

The FP is supplied in pack sizes of 1 or 10 pre-filled syringes, either without needles, with 1 separate needle, or with 2 separate needles per pre-filled syringe.

The description of the composition and packaging material is fully acceptable.

Pharmaceutical development

The FP formulation development of V116 was based on the V114 formulation, with an optimised concentration of polysorbate-20 selected for V116. No adjuvant is added to V116 compared to V114 where aluminium is used.

Characterisation studies were carried out to ensure a robust formulation process that is scalable and stable throughout the shelf-life. The robustness studies evaluated refrigerated and accelerated storage stability of V116 FP formulated with high and low concentrations of the key excipients, including, histidine, sodium chloride, polysorbate 20 (PS-20) and high and low concentrations of PnPs. The finished product quality in the PFS syringe is maintained within this design space with acceptable attributes.

The formulation development history has been thoroughly described and adequately justify the chosen composition. Some minor FP manufacturing changes were introduced after manufacture of the Phase 3 material. No impact on product quality is expected, which is confirmed by the batch analysis results.

The information provided is adequate and sufficient.

Manufacturing process development

The manufacturing process of the V116 finished product includes thawing of MBC, preparation of formulation buffer, preparation of final formulated bulk (FFB), sterile filtration, aseptic filling in PFS, assembly of plunger rod and labelling and packaging.

The section on manufacturing process development for V116 has been sufficiently described and justifies the commercial manufacturing process.

Control strategy

The development of the control strategy for the finished product has been sufficiently described. The applicant has provided the process risk assessment that was used to identify parameters that could affect product quality and process performance. A quality risk assessment was performed during the development of the V116 process to identify parameters with a potential impact on product quality and process performance.

A summary of the methodology and outcomes is provided. The development of V116 was established on prior knowledge and experience from the applicant’s commercial 15-valent pneumococcal conjugate vaccine, VAXNEUVANCE. Due to the similarities and prior knowledge between the two programs, the

V116 quality target product profile (QTPP) was based on the V114 QTPP. The establishment of a QTPP as well as the identification of relevant CQAs and CPPs have been adequately described.

The formulation process has been maintained, with minor optimizations. The information provided on manufacturing process development for V116 presentation is found acceptable.

Container closure system

The development of the container closure system is found sufficiently presented. The primary packaging material for the FP PFS presentation consists of a type 1 glass syringe along with the plunger rod, plunger stopper and tip cap. Needles are provided in certain markets. The plunger rod does not have direct contact with the FP and therefore is not considered a primary packaging component.

The pre-fillable glass syringe and plunger stopper are compliant with appropriate Ph. Eur. Monographs for primary containers and closures. Adequate information on this device has been provided.

Compatibility

The FP does not require reconstitution. Suitability of the syringe container closure systems is demonstrated by compendial testing of the components, a biocompatibility assessment, and FP stability studies, which are adequately discussed.

Furthermore, as part of the qualification of the container closure system, container closure integrity testing has been performed with a validated test and it is agreed to the conclusion by the applicant that the integrity as well as the compatibility have been successfully demonstrated with the product contact components. The information provided on container closure system, microbiological attributes and compatibility is found acceptable.

2.4.6.2. Manufacture of the product and process controls

Description of the manufacturing process and controls

Appropriate GMP compliance documentation has been submitted for all relevant sites involved in the finished product manufacturing.

Description of the manufacturing process and controls

Briefly, the finished product manufacturing process includes; buffer preparation, thawing and sub-dispense of monovalent bulk conjugates, filtration of buffer, addition of each MBC, mixing, bioburden reduction, addition of buffer solution, mixing, bioburden reduction and sterile filtration, filling and stoppering with subsequent visual inspection and storage at 2–8 °C in preparation for assembly, labelling, packaging and storage.

All steps have been described in sufficient detail and are controlled by appropriate IPCs.

The sodium chloride solution is tested for conductivity and the histidine buffer in addition also for pH. Pre-sterilising filtration bioburden and endotoxins are tested at the FFB and sodium chloride solution, sterilising filters are tested for integrity.

The processing times for filtration and filling step has been presented including the temperature intervals. The post-use acceptance criterion for filter integrity was justified in filter validation experiments. The time out of refrigerator during the manufacturing process have been presented and supported with data.

An automated filling machine, equipped with sterile components, aseptically fills the FFB into syringes such that each syringe contains the minimum recoverable volume. The filled syringes are automatically stoppered. During filling, in-process weight checks are performed to ensure the allowable syringe dose weight range is achieved. After each syringe is filled and stoppered, the syringe exits the isolator and is transferred to the automated inspection machine for 100% visual inspection for defects. Manual inspection using qualified inspectors can also be utilized as a means of visually inspecting the final filled containers in place of automated inspection.

The duration of the mixing and the agitation applied have been described and validation data shown that they yield a homogeneous product.

The combination product assembly process is an automated process. The PFS is fed into the syringe assembly and labelling machine, where a plunger rod is threaded to the PFS stopper. The syringe and plunger rod are inspected for plunger rod presence and correct colour. Inspection for the presence of the plastic tip cap is performed after assembly. The label is applied to the unlabelled syringe assembly.

The finished assembled syringe (combination product) is placed into a packaging tray in the tray loading section. The tray contents are inspected for accuracy and completeness before placement into a carton with a package insert. The cartons are arranged into the shipper containers. The finished product is stored refrigerated at 2−8 °C and protected from light for subsequent release and distribution.

Control of critical steps and intermediate

The FP PFS is manufactured by aseptic technique and the solution is passed through filters at the bioburden reduction and the sterile filtration steps. Filter integrity testing is performed both pre- and post-use during the sterile filtration before the aseptic filling step. Bioburden testing is performed for the filtered formulation buffer as well as for the formulated bulk solution. The bioburden testing is run in accordance to Ph. Eur. 2.6.12 and the proposed limit for formulated bulk is found acceptable. Furthermore, the pH is measured for the histidine buffer, and conductivity is measured for the histidine and sodium chloride buffers. The information provided is sufficient and adequate.

Process validation and/or evaluation

The formulation batch size for V116 FP has been qualified. Several PPQ batches were manufactured, demonstrating that all CPPs, IPCs and CQAs meet the pre-determined acceptance criteria. All batches complied with the CPP syringe filling dose weight, the in-process controls, FP specifications, a test for conjugated saccharide content.

Filter validation

The presented filter validation comprises filter compatibility including filter extractables, viability, bacterial retention validation (*B.diminuta*), and bubble point including diffusion test. All results met the acceptance criteria.

Media fill study

The applicant has presented results from the aseptic steps of the filling process where the process was challenged in a process simulation (PSIM) under worst case conditions.

The results show that all integral filled syringes were negative for turbidity (indicating no growth).

Requalification of campaign filling is executed. Media fill data justifying the proposed maximum duration of filtration and filling time has been provided.

The final assembly and packaging PPQ study demonstrates that the process of assembling the V116 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 V116 combination product.

Shipping qualification studies of V116 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 to support the shipments of V116 filled finished product and packaged finished product shipments. These containers are currently in use with other commercial products. The information provided is sufficient.

2.4.6.3. Product specification

Finished product specifications includes testing for appearance (colour, opalescence, sub-visible particles), identity, saccharide content, polysorbate-20 content, pH, osmolality, recoverable volume, syringeablity, plunger break-loose force, plunger glide force, endotoxin, sterility and container closure integrity.

The specifications were established based on clinical manufacturing experience, regulatory guidelines, process capability, analytical capability, and stability performance, in alignment with ICH Q6B. The acceptance criteria in the specifications document applies for both release and stability testing for commercial batches.

Appearance (degree of coloration, opalescence), sub-visible particles, visible particles, pH, osmolality, recoverable volume, endotoxin and sterility are tested according to Ph. Eur. methods.

A specification for visible particles has been introduced for release and stability testing of the FP. As conjugation of the polysaccharide to the carrier is critical for efficacy, a test for the conjugated polysaccharide content for each serotype has been introduced in the specification. Additionally calculated free saccharide content is added to the specification to monitor for any possible deconjugation for each serotype.

Conjugation and free saccharide content

The applicant has discussed potential deconjugation of polysaccharide from CRM_{197} during manufacture and storage of the finished product and potential effect on the potency of the product.

The applicant agreed to include a test for the conjugated polysaccharide content for each serotype in the specification. To monitor for any possible deconjugation for each serotype, the applicant includes the free saccharide content in the specification. Batch analysis results have been provided, and all results met the proposed specifications.

The applicant includes the free saccharide content in the specification. It is determined as the difference between the saccharide content and the conjugated saccharide. Saccharide content and conjugated saccharide content are controlled with release and stability limits. This is considered acceptable as the conjugated saccharide content is critical for efficacy.

Buffers

There is very low variability between batches and indicates reliable reproducibility and manufacture consistency.

Polysorbate-20 content and pH:

The polysorbate content show no to very little variability. Additionally, the applicant has presented data for photostability and concludes that PS-20 is not sensitive to light. The proposal to not include PS-20 content in the stability studies can therefore be accepted.

The pH levels are stable, and the specifications are accepted.

The proposed acceptance criteria for the general tests (physical appearance, pH, subvisible particles, visible particles, extractable volume, syringeability-and functionality, osmolality), safety tests (bacterial endotoxin, sterility, CCIT) are acceptable. The proposed stability specification for opalescence is sufficiently justified by the batch release and long-term stability data.

Impurities

Product-related impurities are regulated by the FP specifications and no new impurities have been identified in the FP PFS presentation. No additional impurities are introduced through the finished product manufacturing process; impurities are described in MBC impurities section. Residual DMSO levels in this range in MBCs are not expected to present a safety concern for the final vaccine.

The applicant has performed an extensive and detailed nitrosamine risk assessment. Analyses of the risks have been described 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.

This information provided is adequate.

Analytical methods

The description of the analytical methods and their validations are acceptable. The applicant has specified which Ph. Eur. methods are used for sterility testing and bacterial endotoxin testing.

In-house methods have been sufficiently described. The serotype-specific capture and detection antibodies used for identity and saccharide content testing of each serotype has been described in detail. All non-compendial methods have been adequately validated.

The method validation and transfer results demonstrate that the analytical procedure for polysorbate-20 content is suitable for its intended purpose. Furthermore, the method validation, transfer, and equivalency assessment results demonstrate that the identity and saccharide content is suitable for its intended purpose. For compendial methods, verification data is available to demonstrate method suitability. Container closer integrity and syringe functionality procedures were found to be suitable for their intended use. The analytical method for the conjugated polysaccharide content and saccharide content for each serotype is sufficiently described and validated.

Batch analysis

Batch analysis data has been provided. Information for all the manufactured FP PFS batches include information with respect to FP batch size, syringe supplier, manufacturing date and site.

The batch analysis data complies with the limits in the proposed FP PFS release specification in place at the time of manufacture and confirm process and product batch-to-batch consistency. In conclusion, the provided batch data demonstrate a reproducible manufacturing of the FP PFS presentation.

Reference standard

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.

Container closure system

The primary packaging components used for the manufacture of the finished product are compliant with appropriate Ph. Eur. monographs for primary containers and closures. A drug device combination assessment has been provided by the Notified body. The objectives of the assessment were found to have been met. Acceptable component dimensions, drawings and specifications for all parts of the syringe are provided in the dossier. Sterilisation of the syringes, stoppers and closures are described, and integrity testing is verified during routine production and stability studies.

Suitability of the container closure system to protect from microbial contamination during storage, transportation and use was demonstrated during long-term stability and shipping validation studies. Suitability was also confirmed by the results of extractables and leachables testing provided. Information on the sterilisation process for the syringe barrels and on the co-packaged sterile needles has also been provided.

The final presentation is presented with or without needles. A CE certificate covering the needles, includes needles of different size, is provided. Information on the needles have been provided including information of the size of the needles.

2.4.6.4. Stability of the product

A shelf life of 2 years is claimed for the finished product when stored at 2-8 °C.

Real time data

Primary stability studies were conducted in line with ICH guidelines. Data through 24 months are available. Batches were tested using stability-indicating methods.

The acceptance criteria are fulfilled in all batches for the studied duration.

In order to allow assessment of any trends, numerical data are provided for break loose force and glide force, and degree of opalescence results are presented in terms of the Ph. Eur. references. No trends are observed. The shelf life starts on the date of manufacture (DOM). The DOM is defined as the date of the addition of the first MBC to the conjugate blend (CB) vessel. The applicant has also provided FP long term and accelerated stability data for conjugated saccharide content and free saccharide content.

The commercial batches will have the same specification limits for release and stability according to the Ph. Eur. monograph. This is noted and found acceptable.

The proposed shelf life of 24 months when stored at 2-8 °C is based on several stability batches data, covering the complete shelf life, at commercial scale and where all commercial FP will be produced. The proposed shelf life is acceptable.

Ancillary data

Batches were put on stability to support high temperature excursions and syringe comparability. Additional accelerated study stability was conducted on several batches to support distribution and temperature excursions. A selection of batches has been subjected to photostability studies. Leachable data has also been investigated for all time and temperature points.

In the accelerated data, all results were within the commercial acceptance criteria and exhibited no observable change. The acceptance criteria were fulfilled in all cases.

In the photostability study no changes were seen comparing the syringe in market packages compared to the control sample. The recommended storage to be "protected from light" is thus justified.

The agreed conditions are stated in section 6.4 in the SmPC "In the event of temporary temperature excursions, stability data indicate that Capvaxive is stable at temperatures up to 25° C for 96 hours. At the end of this time period Capvaxive should be used or discarded." This is endorsed as it may help to reduce vaccine wastage.

The applicant commits to continue all the ongoing stability studies at long-term conditions through the proposed shelf-life. In addition, at least one commercial batch of FP will be placed annually on stability studies at long-term conditions. The real-time stability schedule for post-approval studies have been provided and found acceptable.

In conclusion, based on the stability results the claimed shelf life of 2 years for the finished product when stored at 2-8 °C is considered acceptable. Capvaxive should be administered as soon as possible after being removed from the refrigerator. Stability data indicate that Capvaxive is stable at temperatures up to 25° C for 96 hours. At the end of this time period Capvaxive should be used or discarded.

2.4.6.5. Adventitious agents

The applicant has evaluated the risk for adventitious agents associated with human or animal derived raw materials, or raw materials with exposure to materials of human or animal origin, that are used in the production of the master and working cell banks, active substance intermediates, active substance, or finished product.

There are no live viruses and no cell lines of human or animal origin used in the manufacturing process of V116. The risk of introduction or proliferation of adventitious agents is low. PnPs are derived from fermentation cultures of *Streptococcus pneumoniae*, a cell substrate with negligible risk for carrying viral adventitious agents. No animal-derived products were used in the production of the current master cell banks and working cell banks for all serotypes.

CRM_{197}, a non-toxic mutant of diphtheria toxin from *Corynebacterium diphtheriae*, is expressed in *Pseudomonas fluorescens*, a cell substrate with negligible risk for carrying viral adventitious agents.

BSE/TSE certificates/risk assessment for each raw material have been provided, and the risk was considered negligible, which is endorsed. The materials are in compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01, current version).

2.4.7. Discussion on chemical, pharmaceutical and biological aspects

Very comprehensive documentation has been provided concerning the Pneumococcal polysaccharides of 21 serotypes, the CRM_{197} carrier, the 21 MBCs 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. The quality of the resulting product is highly consistent with a very low batch to batch variability in most attributes. There is also good historical comparability within the serotypes when looking at earlier versions of the processes.

The control of the active substance and finished product has been presented in a satisfactory way.

The stability results support the proposed shelf life for active substance intermediates, active substance and finished product.

Acceptable information has been provided to ensure safety of the product with regards to adventitious agents.

2.4.8. 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.

In conclusion, based on the review of the quality data the marketing authorisation application for Capvaxive is approvable from a quality point of view.

2.4.9. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Capvaxive is a pneumococcal conjugate vaccine that comprises of 21 serotype-specific pneumococcal purified capsular polysaccharides (PnP) from S. pneumoniae (21-valent PCV). Pneumococcal 21-Valent Conjugate Vaccine (V116) targets serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. Each polysaccharides type is conjugated (PnP-conjugates) to the carrier protein CRM197 (Cross Reactive Material 197) which is a nontoxic mutant of diphtheria toxin (originating from Corynebacterium diphtheriae C7) expressed recombinantly in Pseudomonas fluorescens (one V116 dose corresponding to 65 microgram CRM197). V116 is intended for adults (primarily older than 65 years). V116 contains the excipients sodium chloride (NaCl), histidine, polysorbate 20 and water for injections. There is no adjuvant. The non-clinical package comprises of four in-vivo pharmacology studies, two pivotal toxicology GLP-studies and four explorative toxicology studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Non-clinical pharmacology studies (only in-vivo) were conducted in mice (n=4; CD-1 and Swiss-Webster mice) and rhesus macaque (n=2). Some of the animal studies used an early V116 formulation that contained serotype 6C conjugates instead of serotype 6A ('V116-like'). Cross-reactivity between 6A and 6C has been established, so this is acceptable.

Immunogenicity was evaluated in the in-vivo pharmacology studies. Sampled serum in mouse and macaque was analysed for IgG titer by a multiplexed Electrochemiluminescent Assay (ECL) whereas functionality was assessed by a Multiplexed Opsonophagocytosis Assay (MOPA). The MOPA for *S.*

pneumoniae is designed to simultaneously assess functional phagocytic activity of serum antibodies to recognize and kill a number of serotypic pneumococci with various antibiotic resistance in the presence of effector cells (differentiated HL-60 cells) and baby rabbit complement, an exogenous functional complement source.

V116-like IP exposure (0.016 ug to 4 ug; one dose every 2nd week followed 3w later by a final lethal challenge on d52) of Swiss-Webster mice showed, based on IgG and MOPA measurements, a dose-dependent immunogenicity response for some but not all serotypes except for the highest doses of 2 µg and 4 µg at which the response was similar. CD-1 mice (IM-exposed to one dose at 0.4 ug of each conjugate, total doses 2 or 3 times with 21 days intervals) demonstrated immunogenicity for all serotypes. Vaccinated infected mice (challenged intratracheally with a lethal dose of *S. pneumoniae* serotype 24F) had at worst 70% survival compared to at best 20% survival in infected controls. No V116 lot-dependent immunogenicity differences were detected.

T-cell responses were explored to some degree in 7w old CD-1 mice (IM-exposure at one dose at 0.8ug per PnP, total of 3 doses with 28 day intervals). D70 splenocytes were stimulated with CRM_{197} peptides for 18-20 hours and the frequency of CRM_{197}-specific T cells was evaluated by secretion of interferon gamma (IFNγ) or interleukin 4 (IL-4). Overall, there was significantly higher T-cell responses in V116-animals compared to naïve animals.

In a rhesus macaque study using 1ug per pneumococcal capsular polysaccharides-conjugate (PnP-conj.) in 0.25mL (dosed 3 times with 28 days interval), ECL IgG data showed that serotypes 6C, 12F and 24F benefited the most from additional immunizations. Serotypes 3, 19A, and 23B had had the weakest increases in geometric mean titer (GMT). MOPA data demonstrated an increase in GMT except for serotypes 10A and 35B, and only a smaller increase for 15B, 16F, 23A, and 31 all of these serotypes had high MOPA titers preimmunization. In a single dose vaccine comparator study between V116, V114 (1ug per PnP-conj. in 0.25mL), Prevnar 13 (PCV13; 1.1ug per PnP-conj. in 0.25mL) and Pneumovax 23 (PPSV23; 12.5ug per PnP-conj. in 0.25mL), based on IgG ECL GMT, the V114 serotypes were very similar to V116. Compared to PCV13 and PPSV23, V116 had higher GMT for serotypes 3. Compared to PPVS23, serotypes 7F, 15B, 17F and 20 were higher for V116. With MOPA, there were no big differences for the shared serotypes between comparators (serotypes 3, 7F, 19A for all comparators, and 22F and 33F for V116, V114, and PPSV23).

A V116 study in macaque with and without aluminium phosphate adjuvant (at 250 ug/mL) did not support that adjuvant would increase the immunogenic response.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not performed for Capvaxive since the vaccine did not show any systemic effects apart from the expected immune response.

2.5.2.3. Safety pharmacology programme

Standalone safety pharmacology studies were not performed for Capvaxive. The vaccine was tested in non-clinical 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 (see Toxicology section). As such, the absence of dedicated safety pharmacology studies is acceptable.

2.5.2.4. Pharmacodynamic drug interactions

Non-clinical DDI studies were not performed for Capvaxive.

2.5.2.5. Pharmacokinetics

No non-clinical pharmacokinetic studies have been conducted for Capvaxive.

2.5.3. Toxicology

The submitted toxicology package comprises of two pivotal IM-exposure route studies (one D1+D22 exposure + 4w recovery repeat-dose toxicity test in rat and one combined segment I-to-III DART study in rat) and four explorative toxicology studies (three non-GLP studies in rat and one non-GLP study in mouse).

2.5.3.1. Single dose toxicity

N/A

2.5.3.2. Repeat dose toxicity

The repeat-dose toxicity rat study used two Capvaxive IM-exposure of the same dose (42ug in 0.50mL split over two injection sites once on D1 and once on D22) and a recovery period of four weeks. There was no adversity observed for mortality, clinical signs, necropsy, and histopathology. Haematologically, females demonstrated a transient reduction in white blood cell counts (around -20% to -30%) but this could not be correlated with male effects or with any other endpoints. As such, the NOAEL for the study was 42 ug in 0.50 mL. The explorative toxicity studies (using mortality, clinical signs, and body weights as toxicological endpoints) used at most the same maximum dose setup (42 ug split over two injection sites) and did not provide any additional insight into the pivotal repeat-dose toxicity outcomes. Regarding the dose, see discussion section.

2.5.3.3. Genotoxicity

The genetic toxicity/mutagenic potential of Capvaxive was not evaluated. This is acceptable considering that Capvaxive is a vaccine.

2.5.3.4. Carcinogenicity

The carcinogenicity of Capvaxive was not evaluated. This is acceptable considering that Capvaxive is a vaccine.

2.5.3.5. Reproductive and developmental toxicity

One cross-segmental DART study in rat was conducted (premating IM-exposures of F0 dams on -D27 and -D7, during gestation on gestational day (Gd) 6, and during lactation on postnatal day (PND) 7) with one exposure group (dose of 42 ug in a single injection site at 0.25 mL). F1 offspring were evaluated until PND21. With the possible exception of a slight increase in injection site reactions in the F0 animals (weak to moderate swelling) compared to controls, there was no toxicological effects. There were no V116-linked effects on any ovarian, uterine, litter, natural delivery, foetal, or pup endpoints observed. As such, no reproductive or developmental (pre- or postnatal) toxicity was detected in either F0 or F1 animals, giving a NOAEL of 42 ug per 0.25 mL. Antibody titers for exposed dams at Gd21 and PND21 showed a titer fold rise between 1.0x and 31.8x across serotype targets (with serotypes 12F and 24F being the weakest at 1-1.3x and 16F and 7F being the strongest at 22.5x and 31.8x respectively). The data indicates that there is some exposure of foetuses and pups to maternal

antibodies. A correlation assessment of pup (F1) vs maternal (F0) titers on GD21 and PND21 found that the levels in F1 foetus and pup samples were more or less consistent with the responses observed in the corresponding F0 female samples (especially at PND21).

2.5.3.6. Toxicokinetic data

No toxicokinetic data was generated in the repeat-dose or DART studies.

2.5.3.7. Local tolerance

Local tolerance was assessed within the context of the pivotal rat studies. There was no increase in V116-linked reactions in the repeat-dose toxicity study. In the DART study, a slight transient increase of injection sites reactions may have been present after Gd6 (but not at after other exposure days). As a V116 specific effect was not detected in the repeat-dose toxicity studies, and there were no clear or severe adverse effects, this finding is not considered toxicological relevant.

2.5.3.8. Other toxicity studies

The explorative toxicity studies used a maximum dose of 42 ug and between 1 and 4 exposures. The studies were mainly used to help support the design of the repeat-dose toxicity rat study. The toxicological assessment was based on mortality, clinical observations, body weights and, in one study, a limited gross and histomorphological evaluation (heart, injection sites and draining lymph nodes). For rats, the no toxicity was observed, giving a NOAEL of 42 ug/dose (with or without APA). In mice, the maximum dose was 8.4 ug/dose which also corresponded to the NOAEL.

2.5.4. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) that – based on V116 being a PnP-conjugated vaccine - justified the absence of a Phase I+ ERA has been provided. V116 is unlikely to result in a significant risk to the environment.

2.5.5. Discussion on non-clinical aspects

Pharmacology

Overall, the applicant has demonstrated that the animal models manifest some degree of immunogenic response to V116 for the targeted serotypes. Challenge/health protection effects have been less explored. A challenge study in mice (dose-response in Swiss-Webster mice and single dose in CD-1 mice) indicates that V116 has a protective function. There was increased survival rate of V116-immunized mice at all tested doses in Swiss Webster mice and about 80% survival in CD-1 mice. A CD-1 mouse study demonstrated higher T-cell responses in V116-animals compared to naïve animals. The data in the macaques suggest that the V116 is more or less as active as V114 (Vaxneuvance), Prevenar 13 (PCV13) and Pneumovax 23 (PPSV23) for the relatively few serotype targets that are shared.

Pharmacokinetics

No non-clinical pharmacokinetic studies have been conducted for V116. This is in line with the EMA and WHO guidelines (e.g., WHO "Guidelines on Nonclinical Evaluation of Vaccines" from 2005) for vaccines that do not include a novel adjuvant or are not administered via an alternate route of administration.

Toxicology

At a maximum dose of 42 ug (in 0.50 mL), V116 did not generate any clear toxicity and was considered the NOAEL. There were some transient female-only white blood cell count reductions in the repeat-dose toxicity study and a slight increase in transient mild-to-moderate injection site-reactions in the pregnant dams in the DART study, but these findings where not considered sufficient to impact the NOAEL determination.

One issue with the toxicological program that the 42 ug dose is half the clinical dose (84 ug per dose in 0.50 mL). It has not been proven that it is impossible or problematic to administer the full dose of 84 ug per dose to the animals (neither in the in-vivo pharmacology or explorative alternatively pivotal toxicology studies). In both pivotal studies (repeat-dose and DART), 42 ug per dose was sufficient to generate an immunogenic response. Considering that the repeat-dose toxicity test was considered sufficient for Phase 3 trials, and in line with the guidance provided in the scientific advice (EMA/SA/0000074352), previous experience with similar vaccines, plus the absence of any unexpected toxicological findings and concerns in the repeat-dose and DART studies, the maximum dose is acceptable.

As such, the SmPC 4.6 and 5.3 texts that state that no toxicity or hazard for humans has been observed are acceptable.

As a PnP-vaccine, V116 is unlikely to result in a significant risk to the environment.

2.5.6. Conclusion on the non-clinical aspects

Overall, the non-clinical program did not generate any signs that where of concern.

2.6. Clinical aspects

2.6.1. 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	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria

V116-001 A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults.	Phase 1 V116: 30 V116-2: 30 PPSV23: 30 Phase 2 V116: 254 PPSV23:254 Phase 1: 06-DEC-2019 Phase 2 23-SEP-2020 first participant first visit Enrolment and study finalized	a randomized, active-controlled, parallel-group, multisite, double-blind, dose-finding study	Phase 1 0.5 mL intramuscular dose of V116 or 1.0 mL of V116 or 0.5 mL of PPSV23 on Day 1 Phase 2: 1.0 mL intramuscular dose of V116 or 0.5 mL of PPSV23 on Day 1	Phase 1: healthy males or females 18 to 49 years of age, pneumococcal vaccine naive. Phase 2: adults ≥50 years of age, pneumococcal vaccine naïve.
V116-003 A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults	Cohort 1 V116: 1179 PCV20: 1177 Cohort 2 V116: 200 PCV20: 100 13-JUL-2022 first participant first visit Enrolment and study finalized	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	0.5 mL intramuscular dose of V116 or 0.5 mL intramuscular dose of PCV20 on Day 1	Adult males/female without prior administration of any pneumococcal vaccine Cohort 1 Age: ≥50 years Cohort 2 Age: 18 to 49 years
V116-004 A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age	V116 Lot 1: 539 V116 Lot 2: 536 V116 Lot 3: 541 PPSV23: 541 12-AUG-2022 first participant first visit Enrolment and study finalized	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	0.5 mL intramuscular dose of V116 Lot 1, Lot 2, or Lot 3 or 0.5 mL intramuscular dose of PPSV23 on Day 1	pneumococcal vaccine-naïve adults 18 to 49 years of age
V116-005 A Phase 3 Randomized, Double-blind, Placebo- Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with	V116: 1052 QIV: 1072 Placebo: 1057 23-SEP-2022 first participant first visit Enrolment and study finalized	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, placebo-controlled	Concomitant Group: 0.5 mL intramuscular doses of: Day 1: V116 + QIV Day 30:Placebo Sequential Group: 0.5 mL intramuscular doses of:	Adult male or female with or without prior administration of any pneumococcal vaccine Age: ≥50 years

Influenza Vaccine in Adults 50 Years of Age or Older			Day 1: Placebo+ QIV Day 30: V116	
V116-006 A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older	Cohort 1 V116: 230 PCV15: 117 PPSV23: 1 Cohort 2 V116: 174 PPSV23: 85 Cohort 3 V116: 105 12-JUL-2022 first participant first visit Enrolment and study finalized	Multicenter, immunogenicity, safety, tolerability Cohort 1 (prior PPSV23): Parallel assignment, double-blind, active comparator Cohort 2 (prior PCV13): Parallel assignment, double-blind, active comparator Cohort 3 (prior PCV13+PPSV23, PCV15+PPSV23, PPSV23+PCV13, PCV15): Single arm, open-label	Cohort 1 0.5 mL intramuscular dose of V116 or PCV15 on Day 1 Cohort 2 0.5 mL intramuscular dose of V116 or PPSV23 on Day 1 Cohort 3 0.5 mL intramuscular dose of V116 on Day	Adult Males/females with prior pneumococcal vaccine experience Age: ≥50 years
V116-007 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV	V116+Placebo group: 155 participants received V116 and 154 received Placebo PCV15+PPSV23 group: 156 participants received PCV15 and 151 received PPSV23 13-JUL-2022 first participant first visit Enrolment finalized and study ongoing	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	V116+Placebo group: 0.5 mL intramuscular dose of V116 followed by 0.5 mL intramuscular dose of Placebo 8 weeks later PCV15+PPSV23 group: 0.5 mL intramuscular dose of PCV15 followed by 0.5 mL intramuscular dose of PPSV23 8 weeks later	Pneumococcal vaccine-naïve or pneumococcal vaccine-experienced adult males or females living with HIV Age: ≥18 years of age
V116-010 A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and	V116: 739 PPSV23: 741 07-NOV-2022 first participant first visit Enrolment finalized and study ongoing	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-	0.5 mL intramuscular dose of V116 or 0.5 mL intramuscular dose of	Adult males/females without prior administration of any pneumococcal vaccine

Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 50 Years of Age or Older		blind, active comparator	PPSV23 on Day 1	Age: ≥50 years

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No specific pharmacokinetic studies were conducted with the V116 vaccine regimen. Pharmacokinetic studies are generally not considered informative for the evaluation of vaccines.

2.6.2.2. Pharmacodynamics

The pharmacodynamic profile of V116 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.

Mechanism of action

V116 consists of 21 capsular polysaccharides from serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B, each conjugated to CRM_{197} protein. CRM_{197} carrier protein originating from Corynebacterium diphtheriae C7. Conjugation of polysaccharides to proteins changes the nature of the immune response to the polysaccharide antigens from a T-cell-independent to T-cell-dependent response. V116 elicits a T-cell dependent immune response to induce serotype- specific antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

Assays

This marketing application is based on the inference of V116 effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of non-inferior immune responses to the shared serotypes and superiority of non- shared serotypes in another pneumococcal conjugate vaccine Prevenar 20 (PCV20) and pneumococcal polysaccharide vaccine Pneumovax 23 (PPSV23). PCV20 was licensed using Prevenar 13 (PCV13) as an active comparator to demonstrate non-inferior immune responses to the shared serotypes. PCV13 has demonstrated efficacy for the prevention of pneumococcal disease in immunocompetent adults ≥65 years of age. There is no immunological threshold level of antibody concentration that correlates with protection against pneumococcal disease in adults. Opsonophagocytic antibodies (OPAs) are surrogate markers for vaccine efficacy against pneumococcal disease and have been shown to correlate with vaccine-induced protection. In the V116 Phase 3 program, OPA geometric mean titres (GMTs) measured using validated multiplexed opsonophagocytic assay (MOPA) were the primary immunogenicity endpoints to support immunobridging V116 to PCV20 and PPSV23. Evaluation of serotype-specific total IgG responses was generally a secondary objective measured using pneumococcal electrochemiluminescence (Pn ECL) assays. In co-administration study with influenza virus vaccines, also immune response to influenza viruses were evaluated using HAI assay.

2.6.3. Discussion on clinical pharmacology

The evaluation of the protective effect of V116 is based on bridging clinical immunogenicity results to PCV20 and PPSV23, which in turn are immune bridged to the PCV13 and earlier versions of Pneumovax with less serotypes. These earlier versions of vaccines have efficacy data, but the PCV20 and PPSV23 actually have only immunogenicity data. CHMP observes this strategy so called "bridge- to bridge" which was not supported by CHMP during Central Scientific Advice EMA/SA/0000074352. Instead CHMP recommended PCV13 followed by PPSV23 as comparator of choice, to avoid a bridge to a bridge situation to establish for efficacy, but at the same time cover majority of overlapped serotypes between V116 and comparators. Immunobridging directly to PCV13 was expected from CHMP as clinical efficacy of PCV13 has been demonstrated.

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 opsonophagocytic process. The Pn ECL measures all antibodies against specific serotypes. The MOPA was chosen as the main immune parameter to bridge towards PCV20 and PPSV23 and to predict clinical benefit. The use of OPA GMTs as the main immune parameter was discussed and agreed with during scientific advice. Both assays were validated and shown to be fit for purpose for most of the aspects. Specificity for MOPA for some serotypes was lower than expected and therefore explanation and possible influence for immunology results was requested. The applicant described the efforts done to improve the specificity. Mainly, the Sponsor´s own produced polysaccharides helped to improve the specificity. We endorse the efforts the applicant has done for specificity improvements and agree that the assay specificity is sufficient to support the clinical sample testing. The Pn ECL is fit- to purpose and is suitable to support the MOPA results.

As in SmPC 5.1 it was stated that there is a positive correlation between OPA responses and anti-capsular Immunoglobulin G (IgG) responses, the applicant was asked to submit such correlation analysis for each of the 21 serotypes. It is especially important in light of the 5 serotypes that had lower than expected specificity in OPA test. Pearsons´s correlation analysis was submitted by the applicant. The samples were from study V116-003 Cohort 1, which includes pneumococcal vaccine naïve individuals 50 years of age and older. The 95% CI result ranged from 0.039 (33F, Day 30) to 0.67 (15C, Day1). According to Pearson classification the correlation is indeed positive, but ranging from weak to strong depending on the serotype. The applicant stated that correlations between the MOPA and IgG responses are positive at Day 1 and Day 30 for all 21 serotypes in V116 and therefore the sentence in SmPC is correct, which is agreed.

Also, the applicant describes IK assay as a support for MOPA, but no results from IK was presented. The applicant explained that all Phase 3 blood samples intended to be tested for immunogenicity, were controlled for Intrinsic Killing (IK) ability. The unspecific, vaccine induced antibody independent bacterial killing ability was detected among less than 2% of the samples. It shows that IK is rare. Theses samples were removed from the analysis, as described in the study protocol.

In co-administration study with influenza virus vaccines, also immune response to influenza viruses were evaluated using HAI assay. This assay is fully validated and acceptable.

2.6.4. Conclusions on clinical pharmacology

The evaluation of the beneficial effect of V116 is based on bridging clinical immunogenicity results to PCV20 and PPSV23. These vaccines provide the largest overlap of serotypes with V116, but do not

have clinical efficacy data. Instead, earlier versions of these vaccines with less serotypes have demonstrated efficacy against pneumococcal disease. The bioassays used in immunogenicity studies are validated and generally acceptable.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

V116-001 was a randomized, double-blind, comparator-controlled study to assess the safety, tolerability, and immunogenicity of V116 compared with PPSV23.

V116-001 (Phase 1)

The Phase 1 part of V116-001 enrolled 90 pneumococcal vaccine-naïve adults 18 to 49 years of age. Participants were randomly assigned in a 1:1:1 ratio to receive a single dose of V116-1 (1.0x dose [0.5 mL] with 2 µg/each PnPs), V116-2 (2.0x dose [1.0 mL] with 4 µg/each PnPs), or PPSV23 (0.5 mL). V116-1 and V116-2 were both well tolerated with safety profiles that were generally comparable to PPSV23. In this dose-ranging study, both dose levels of V116 were also immunogenic, eliciting robust immune responses to all serotypes contained in the vaccine, as assessed by OPA GMTs and IgG GMCs. Although a direct comparison of V116-1 and V116-2 was not an objective of the study, a dose-response was observed and V116-2 elicited higher immune responses than V116-1 for nearly all serotypes.

The siDMC reviewed the final unblinded cumulative safety, tolerability, and immunogenicity data for all 90 participants who received blinded study vaccine and recommended the study proceed to Phase 2. Additionally, the Sponsor study team reviewed the unblinded aggregate data and, in conjunction with the recommendation of the siDMC, selected V116-2, with 4 µg/each PnPs per dose, for further evaluation in the Phase 2 part of the study.

V116-001 (Phase 2)

The Phase 2 part of V116-001 enrolled 510 pneumococcal vaccine-naïve adults ≥50 years of age. Participants were randomly assigned in a 1:1 ratio to receive a single dose of V116 (4 µg/each PnPs per dose) or PPSV23. Immune responses to V116 were shown to be noninferior to PPSV23 for all common serotypes and superior to PPSV23 for all serotypes unique to V116, based on serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination.

Results from V116-001 confirmed the dose of V116 and supported the subsequent Phase 3 clinical development of V116 with 4µg/PnPs in a 0.5 mL prefilled syringe.

2.6.5.2. Main studies

V116-003

A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults

Methods

Design	Number of Participants by Intervention Group[a]	Study Population	Primary Endpoint(s)
Double-blind, randomized, active-comparator study to evaluate the safety, tolerability, and immunogenicity of V116	Cohort 1 Randomization ratio V116:PCV20 = 1:1 V116: Randomized: 1181 Vaccinated: 1179 Completed: 1160 PCV20: Randomized: 1181 Vaccinated: 1177 Completed: 1152 Cohort 2 Randomization ratio V116:PCV20 = 2:1 V116: Randomized: 201 Vaccinated: 200 Completed: 195 PCV20: Randomized: 100 Vaccinated: 100 Completed: 96	Cohort 1 Pneumococcal vaccine-naïve adults ≥50 years of age Sex: 999 M / 1357 F Median Age: 65.0 years *Stratification factor*: Age: 50 to 64 years: 1176 65 to 74 years: 928 75-84 years: 225 ≥85 years: 27 Cohort 2 Pneumococcal vaccine-naïve adults 18 to 49 years of age Sex: 99 M / 201 F Median Age: 35.0 years	• Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs (Cohort 1 and Cohort 2) • Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116 (Cohort 1) • Proportion of participants who achieve a ≥4-fold rise (baseline to 30 days postvaccination) in OPA responses for the serotypes unique to V116 (Cohort 1) • Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116 (Cohort 2)

Study Participants

Pneumococcal vaccine-naïve adults: Cohort 1: ≥50 years old. Cohort 2: 18-49 years old.

Study sites (112) were in the following 11 countries: Australia, Belgium, Chile, Germany, New Zealand, Puerto Rico, South Korea, Sweden, Taiwan, Turkey, and the USA.

Treatments

One intramuscular injection with standard dose of 0.5 ml V116 or PCV20.

Objectives and endpoints

Primary immunogenicity objectives and endpoints
Cohort 1
Objective: To compare the serotype specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V116 versus PCV20 **Hypothesis (H1)**: V116 is noninferior to PCV20 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 10 common serotypes in V116 and PCV20. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [V116/PCV20] to be >0.5.) **Hypothesis (H2)**: V116 is superior to PCV20 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 11 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PCV20] to be >2.0.)

Endpoint: Serotype-specific OPA responses
Objective: To compare the proportions of participants with a ≥4-fold rise in serotype- specific OPA responses from baseline to 30 days postvaccination with V116 versus PCV20 for the unique serotypes in V116 **Hypothesis (H3)**: V116 is superior to PCV20 as assessed by the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination for the 11 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the differences [V116 – PCV20] between the proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination to be >0.1.). **Endpoint:** Serotype-specific OPA responses
Cohort 2
Objective: To compare the serotype specific OPA GMTs in adults 18 to 49 years of age from Cohort 2 to adults 50 to 64 years of age from Cohort 1 at 30 days postvaccination with V116 **Hypothesis (H4)**: V116 in participants 18 to 49 years of age immunobridges to V116 in participants 50 to 64 years of age as assessed by serotype-specific OPA GMTs at 30 days postvaccination for all 21 serotypes in V116. (The statistical criterion for immunobridging requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116 18 to 49 group/V116 50 to 64 group] to be >0.5.) **Endpoint:** Serotype-specific OPA responses
Secondary objectives
Cohort 1 and Cohort 2
Objective: To evaluate serotype specific cross-reactive OPA responses at 30 days postvaccination with V116 in adults ≥50 years of age from Cohort 1 and adults 18 to 49 years of age from Cohort 2 for serotypes within a serogroup **Hypothesis (H5)**: V116 induces an acceptable antibody response for adults ≥50 years of age as assessed by the proportions of participants with a ≥4-fold rise in serotype-specific cross-reactive OPA responses from baseline to 30 days postvaccination for serotypes within a serogroup in V116. (The statistical criterion for an acceptable antibody response requires the lower bound of the 95% CI of proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for V116 to be >0.5.) **Hypothesis (H6)**: V116 in participants 18 to 49 years of age immunobridges to V116 in participants 50 to 64 years of age as assessed by serotype specific cross-reactive OPA GMTs at 30 days post-vaccination for serotypes within a serogroup in V116. (The statistical criterion for immunobridging requires the lower bound of the 2-sided 95% CI of the cross-reactive OPA GMT ratio [V116 18 to 49 group/V116 50 to 64 group] to be >0.5.) **Endpoint:** Serotype specific OPA responses
Cohort 1
Objective: To evaluate the serotype- specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V116 compared with PCV20. **Endpoint:** Serotype-specific IgG responses

Objective: To evaluate the serotype- specific geometric mean fold rise (GMFR) and proportions of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days post- vaccination with V116 and separately for PCV20 **Endpoint:** Serotype-specific OPA and IgG responses
Tertiary/Exploratory Objectives
Cohort 2
Objective: To evaluate the serotype specific OPA GMTs and IgG GMCs at 30 days postvaccination with V116 and separately for PCV20 **Endpoint:** Serotype-specific OPA and IgG responses
Objective: To evaluate the serotype- specific GMFR and proportions of participants with a ≥4-fold rise in serotype- specific OPA and IgG responses from baseline to 30 days postvaccination with V116 and separately for PCV20. **Endpoint:** Serotype-specific OPA and IgG responses
Cohort 1 and Cohort 2 (separately)
Objective: To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination. **Endpoint:** Serotype-specific OPA and IgG responses

Sample size

This study consisted of 2 cohorts, enrolling a total of approximately 2600 participants.

Cohort 1 was to randomize approximately 1150 participants into the V116 group and 1150 participants into the PCV20 group. The overall power for all the primary hypotheses was approximately 90% at an overall 1-sided 2.5% alpha-level.

Cohort 2 was to randomize approximately 200 participants into the V116 group and 100 participants into the PCV20 group. This study then had >90% power to demonstrate noninferiority in OPA GMTs between participants 18 to 49 years of age in the V116 group from Cohort 2 (approximately 200 participants) and participants 50 to 64 years of age in the V116 group from Cohort 1 (approximately 575 participants) at an overall 1-sided 2.5% alpha-level.

Randomisation and blinding (masking)

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented in an IRT system.

In Cohort 1 (≥50 years of age), participants will be assigned randomly in a 1:1 ratio to receive either V116 or PCV20. Intervention randomisation will be stratified according to participant age at time of randomisation (50 to 64 vs. 65 to 74 vs. 75 to 84 vs. ≥85 years of age). At least 50% of participants in Cohort 1 will be ≥65 years of age.

In Cohort 2 (18-49 years of age), participants will be assigned randomly in a 2:1 ratio to receive either V116 or PCV20. No stratification based on age or other characteristics will be used.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Because V116 and PCV20 have a different appearance, an unblinded pharmacist (or qualified study-site personnel) will be responsible for receiving, maintaining, preparing and/or dispensing, and administering these study vaccines. Blinded site personnel will be responsible for all other study procedures/assessments.

Statistical methods

Table 1. Analysis strategy for immunogenicity variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
Cohort 1: OPA GMTs at 30 days postvaccination for the 21 serotypes in V116	P	cLDA[b] (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
Cohort 1: Proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for OPA responses for the unique serotypes in V116	P	Stratified M&N[c] (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
Cohort 2: OPA GMTs at 30 days postvaccination for the 21 serotypes in V116	P	LDA[d] (estimate, 95% CI, p-values)	PP	Model-based
Cohort 1: Proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for OPA responses for the cross-reactive serotypes	P	Clopper-Pearson (estimate, 95% CI, p-values)	PP	Missing data will not be imputed
Cohort 2: OPA GMTs at 30 days postvaccination for the cross-reactive serotypes	P	LDA[d] (estimate, 95% CI, p-values)	PP	Model-based
Cohort 1: IgG GMCs at 30 days postvaccination for the 21 serotypes in V116	P	cLDA[b] (estimate, 95% CI)	PP	Model-based
Cohort 1: GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for both OPA and IgG responses for the 21 serotypes in V116	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

cLDA=constrained longitudinal data analysis; FAS=full analysis set; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titer; IgG=immunoglobulin G; LDA= longitudinal data analysis; M&N=Miettinen and Nurminen; OPA=opsonophagocytic activity; PP=per-protocol.

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

[b] cLDA model with terms for vaccination group, time, the interaction of time-by-vaccination, age stratum (ie, 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years) at baseline, and the interaction of time-by-age stratum.

[c] Stratified analysis using the M&N method [Miettinen, O. and Nurminen, M. 1985] with stratification by the participant's age at the time of randomization (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years).

[d] LDA model with terms for time, age group (18 to 49 years and 50 to 64 years), and the interaction of time-by-age group.

Cohort 1 includes participants ≥50 years of age; Cohort 2 includes participants 18 to 49 years of age.

Baseline is the day of vaccination (Day 1); 30 days postvaccination is the day of the Visit 3 blood draw (Day 30).

Multiplicity

The study was to meet its primary immunogenicity objectives if noninferiority was demonstrated with respect to the OPA GMTs for the 10 common serotypes (via H1), and superiority was demonstrated with respect to both OPA GMTs and the proportions of participants with ≥4-fold rises in OPA responses for the 11 unique serotypes (via H2 and H3). All hypotheses were to be tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach was to control the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was required.

The study was to meet its first secondary immunogenicity objective if noninferiority was demonstrated for the V116 participants 18 to 49 years of age compared with the V116 participants 50 to 64 years of age with respect to the OPA GMTs for all 21 serotypes in V116 (via H4). H4 was to be tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach controls the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was required.

There were 2 secondary hypotheses (H5 and H6) to assess the cross-reactive antibody responses induced by V116 for serotypes within a serogroup in V116. A stepwise testing procedure between H5 and H6 was to be used to control the 1-sided type-I error rate at 0.025 within each cross-reactive serotype. More specifically, a serotype was first to be tested for the acceptability of cross-reactive antibody responses induced by V116 among adults ≥50 years of age (via H5) at a 1 sided 0.025 alpha-level. If the prespecified success criterion for the serotype was met for H5, then H6 was to be tested for that successful serotype to assess whether V116 in adults 18 to 49 years of age from Cohort 1 is noninferior to V116 in adults 50 to 64 years of age at a 1-sided 0.025 alpha-level. If the prespecified success criterion for the serotype was not met for H5, then H6 was not to be tested for that serotype. Testing in this manner controlled the 1-sided type 1 error rate within each cross-reactive serotype at 0.025.

Results

Participant flow

Of the 2663 randomized participants, 2656 were vaccinated, and 2603 (97.7%) completed the study. Most (>97%) of the randomized participants in each cohort were included in the OPA and IgG analyses for the PP population for at least 1 timepoint.

Cohort 1:

- V116 group: 1181 randomized, 1179 vaccinated, 1160 completed the study, 21 discontinued
- PCV20 group: 1181 randomized, 1177 vaccinated, 1152 completed the study, 29 discontinued

Cohort 2:

- V116 group: 201 randomized, 200 vaccinated, 195 completed the study, 6 discontinued.
- PCV20 group: 100 randomized, 100 vaccinated, 96 completed the study, 4 discontinued.

Table 2. Disposition of participants (all randomized participants) (Cohort 1 and Cohort 2)

	V116		PCV20		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	1,382		1,281		2,663	
Vaccinated at Visit 1						
V116	1,379	(99.8)	0	(0.0)	1,379	(51.8)
PCV20	0	(0.0)	1,277	(99.7)	1,277	(48.0)
Trial Disposition						
Completed	1,355	(98.0)	1,248	(97.4)	2,603	(97.7)
Discontinued	27	(2.0)	33	(2.6)	60	(2.3)
Death	4	(0.3)	2	(0.2)	6	(0.2)
Lost To Follow-Up	15	(1.1)	18	(1.4)	33	(1.2)
Physician Decision	0	(0.0)	2	(0.2)	2	(0.1)
Randomized By Mistake Without Study Treatment	1	(0.1)	2	(0.2)	3	(0.1)
Withdrawal By Subject	5	(0.4)	9	(0.7)	14	(0.5)
Other	2	(0.1)	0	(0.0)	2	(0.1)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adex]

Recruitment

First Participant First Visit	13-JUL-2022
Last Participant Last Visit	18-MAY-2023
Last Data Available	21-JUN-2023
Database Lock Date	22-JUN-2023

Conduct of the study

The study protocol was amended twice. First, to update the country- specific requirements for South Korea and the second time to revise the superiority success criterion for 15C.

Important protocol deviations were reported for 222 (8.3%) participants. The most frequently reported clinically important protocol deviations were due to immunogenicity samples not drawn or samples unable to be tested due to an error by the site in processing and/or handling of the sample (n=66), immunogenicity samples drawn outside the protocol-defined reporting period (n=52), or participant administered improperly stored study intervention that was unacceptable for use (n=51). The protocol deviations were comparably distributed between intervention groups.

Baseline data

Among the vaccinated participants (n=2656):

Overall Median Age (Range): 63.0 years (18 to 97 years)

Sex: 1098 (41.3%) male, 1558 (58.7%) female

Ethnicity: 2048 (77.1%) not Hispanic or Latino, 583 (22.0%) Hispanic or Latino, 18 (0.7%) not reported, 7 (0.3%) unknown

Race: 9 (0.3%) American Indian or Alaska Native, 369 (13.9%) Asian, 258 (9.7%) black or African American, 71 (2.7%) multiple, 36 (1.4%) Native Hawaiian or Other Pacific Islander, 1912 (72.0%) white, 1 (0.0%) missing

Demographics and baseline characteristics were generally comparable between intervention groups.

Numbers analysed

Participants Accounting of OPA Analyses (Per Protocol Population).

	V116		PCV20		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	1181		1181		2362	
Participants included in analyses by timepoint						
Day 1	1149	(97.3)	1151	(97.5)	2300	(97.4)
Day 30	1093	(92.5)	1077	(91.2)	2170	(91.9)
At least one timepoint	1162	(98.4)	1165	(98.6)	2327	(98.5)
Both Day 1 and Day 30 timepoints	1080	(91.4)	1063	(90.0)	2143	(90.7)

Outcomes and estimation

Primary Immunogenicity Endpoints

The studies will only have met the primary objectives in case non-inferiority is shown with respect to the OPA GMTs for the common serotypes, and superiority with respect to both OPA GMTs and the proportions of participants with ≥4-fold rises in OPA responses for the unique serotypes. As not all 3 primary objectives were met, no type I error-controlled claim regarding statistical non-inferiority or superiority can be made.

- In adults ≥50 years of age (Cohort 1), V116 met the predefined criterion for noninferiority to PCV20 (lower bound of 95% CI of the OPA GMT ratio [V116/PCV20] >0.5) for each of the 10 common serotypes at 30 days postvaccination

Table 3. Analysis of postvaccination OPA GMTs for common serotypes (per-protocol population) (cohort 1) (v116-003)

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMT Ratio[a] (V116 / PCV20) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
3	1154	274.0	1161	176.7	1.55 (1.40, 1.72)	<0.001
6A	1148	2302.0	1153	2972.5	0.77 (0.68, 0.88)	<0.001
7F	1152	3637.4	1158	3429.9	1.06 (0.95, 1.18)	<0.001
8	1155	2501.3	1158	1811.1	1.38 (1.25, 1.53)	<0.001
10A	1161	3893.4	1159	4678.0	0.83 (0.75, 0.93)	<0.001
11A	1145	3232.6	1150	2092.8	1.54 (1.39, 1.72)	<0.001
12F	1160	2641.2	1161	2499.6	1.06 (0.92, 1.21)	<0.001
19A	1159	2136.1	1162	2817.8	0.76 (0.69, 0.84)	<0.001
22F	1147	3874.5	1154	4770.1	0.81 (0.72, 0.92)	<0.001

33F	1154	13558.9	1157	11742.1	1.15 (1.01, 1.32)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of non-inferiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/PCV20) being > 0.5 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adimm]

- In adults ≥50 years of age (Cohort 1), V116 met the predefined criteria for superiority to PCV20 (lower bound of the 95% CI of the OPA GMT ratio [V116/PCV20] >2.0) for 10 of 11 serotypes unique to V116 at 30 days postvaccination. V116 did not meet the predefined criterion for superiority to PCV20 for serotype 15C (lower bound of the 95% CI of the OPA GMT ratio was 1.77)

Table 4. Analysis of postvaccination OPA GMTs for unique serotypes (per-protocol population) (Cohort 1) (V116-003)

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMT Ratio[a] (V116 / PCV20) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
9N	1147	7470.7	1150	1640.4	4.55 (4.12, 5.04)	<0.001
15A	1107	5237.2	1102	1589.0	3.30 (2.91, 3.74)	<0.001
15C	1153	4216.2	1158	2072.3	2.03 (1.77, 2.34)	0.406
16F	1151	4868.2	1153	846.3	5.75 (5.16, 6.41)	<0.001
17F	1148	7764.9	1156	460.4	16.86 (14.90, 19.09)	<0.001
20A	1161	6099.2	1155	631.1	9.66 (8.66, 10.79)	<0.001
23A	1132	3737.2	1104	461.5	8.10 (6.86, 9.55)	<0.001
23B	1160	1082.5	1160	107.3	10.09 (8.48, 12.00)	<0.001
24F	1153	2728.6	1130	70.5	38.71 (33.87, 44.25)	<0.001
31	1153	3132.5	1154	144.4	21.69 (18.68, 25.18)	<0.001
35B	1153	8527.8	1159	1383.0	6.17 (5.59, 6.80)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of superiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/PCV20) being > 2.0 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adimm]

- In adults ≥50 years of age (Cohort 1), V116 met the predefined criteria for superiority to PCV20 (lower bound of 95% CI of the differences [V116 – PCV20] >0.1 [10 percentage points]) for 10 of 11 serotypes unique to V116 based on the proportion of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. V116 did not meet the predefined criterion for superiority to PCV20 for serotype 15C (lower bound of 95% CI of the difference [V116 – PCV20] was 5.6 percentage points)

Table 5. Analysis of the proportions of participants with a ≥4-fold rise in OPA responses for unique serotypes (per-protocol population) (Cohort 1) (V116-003)

Pneumococcal Serotype	V116 (N=1179)	PCV20 (N=1177)	Percentage Point Difference (V116 - PCV20)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-Value[ab] (1-sided)
9N	64.7 (595/920)	19.9 (195/978)	44.7 (40.7, 48.6)	<0.001
15A	66.7 (462/693)	35.8 (253/706)	30.9 (25.8, 35.8)	<0.001
15C	83.4 (794/952)	74.2 (695/937)	9.2 (5.6, 12.9)	0.665
16F	71.9 (654/910)	20.8 (200/961)	51.1 (47.1, 54.9)	<0.001
17F	75.8 (653/862)	9.5 (90/952)	66.3 (62.8, 69.6)	<0.001
20A	67.3 (675/1003)	9.6 (97/1011)	57.7 (54.2, 61.1)	<0.001
23A	78.9 (598/758)	36.8 (270/734)	42.2 (37.6, 46.6)	<0.001
23B	85.5 (873/1021)	49.6 (506/1021)	35.9 (32.1, 39.6)	<0.001
24F	80.5 (745/925)	6.3 (55/872)	74.2 (71.1, 77.1)	<0.001
31	76.5 (698/912)	17.9 (171/954)	58.6 (54.8, 62.1)	<0.001
35B	60.0 (550/917)	6.8 (67/988)	53.2 (49.6, 56.6)	<0.001

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

[b] A conclusion of superiority is based on the lower bound of the 95% CI for the difference [V116 - PCV20] between the percentages of participants with a ≥4-fold rise from baseline to 30 days postvaccination being >10 percentage points (one-sided p-value < 0.025).

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

CI=confidence interval; OPA=opsonophagocytic activity; PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adimm]

- V116 in participants 18 to 49 years of age (Cohort 2) met the predefined criteria for immunobridging to V116 in participants 50 to 64 years of age (Cohort 1) for all 21 serotypes (lower bound of the 95% CI of the OPA GMT ratio [V116 18 to 49 Years group/V116 50 to 64 Years group] >0.5) at 30 days postvaccination.

Table 6. Analysis of postvaccination OPA GMTs to compare participants 18-49 years with participants 50-64 years for 21 serotypes in v116 (per-protocol population) (V116-003)

Pneumococcal Serotype	V116 18-49 Years (N = 200)		V116 50-64 Years (N = 589)		GMT Ratio[a] (V116 18-49 Years / V116 50-64 Years) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
3	194	308.6	572	282.7	1.09 (0.90, 1.33)	<0.001
6A	196	5289.6	569	2572.9	2.06 (1.61, 2.62)	<0.001
7F	198	6447.2	571	4278.8	1.51 (1.23, 1.84)	<0.001
8	197	4516.0	571	3004.7	1.50 (1.26, 1.79)	<0.001
9N	197	17283.2	570	8791.4	1.97 (1.59, 2.43)	<0.001
10A	197	6808.1	575	4382.6	1.55 (1.26, 1.92)	<0.001
11A	196	5871.6	564	3785.8	1.55 (1.26, 1.91)	<0.001
12F	196	6150.4	574	3561.2	1.73 (1.37, 2.17)	<0.001
15A	184	11319.2	550	5901.2	1.92 (1.55, 2.37)	<0.001
15C	195	10194.0	570	5708.0	1.79 (1.36, 2.35)	<0.001
16F	193	8877.0	571	5720.0	1.55 (1.26, 1.91)	<0.001
17F	194	16070.6	568	10068.0	1.60 (1.26, 2.02)	<0.001
19A	198	2773.2	574	2374.6	1.17 (0.97, 1.40)	<0.001
20A	197	13150.0	575	7562.7	1.74 (1.39, 2.18)	<0.001
22F	198	9299.6	568	4683.6	1.99 (1.58, 2.49)	<0.001
23A	192	8848.7	561	4739.5	1.87 (1.43, 2.44)	<0.001
23B	198	2140.1	575	1420.9	1.51 (1.11, 2.04)	<0.001
24F	197	4137.6	570	3047.2	1.36 (1.10, 1.67)	<0.001
31	195	8005.6	570	3820.7	2.10 (1.63, 2.69)	<0.001
33F	197	34805.5	570	17607.4	1.98 (1.52, 2.57)	<0.001
35B	198	13933.4	573	9053.9	1.54 (1.26, 1.87)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from an LDA model.

[b] A conclusion of immunobridging is based on the lower bound of the 95% CI for the estimated GMT ratio (V116 18-49 Years/V116 50-64 Years) being > 0.5 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; GMT=geometric mean titer (1/dil); LDA=longitudinal data analysis; OPA=opsonophagocytic activity.

Source: [P003V116: adam-adsl; adimm]

Key Secondary Immunogenicity Endpoints

- In adults ≥50 years of age (Cohort 1) vaccinated with V116, the percentage of participants with a ≥4-fold rise in cross-reactive OPA responses from baseline to 30 days postvaccination was 49.3% (95% CI: 46.0, 52.6) for serotype 6C (cross reactive to serotype 6A) and 64.7% (95% CI: 61.4, 67.8) for serotype 15B (cross reactive to serotype 15C).

- V116 met the predefined criterion for an acceptable antibody response (lower bound of 95% CI of the percentage of participants with a ≥4-fold rise in OPA responses >50%) for serotype 15B; V116 did not meet the predefined criterion for an acceptable antibody response for serotype 6C.

- For serotype 15B (cross reactive to serotype 15C), V116 in participants 18 to 49 years of age (Cohort 2) met the predefined criterion for immunobridging to V116 in participants 50 to 64 years of age (Cohort 1) (lower bound of the 95% CI of the OPA GMT ratio [V116 18 to 49 Years group/V116 50 to 64 Years group] >0.5) at 30 days postvaccination. The immunobridging hypothesis was not tested for serotype 6C (cross reactive to serotype 6A) in accordance with the statistical analysis plan.

- In adults ≥50 years of age (Cohort 1), between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs (Tables 7 and 8)

Table 7. Analysis of postvaccination IgG GMCs for common serotypes (per-protocol population) (Cohort 1) (V116-003)

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMC Ratio[a] (V116 / PCV20) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
3	1166	0.78	1167	0.53	1.47 (1.35, 1.60)
6A	1166	4.30	1167	5.45	0.79 (0.70, 0.89)
7F	1166	6.97	1167	6.57	1.06 (0.95, 1.18)
8	1166	10.02	1167	7.00	1.43 (1.29, 1.59)
10A	1166	11.98	1167	14.66	0.82 (0.72, 0.92)
11A	1166	7.20	1167	5.87	1.23 (1.11, 1.36)
12F	1166	1.73	1167	1.57	1.10 (0.96, 1.26)
19A	1166	8.39	1167	12.02	0.70 (0.63, 0.77)
22F	1166	4.39	1167	5.48	0.80 (0.72, 0.90)
33F	1166	13.81	1167	13.02	1.06 (0.95, 1.18)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adimm]

Table 8. Analysis of postvaccination IgG GMCs for unique serotypes (per-protocol population) (Cohort 1) (V116-003)

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMC Ratio[a] (V116 / PCV20) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
9N	1166	7.72	1167	1.43	5.41 (4.82, 6.06)
15A	1166	13.88	1166	2.04	6.79 (6.03, 7.64)
15C	1166	12.39	1167	5.04	2.46 (2.17, 2.79)
16F	1166	2.86	1167	0.33	8.75 (7.95, 9.64)
17F	1166	14.16	1167	0.84	16.75 (15.25, 18.41)
20A	1166	19.03	1167	1.47	12.92 (11.81, 14.13)
23A	1166	3.78	1167	0.59	6.42 (5.69, 7.24)
23B	1166	5.13	1167	1.58	3.25 (2.91, 3.64)
24F	1166	6.87	1167	0.33	21.08 (18.97, 23.43)
31	1166	3.07	1167	0.27	11.31 (10.36, 12.34)
35B	1166	19.98	1167	1.41	14.13 (12.97, 15.40)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PCV20=pneumococcal 20-valent conjugate vaccine.

Source: [P003V116: adam-adsl; adimm]

GMFRs and 4-fold rises for OPA antibodies for all serotypes in V116-003 Cohort 1 are presented below.

Serotype	**Endpoint**	**V116 (N = 1179)**			**PCV20 (N = 1177)**		
		n	**Observed Response**	**95% CIa**	**n**	**Observed Response**	**95% CI[a]**
Common Serotypes							
3	GMT (Day 1)	1095	22.4	(20.8, 24.2)	1086	22.9	(21.3, 24.7)
	GMT (Day 30)	1025	273.4	(254.3, 293.9)	1012	177.0	(164.0, 191.1)
	GMFR	966	8.4	(7.7, 9.1)	937	5.4	(5.0, 5.8)
	% ≥ 4-fold rise	966	71.3% (689/966)	(68.4, 74.2)	937	59.1% (554/937)	(55.9, 62.3)
6A	GMT (Day 1)	1067	89.7	(80.5, 99.9)	1062	94.5	(84.6, 105.5)
	GMT (Day 30)	1035	2284.8	(2084.2, 2504.6)	1022	2977.7	(2717.4, 3262.9)
	GMFR	954	18.1	(16.2, 20.2)	931	22.6	(20.1, 25.5)
	% ≥ 4-fold rise	954	76.8% (733/954)	(74.0, 79.5)	931	79.9% (744/931)	(77.2, 82.4)
7F	GMT (Day 1)	1088	176.4	(155.9, 199.6)	1089	190.7	(168.7, 215.7)
	GMT (Day 30)	1031	3629.0	(3355.5, 3924.8)	1030	3433.1	(3167.8, 3720.6)
	GMFR	967	16.5	(14.4, 18.8)	961	14.7	(12.9, 16.8)

Serotype	Endpoint	V116 (N = 1179)			PCV20 (N = 1177)		
		n	Observed Response	95% CIa	n	Observed Response	95% CI[a]
	% ≥ 4-fold rise	967	71.0% (687/967)	(68.1, 73.9)	961	65.9% (633/961)	(62.8, 68.9)
8	GMT (Day 1)	1098	93.6	(82.3, 106.5)	1092	105.1	(92.7, 119.2)
	GMT (Day 30)	1056	2482.5	(2318.8, 2657.8)	1037	1826.3	(1692.1, 1971.1)
	GMFR	999	22.0	(19.3, 25.0)	971	14.2	(12.5, 16.2)
	% ≥ 4-fold rise	999	75.8% (757/999)	(73.0, 78.4)	971	67.4% (654/971)	(64.3, 70.3)
10A	GMT (Day 1)	1110	196.1	(170.9, 225.1)	1117	185.8	(162.0, 213.0)
	GMT (Day 30)	1072	3894.2	(3600.3, 4212.1)	1020	4640.2	(4282.5, 5027.8)
	GMFR	1021	16.7	(14.8, 18.9)	978	20.8	(18.3, 23.8)
	% ≥ 4-fold rise	1021	71.9% (734/1021)	(69.0, 74.6)	978	74.1% (725/978)	(71.3, 76.9)
11A	GMT (Day 1)	1056	160.1	(139.5, 183.7)	1060	156.5	(136.9, 178.8)
	GMT (Day 30)	979	3214.3	(2976.3, 3471.4)	979	2084.7	(1928.3, 2253.8)
	GMFR	890	17.4	(15.1, 20.0)	889	11.6	(10.1, 13.3)
	% ≥ 4-fold rise	890	70.0% (623/890)	(66.9, 73.0)	889	61.5% (547/889)	(58.2, 64.7)
12F	GMT (Day 1)	1122	21.4	(19.2, 23.7)	1136	20.6	(18.6, 22.8)
	GMT (Day 30)	1069	2637.7	(2402.0, 2896.6)	1047	2506.3	(2270.3, 2766.7)
	GMFR	1031	77.4	(68.5, 87.4)	1022	73.5	(64.8, 83.4)
	% ≥ 4-fold rise	1031	89.0% (918/1031)	(87.0, 90.9)	1022	87.1% (890/1022)	(84.9, 89.1)
19A	GMT (Day 1)	1124	225.8	(204.0, 249.9)	1122	231.8	(209.7, 256.2)
	GMT (Day 30)	1059	2121.4	(1979.0, 2274.2)	1030	2819.2	(2610.9, 3044.2)
	GMFR	1024	8.6	(7.7, 9.5)	990	11.0	(9.9, 12.2)
	% ≥ 4-fold rise	1024	64.4% (659/1024)	(61.3, 67.3)	990	70.2% (695/990)	(67.2, 73.0)
22F	GMT (Day 1)	1037	165.1	(143.7, 189.7)	1063	150.9	(131.5, 173.3)
	GMT (Day 30)	1046	3880.5	(3570.5, 4217.5)	1026	4768.9	(4368.9, 5205.6)
	GMFR	936	19.1	(16.6, 22.1)	935	25.5	(21.9, 29.8)
	% ≥ 4-fold rise	936	70.5% (660/936)	(67.5, 73.4)	935	74.4% (696/935)	(71.5, 77.2)
33F	GMT (Day 1)	1092	1330.7	(1220.0, 1451.6)	1100	1296.7	(1188.7, 1414.5)
	GMT (Day 30)	999	13506.5	(12235.8, 14909.1)	995	11668.9	(10626.3, 12813.8)
	GMFR	937	9.9	(8.9, 11.1)	938	8.5	(7.6, 9.5)
	% ≥ 4-fold rise	937	67.7% (634/937)	(64.6, 70.7)	938	61.5% (577/938)	(58.3, 64.6)
Unique Serotypes							
9N	GMT (Day 1)	1102	783.3	(711.0, 862.9)	1107	776.2	(705.7, 853.8)
	GMT (Day 30)	965	7451.1	(6915.9, 8027.7)	1021	1632.0	(1504.6, 1770.2)
	GMFR	920	8.9	(8.0, 9.9)	978	2.0	(1.9, 2.2)
	% ≥ 4-fold rise	920	64.7% (595/920)	(61.5, 67.8)	978	19.9% (195/978)	(17.5, 22.6)
15A	GMT (Day 1)	875	535.8	(476.5, 602.4)	918	495.3	(439.8, 557.9)
	GMT (Day 30)	925	5243.1	(4847.7, 5670.8)	890	1584.5	(1427.0, 1759.3)
	GMFR	693	9.4	(8.2, 10.8)	706	3.1	(2.7, 3.5)
	% ≥ 4-fold rise	693	66.7% (462/693)	(63.0, 70.2)	706	35.8% (253/706)	(32.3, 39.5)

Serotype	Endpoint	V116 (N = 1179)			PCV20 (N = 1177)		
		n	Observed Response	95% CIa	n	Observed Response	95% CI[a]
15C	GMT (Day 1)	1118	80.9	(71.9, 91.0)	1112	76.1	(67.6, 85.7)
	GMT (Day 30)	987	4224.8	(3822.4, 4669.6)	983	2038.8	(1829.2, 2272.4)
	GMFR	952	38.0	(33.3, 43.3)	937	20.3	(17.8, 23.1)
	% ≥ 4-fold rise	952	83.4% (794/952)	(80.9, 85.7)	937	74.2% (695/937)	(71.2, 76.9)
16F	GMT (Day 1)	1080	423.4	(388.4, 461.5)	1096	401.2	(368.2, 437.2)
	GMT (Day 30)	981	4821.6	(4466.0, 5205.5)	1018	843.6	(768.9, 925.5)
	GMFR	910	9.5	(8.7, 10.4)	961	1.9	(1.7, 2.0)
	% ≥ 4-fold rise	910	71.9% (654/910)	(68.8, 74.8)	961	20.8% (200/961)	(18.3, 23.5)
17F	GMT (Day 1)	1078	400.7	(357.1, 449.5)	1094	374.7	(334.2, 420.1)
	GMT (Day 30)	932	7820.2	(7208.1, 8484.3)	1014	453.9	(403.1, 511.1)
	GMFR	862	17.3	(15.3, 19.7)	952	1.2	(1.1, 1.3)
	% ≥ 4-fold rise	862	75.8% (653/862)	(72.7, 78.6)	952	9.5% (90/952)	(7.7, 11.5)
20A	GMT (Day 1)	1129	563.4	(510.5, 621.8)	1120	540.2	(489.3, 596.5)
	GMT (Day 30)	1035	6128.5	(5647.7, 6650.1)	1046	623.7	(565.6, 687.7)
	GMFR	1003	10.3	(9.2, 11.4)	1011	1.2	(1.1, 1.2)
	% ≥ 4-fold rise	1003	67.3% (675/1003)	(64.3, 70.2)	1011	9.6% (97/1011)	(7.8, 11.6)
23A	GMT (Day 1)	917	130.1	(113.5, 149.1)	935	126.3	(110.3, 144.8)
	GMT (Day 30)	973	3728.4	(3364.6, 4131.6)	903	470.7	(405.1, 546.9)
	GMFR	758	21.8	(19.0, 25.0)	734	3.1	(2.7, 3.6)
	% ≥ 4-fold rise	758	78.9% (598/758)	(75.8, 81.7)	734	36.8% (270/734)	(33.3, 40.4)
23B	GMT (Day 1)	1125	13.8	(12.5, 15.3)	1131	13.3	(12.1, 14.7)
	GMT (Day 30)	1056	1077.7	(960.0, 1209.8)	1050	106.3	(92.1, 122.8)
	GMFR	1021	51.4	(45.3, 58.2)	1021	6.1	(5.4, 6.9)
	% ≥ 4-fold rise	1021	85.5% (873/1021)	(83.2, 87.6)	1021	49.6% (506/1021)	(46.4, 52.7)
24F	GMT (Day 1)	1046	66.3	(58.2, 75.6)	1041	66.9	(58.7, 76.4)
	GMT (Day 30)	1032	2750.3	(2521.4, 2999.9)	961	72.9	(63.2, 84.0)
	GMFR	925	29.0	(25.6, 32.8)	872	1.1	(1.0, 1.1)
	% ≥ 4-fold rise	925	80.5% (745/925)	(77.8, 83.0)	872	6.3% (55/872)	(4.8, 8.1)
31	GMT (Day 1)	1085	88.3	(77.5, 100.6)	1091	90.5	(79.4, 103.0)
	GMT (Day 30)	980	3041.1	(2762.1, 3348.2)	1017	146.8	(127.9, 168.4)
	GMFR	912	28.7	(24.9, 33.1)	954	1.5	(1.4, 1.7)
	% ≥ 4-fold rise	912	76.5% (698/912)	(73.6, 79.3)	954	17.9% (171/954)	(15.5, 20.5)
35B	GMT (Day 1)	1096	1155.2	(1057.7, 1261.7)	1118	1226.2	(1130.2, 1330.4)
	GMT (Day 30)	974	8351.9	(7780.3, 8965.5)	1029	1400.3	(1286.5, 1524.2)
	GMFR	917	7.2	(6.5, 7.9)	988	1.2	(1.1, 1.2)
	% ≥ 4-fold rise	917	60.0% (550/917)	(56.7, 63.2)	988	6.8% (67/988)	(5.3, 8.5)

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

Serotype	Endpoint	V116 (N = 1179)			PCV20 (N = 1177)		
		n	Observed Response	95% CIa	n	Observed Response	95% CI[a]

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Day 1 is prevaccination, and Day 30 is 30 days following vaccination.
GMFR and % ≥4-fold rise are calculated Israel, New Zealand, South Korea, Spain, Taiwan, Türkiye, and United Kingdom.

Day 1 to Day 30.
CI=confidence interval; GMFR=geometric mean fold-rise; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV20=pneumococcal 20-valent conjugate vaccine.

Summary of main efficacy results from V116-003

Title: A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults		
Study identifier	Protocol Number: V116-003 IND: 19316 EudraCT: 2022-000258-27 NCT: NCT05425732	
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	10 months not applicable not applicable
Hypothesis	Superiority and noninferiority	
Treatment groups	V116 (Cohort 1)	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=1181
	PCV20 (Cohort 1)	Single IM dose of PCV20 on Day 1 (Visit 1) Randomized N=1181
	V116 (Cohort 2)	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=201
	PCV20 (Cohort 2)	Single IM dose of PCV20 on Day 1 (Visit 1) Randomized N=100
Endpoints and definitions	Primary endpoint (Cohort 1): OPA GMTs for common serotypes	To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 versus PCV20 for the common serotypes in V116 and PCV20
	Primary endpoint (Cohort 1): OPA GMTs for unique serotypes	To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 versus PCV20 for the unique serotypes in V116
	Primary endpoint (Cohort 1): ≥4-fold rise in OPA responses	To compare the proportions of participants with a ≥4-fold rise in serotypes-specific OPA responses form baseline to 30 days postvaccination with V116 versus PCV20 for the unique serotypes in V116
	Primary endpoint (Cohort 2): OPA GMTs	To compare the serotype-specific OPA GMTs in adults 18 to 49 years of age from Cohort 2 to adults 50 to 64 years of age from Cohort 1 at 30 days postvaccination with V116
	Secondary endpoint (Cohort 1 and 2): ≥4-fold rise in cross-reactive OPA responses	To evaluate serotype-specific cross-reactive OPA responses at 30 days postvaccination in adults ≥50 years of age from Cohort 1 and adults 18

		to 49 years of age from Cohort 2 for serotypes within a serogroup	
	Secondary endpoint (Cohort 1 and 2): cross-reactive OPA GMTs	To evaluate serotype-specific cross-reactive OPA responses at 30 days postvaccination in adults 18 to 49 years from Cohort 2 to V116 in participants 50 to 64 years of age from Cohort 1 as assessed by serotype-specific cross-reactive OPA GMTs at 30 days postvaccination	
	Secondary endpoints (Cohort 1): serotype-specific IgG GMCs	To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V116 compared with PCV20	
Database lock	22-JUN-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination Within both cohorts, the majority of randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint (>97%) and for both Day 1 and Day 30 timepoints (>89%).		
Descriptive statistics and estimate variability	**Primary Endpoint (Cohort 1): OPA GMTs for common serotypes**		
	Intervention group	V116 (Cohort 1)	PCV20 (Cohort 1)
	Number of participants	Table 3 Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population) (Cohort 1)	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (V116/PCV20)	Table 3 Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population) (Cohort 1)	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>0.50 for all common serotypes	
	One-sided p-value	$p<0.001$ for all common serotypes	
Analysis description	**Primary Endpoint (Cohort 1): OPA GMTs for unique serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116 (Cohort 1)	PCV20 (Cohort 1)
	Number of participants	Table 4 Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population) (Cohort 1)	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (V116/PCV20)	Table 4 Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population) (Cohort 1)	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>2.0 for all unique serotypes (except for 15C, which was 1.77)	
	One-sided p-value	$p<0.001$ for all unique serotypes (except for 15C; $p=0.406$)	
Analysis description	**Primary Endpoint (Cohort 1): ≥4-fold rise in OPA responses for unique serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116 (Cohort 1)	PCV20 (Cohort 1)
	Number of participants	Table 5 Analysis of the Proportions of Participants With a ≥4-Fold Rise in OPA Responses for Unique Serotypes (Per-Protocol Population)	
	Proportion of participants with a ≥4-fold rise in serotype-specific OPA responses		

Effect estimate per comparison	Difference (V116-PCV20) between the percentages of participants with a ≥4-fold rise	Table 5 Analysis of the Proportions of Participants With a ≥4-Fold Rise in OPA Responses for Unique Serotypes (Per-Protocol Population)	
	95% CI		
	Lower bound of the 95% CI for the difference [V116 - PCV20] between the percentages of participants with a ≥4-fold rise	>10 percentage points for all serotypes (except for 15C, which was 5.6)	
	One-sided p-value	$p<0.001$ for all unique serotypes (except for 15C; $p=0.665$)	
Analysis description	**Primary Endpoint (Cohort 2): OPA GMTs**		
Descriptive statistics and estimate variability	Intervention group	V116 (ages 50-64 from Cohort 1)	V116 (Cohort 2)
	Number of participants	Table 6 Analysis of Postvaccination OPA GMTs to Compare Participants 18-49 Years with Participants 50-64 Years for 21 Serotypes in V116 (Per-Protocol Population)	
	Serotype-specific OPA GMT		
Effect estimate per comparison	OPA GMT ratio (V116 (Cohort 2)/V116 (ages 50-64 from Cohort 1))	Table 6 Analysis of Postvaccination OPA GMTs to Compare Participants 18-49 Years with Participants 50-64 Years for 21 Serotypes in V116 (Per-Protocol Population),	
	95% CI		
	Lower bound of the 95% CI of the OPA GMT ratio (Cohort 2)/V116 (ages 50-64 from Cohort 1)	>0.5 for all serotypes	
	One-sided p-value	$p<0.001$ for all serotypes	
Analysis description	**Secondary Endpoint (Cohort 1): ≥4-fold rise in cross-reactive OPA responses**		
Descriptive statistics and estimate variability	Intervention group	V116 (Cohort 1)	
	Number of participants	Serotype 6C: n=912 Serotype 15B: n=883	
	Proportions of participants in V116 with a ≥4-fold rise in OPA responses for serotypes 6C and 15B	Serotype 6C: 49.3% Serotype 15B: 64.7%	
Effect estimate per comparison	95% CI	Serotype 6C: (46.0, 52.6) Serotype 15B: (61.4, 67.8)	
	Lower bound of the 95% CI of the proportion of participants with a ≥4-fold rise	Serotype 6C: 46.0 Serotype 15B: >50.	
	One-sided p-value	Serotype 6C: 0.667 Serotype 15B: <0.001.	
Analysis description	**Secondary Endpoint (Cohort 1 and 2): Cross-reactive OPA GMTs**		
Descriptive statistics and estimate variability	Intervention group	V116 (ages 50-64 from Cohort 1)	V116 (Cohort 2)
	Number of participants	Serotype 6C: n=570 Serotype 15B: n=566	Serotype 6C: n=194 Serotype 15B: n=192
	Serotype-specific OPA GMT	Serotype 6C: 1254.7 Serotype 15B: 5438.9	Serotype 6C: 2577.2 Serotype 15B: 10976.7

Effect estimate per comparison	OPA GMT ratio (V116 (Cohort 2)/V116 (ages 50-64 from Cohort 1))	Serotype 6C: 2.05 Serotype 15B: 2.02	
	95% CI	Serotype 6C: (1.52, 2.77) Serotype 15B: (1.57, 2.60)	
	Lower bound Lower bound of the 95% CI of the OPA GMT ratio (Cohort 2)/V116 (ages 50-64 from Cohort 1)	Serotype 6C: >0.5 Serotype 15B: >0.5	
	One-sided p-value	Serotype 6C: NT Serotype 15B: <0.001.	
Analysis description	**Secondary Endpoint (Cohort 1): Serotype-specific IgG GMCs**		
Descriptive statistics and estimate variability	Intervention group	V116 (Cohort 1)	PCV20 (Cohort 1)
	Number of participants	Table 7 Analysis of Postvaccination IgG GMCs for Common Serotypes (Per-Protocol Population) (Cohort 1)	
	Serotype-specific IgG GMC		
Effect estimate per comparison	Serotype-specific IgG GMC ratio (V116/PCV20)	Table 8 Analysis of Postvaccination IgG GMCs for Unique Serotypes ,(Per-Protocol Population) (Cohort 1)	
	95% CI		

V116-010

A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 50 Years of Age or Older

Methods

Design	Number of Participants by Intervention Group[a]	Study Population	Primary Endpoint(s)
Double-blind, randomized, active-comparator study to evaluate the safety, tolerability, and immunogenicity of V116	Randomization ratio V116:PPSV23 = 1:1 V116: 741 randomized 739 vaccinated 733 completed PPSV23: 743 randomized 741 vaccinated 735 completed	Pneumococcal vaccine-naïve adults ≥50 years of age Sex: 663 M/817 F Median age: 65.0 years *Stratification factor:* Age: 50 to 64 years: 684 65 to 74 years: 654 ≥75 years: 142	• Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs • Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116 • Proportion of participants who achieve a ≥4-fold rise (baseline to 30 days postvaccination) in OPA responses for the serotypes unique to V116

Study participants

Pneumococcal vaccine-naïve adults ≥50 years old.

Clinical investigator study sites were located in 11 countries: Argentina, Australia, Colombia, Germany, Israel, New Zealand, South Korea, Spain, Taiwan, Türkiye, and United Kingdom.

Treatments

One intramuscular injection with standard dose of 0.5 ml V116 or PPSV23.

Objectives and outcomes/endpoints

Primary immunogenicity objectives and endpoints
Objective: To compare the serotype specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V116 versus PPSV23 **Hypothesis (H1)**: V116 is noninferior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 12 common serotypes in V116 and PPSV23. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [V116/ PPSV23] to be >0.5.) **Hypothesis (H2)**: V116 is superior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 9 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/ PPSV23] to be >2.0.) **Endpoint:** Serotype-specific OPA responses
Objective: To compare the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination with V116 versus PPSV23 for the unique serotypes in V116. **Hypothesis (H3):** V116 is superior to PPSV23 as assessed by the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination for the 9 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the differences [V116 – PPSV23] between the proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination to be >0.1.). **Endpoint:** Serotype-specific OPA responses.
Secondary Objectives
Objective: To evaluate serotype-specific cross-reactive OPA responses from baseline to 30 days postvaccination with V116 for serotypes within a serogroup. **Hypothesis (H4):** V116 induces an acceptable antibody response as assessed by the proportions of participants with a ≥4-fold rise in serotype-specific cross-reactive OPA responses from baseline to 30 days postvaccination for serotypes within a serogroup in V116. (The statistical criterion for an acceptable antibody response requires the lower bound of the 95% CI of proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for V116 to be >0.5.) **Endpoint:** Serotype-specific OPA responses.
Objective: To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V116 compared with PPSV23. **Endpoint:** Serotype-specific IgG responses.
Objective: To evaluate the serotype-specific geometric mean fold rise (GMFR) and proportions of

participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination with V116 and separately for PPSV23. **Endpoint:** Serotype-specific OPA and IgG responses.
Tertiary/Exploratory Objectives
Objective: To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination. **Endpoint:** Serotype-specific OPA and IgG responses

Sample size

The planned enrollment total was 1400 participants. This study aimed to randomize approximately 700 participants into the V116 group and 700 participants into the PPSV23 group. The overall power for all the primary hypotheses is >90% at an overall 1-sided 2.5% alpha-level.

Randomisation and blinding (masking)

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive either V116 or PPSV23. Intervention randomization in the overall study will be stratified according to participant age at time of randomization (50 to 64 vs. 65 to 74 vs. ≥75 years of age); at least 50% of participants will be ≥65 years of age.

A double-blinding technique will be used. V116 and PPSV23 will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel.

The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the clinical evaluation of the participants are unaware of the intervention assignment.

Because V116 and PPSV23 have a different appearance, the unblinded pharmacist (or qualified study-site personnel) will be responsible for receiving, maintaining, preparing and/or dispensing, and administering these study vaccines. Blinded site personnel will be responsible for all other study procedures/ assessment. An unblinded Clinical Research Associate will monitor vaccine accountability at the study site. All Sponsor personnel or delegate(s) directly involved with the conduct of this study will remain blinded to the participant-level intervention assignment until all participants have completed the Month 6 visit. The participant and investigator will remain blinded to the participant-level intervention assignment throughout the duration of the study.

Statistical methods

Table 9. Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs at 30 days postvaccination for the 21 serotypes in V116	P	cLDA[b] (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
Proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for OPA responses for the unique serotypes in V116	P	Stratified M&N[c] (estimate, 95% CI, p-values)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
Proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for OPA responses for the cross-reactive serotypes	P	Clopper-Pearson (estimate, 95% CI, p-values)	PP	Missing data will not be imputed
IgG GMCs at 30 days postvaccination for the 21 serotypes in V116	P	cLDA[b] (estimate, 95% CI)	PP	Model-based
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for both OPA and IgG responses for the 21 serotypes in V116	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI=confidence interval; cLDA=constrained longitudinal data analysis; FAS=full analysis set; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titer; IgG=immunoglobulin G; M&N=Miettinen and Nurminen; OPA=opsonophagocytic activity; PP=per-protocol.

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

[b] cLDA model with terms for vaccination group, time, the interaction of time-by-vaccination, age stratum (ie, 50 to 64 years, 65 to 74 years, and ≥75 years), and interaction of time-by-age stratum.

[c] Stratified analysis using the M&N method [Miettinen, O. and Nurminen, M. 1985] with stratification by the participant's age at the time of randomization (50 to 64 years of age, 65 to 74 years of age, and ≥75 years of age).

Baseline is the day of vaccination (Day 1); 30 days postvaccination is the day of the Visit 3 blood draw (Day 30).

Multiplicity

The study will be considered to have met its primary immunogenicity objectives if noninferiority is demonstrated with respect to OPA GMTs for the 12 common serotypes, and superiority is demonstrated with respect to both OPA GMTs and the proportions of participants with ≥4-fold rises in OPA responses for the 9 unique serotypes in V116. Since comparisons are made individually for each of the 21 serotypes, this approach controls the 1-sided type-I error rate at 0.025, and no multiplicity adjustment is required.

The secondary hypothesis (H4) will be used to assess the cross-reactive antibody responses induced by V116 for serotypes within a serogroup in V116. Each cross-reactive serotype will be tested for the

acceptability of cross-reactive antibody responses induced by V116 at a 1-sided 0.025 alpha-level. If 1 cross-reactive serotype succeeds but the other cross-reactive serotype fails on the prespecified statistical criteria, the study will be considered to have met the secondary acceptability objective for the successful cross-reactive serotype. The 1-sided type-I error rate within each cross-reactive serotype will be controlled at 0.025.

Results

Participant flow

As of the database lock, 1484 participants were randomized (741 in the V116 group and 743 in the PPSV23 group). Of the 1484 randomized participants, 1480 were vaccinated, and 1468 (98.9%) completed the base study. The majority of randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint.

Table 10. Disposition of participants (all randomized participants)

	V116		PPSV23		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	741		743		1,484	
Vaccinated at Visit 1						
V116	739	(99.7)	0	(0.0)	739	(49.8)
PPSV23	0	(0.0)	741	(99.7)	741	(49.9)
Trial Disposition						
Completed	733	(98.9)	735	(98.9)	1,468	(98.9)
Discontinued	8	(1.1)	8	(1.1)	16	(1.1)
Lost To Follow-Up	3	(0.4)	4	(0.5)	7	(0.5)
Protocol Deviation	1	(0.1)	2	(0.3)	3	(0.2)
Withdrawal By Subject	4	(0.5)	2	(0.3)	6	(0.4)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P010V116: adam-adsl; adex]

Recruitment

Study is on-going.

First Participant First Visit	07-NOV-2022
Last Participant Last Visit	27-SEP-2023
Last Data Available	30-OCT-2023
Database Lock Date	31-OCT-2023

Conduct of the study

The study protocol was amended once to update the superiority success criterion for serotype 15C. Important protocol deviations were reported for 91 (6.1%) participants. Of these, 67 participants had important protocol deviations that were considered to be clinically important.

The most frequently reported clinically important protocol deviations were due to immunogenicity blood sample not drawn or sample could not be tested due to an error by the site in processing and/or handling of the sample (n=19) and immunogenicity blood sample drawn outside the protocol-defined window (n=17). The protocol deviations were comparably distributed between intervention groups.

Baseline data

Among the vaccinated participants (n=1480):

• Overall Median Age (Range): 65.0 years (50 to 90 years).

• Sex: 663 (44.8%) male, 817 (55.2%) female.

• Ethnicity: 1147 (77.5%) not Hispanic or Latino, 312 (21.1%) Hispanic or Latino, 16 (1.1%) not reported, 5 (0.3%) unknown.

• Race: 9 (0.6%) American Indian or Alaska Native, 291 (19.7%) Asian, 4 (0.3%) Black or African American, 243 (16.4%) Multiple, 12 (0.8%) Native Hawaiian or Other Pacific Islander, 920 (62.2%) White, 1 (0.1%) missing.

Demographics and baseline characteristics were generally comparable between intervention groups.

Numbers analysed

• V116 group: 741 randomized, 739 vaccinated, 733 completed the base study, 8 discontinued

• PPSV23 group: 743 randomized, 741 vaccinated, 735 completed the base study, 8 discontinued

Outcomes and estimation

Primary Immunogenicity Endpoints

The studies will only have met the primary objectives in case non-inferiority is shown with respect to the OPA GMTs for the common serotypes, and superiority with respect to both OPA GMTs and the proportions of participants with ≥4-fold rises in OPA responses for the unique serotypes. As not all 3 primary objectives were met, no type I error controlled claim regarding statistical non-inferiority or superiority can be made.

• V116 met the predefined criterion for noninferiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >0.5) for each of the 12 common serotypes at 30 days postvaccination

Table 11. Analysis of postvaccination OPA GMTs for common serotypes (per-protocol population) (V116-010)

Pneumococcal Serotype	V116 (N = 739)		PPSV23 (N = 741)		GMT Ratio[a] (V116 / PPSV23) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
3	725	230.4	729	211.5	1.09 (0.96, 1.23)	<0.001
7F	729	4876.7	732	3314.6	1.47 (1.29, 1.68)	<0.001
8	730	3379.6	733	2882.1	1.17 (1.04, 1.32)	<0.001
9N	728	7346.6	729	6545.9	1.12 (1.00, 1.26)	<0.001
10A	725	4382.9	726	2818.7	1.55 (1.37, 1.77)	<0.001
11A	728	3711.1	729	1809.7	2.05 (1.82, 2.31)	<0.001

12F	728	3031.8	732	1854.9	1.63 (1.40, 1.90)	<0.001
17F	722	8215.7	730	4060.5	2.02 (1.77, 2.31)	<0.001
19A	731	2670.0	732	1879.9	1.42 (1.26, 1.60)	<0.001
20A	730	6966.1	733	4208.4	1.66 (1.46, 1.88)	<0.001
22F	725	4724.1	728	3084.9	1.53 (1.34, 1.75)	<0.001
33F	727	15497.3	731	17483.0	0.89 (0.76, 1.04)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of non-inferiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/PPSV23) being > 0.5 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titers (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P010V116: adam-adsl; adimm]

- V116 met the predefined criterion for superiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >2.0) for each of the 9 serotypes unique to V116 at 30 days postvaccination

Table 12. Analysis of postvaccination OPA GMTs for unique serotypes (per-protocol population) (V116-010)

Pneumococcal Serotype	V116 (N = 739)		PPSV23 (N = 741)		GMT Ratio[a] (V116 / PPSV23) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
6A	729	3193.9	730	964.0	3.31 (2.84, 3.87)	<0.001
15A	715	6746.5	703	1462.1	4.61 (3.99, 5.33)	<0.001
15C	729	7604.8	730	2605.0	2.92 (2.50, 3.42)	<0.001
16F	726	6675.4	723	1482.2	4.50 (3.99, 5.09)	<0.001
23A	711	4804.2	690	837.2	5.74 (4.81, 6.85)	<0.001
23B	730	2252.6	726	137.2	16.42 (13.46, 20.03)	<0.001
24F	723	4568.0	705	1346.7	3.39 (2.97, 3.87)	<0.001
31	730	5040.7	731	423.9	11.89 (10.16, 13.91)	<0.001
35B	728	10707.5	732	1735.0	6.17 (5.54, 6.87)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of superiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/PPSV23) being > 2.0 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titers (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent

(23-valent).

Source: [P010V116: adam-adsl; adimm]

- V116 met the predefined criteria for superiority to PPSV23 (lower bound of 95% CI of the differences [V116 – PPSV23] >0.1 [10 percentage points]) for 8 of 9 serotypes unique to V116 based on the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. V116 did not meet the predefined criterion for superiority to PPSV23 for serotype 15C (lower bound of the 95% CI of the percentage point difference [V116 – PPSV23] was 7.5 percentage points)

Table 13. Analysis of the proportions of participants with a ⩾4-fold rise in OPA responses for unique serotypes (per-protocol population) (V116-010)

Pneumococcal Serotype	V116 (N=739)	PPSV23 (N=741)	Percentage Point Difference (V116 - PPSV23)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)[ab]	p-Value[ab] (1-sided)
6A	79.1 (495/626)	53.0 (332/626)	26.0 (20.9, 31.0)	<0.001
15A	69.7 (364/522)	30.3 (159/524)	39.4 (33.6, 44.8)	<0.001
15C	87.9 (551/627)	76.2 (483/634)	11.7 (7.5, 15.9)	0.214
16F	63.2 (382/604)	20.3 (125/616)	42.9 (37.8, 47.8)	<0.001
23A	70.6 (336/476)	34.7 (148/426)	35.9 (29.6, 41.8)	<0.001
23B	86.6 (562/649)	44.1 (279/632)	42.4 (37.6, 47.0)	<0.001
24F	50.5 (278/551)	14.6 (74/507)	35.9 (30.6, 41.0)	<0.001
31	74.4 (487/655)	18.3 (119/652)	56.2 (51.5, 60.5)	<0.001
35B	63.8 (421/660)	5.2 (35/678)	58.7 (54.6, 62.7)	<0.001

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

[b] A conclusion of superiority is based on the lower bound of the 95% CI for the difference [V116 - PPSV23] between the percentages of participants with a ≥4-fold rise from baseline to 30 days postvaccination being >10 percentage points (1-sided p-value < 0.025).

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

CI=confidence interval; OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P010V116: adam-adsl; adimm]

Key Secondary Immunogenicity Endpoints

- Among participants vaccinated with V116, the percentage of participants with a ≥4-fold rise in cross-reactive OPA responses from baseline to 30 days postvaccination was 52.7% (95% CI: 48.7, 56.7) for serotype 6C (cross-reactive to serotype 6A) and 72.6% (95% CI: 68.8, 76.2) for serotype 15B (cross-reactive to serotype 15C).

- V116 met the predefined criterion for an acceptable antibody response (lower bound of the 95% CI of the percentage of participants with a ≥4-fold rise in OPA responses >50%) for serotype 15B; V116 did not meet the predefined criterion for an acceptable antibody response for serotype 6C.
- Between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs.

Table 14. Analysis of postvaccination IgG GMCs for common serotypes (per-protocol population) (V116-010)

Pneumococcal Serotype	V116 (N = 739)		PPSV23 (N = 741)		GMC Ratio[a] (V116 / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
3	731	0.79	734	0.69	1.14 (1.04, 1.25)
7F	731	9.35	734	5.02	1.86 (1.65, 2.10)
8	731	13.83	734	11.85	1.17 (1.04, 1.31)
9N	731	11.21	734	7.23	1.55 (1.37, 1.76)
10A	731	15.05	734	7.41	2.03 (1.79, 2.31)
11A	731	8.83	734	4.01	2.20 (1.97, 2.46)
12F	731	2.28	734	1.14	1.99 (1.72, 2.30)
17F	731	16.39	734	6.85	2.39 (2.12, 2.70)
19A	731	9.54	734	6.42	1.49 (1.32, 1.67)
20A	731	22.97	734	12.32	1.86 (1.65, 2.10)
22F	731	5.32	734	3.00	1.77 (1.55, 2.02)
33F	731	19.12	734	15.70	1.22 (1.08, 1.37)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P010V116: adam-adsl; adimm]

Table 15. Analysis of postvaccination IgG GMCs for unique serotypes (per-protocol population) (V116-010)

Pneumococcal Serotype	V116 (N = 739)		PPSV23 (N = 741)		GMC Ratio[a] (V116 / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
6A	731	5.79	734	1.53	3.78 (3.29, 4.35)
15A	731	17.98	734	2.01	8.92 (7.89, 10.09)

15C	731	19.27	734	5.61	3.43 (3.01, 3.92)
16F	731	3.48	734	0.35	9.84 (8.83, 10.97)
23A	731	4.21	734	0.56	7.59 (6.68, 8.61)
23B	731	5.74	734	1.20	4.79 (4.26, 5.38)
24F	731	8.52	734	0.40	21.19 (18.98, 23.65)
31	731	3.48	734	0.40	8.69 (7.82, 9.65)
35B	731	22.26	734	1.43	15.53 (14.13, 17.07)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P010V116: adam-adsl; adimm]

GMFRs and 4-fold rises for OPA antibodies for all serotypes in V116-010 Per-Protocol Population are presented below.

Serotype	**Endpoint**	**V116 (N = 739)**			**PPSV23 (N = 741)**		
		n	**Observed Response**	**95% CIa**	**n**	**Observed Response**	**95% CI[a]**
Common Serotypes							
3	GMT (Day 1)	676	20.7	(19.0, 22.7)	664	21.4	(19.5, 23.6)
	GMT (Day 30)	644	229.8	(210.6, 250.7)	651	213.0	(193.9, 234.0)
	GMFR	595	7.5	(6.8, 8.3)	586	6.8	(6.2, 7.5)
	% ≥ 4-fold rise	595	69.2% (412/595)	(65.4, 72.9)	586	66.9% (392/586)	(62.9, 70.7)
7F	GMT (Day 1)	694	223.7	(191.9, 260.7)	686	194.3	(165.9, 227.6)
	GMT (Day 30)	676	4959.3	(4554.4, 5400.1)	694	3268.2	(2935.4, 3638.6)
	GMFR	641	18.3	(15.8, 21.1)	648	14.0	(12.2, 16.1)
	% ≥ 4-fold rise	641	75.2% (482/641)	(71.7, 78.5)	648	69.9% (453/648)	(66.2, 73.4)
8	GMT (Day 1)	696	79.8	(68.5, 92.9)	699	83.5	(72.1, 96.7)
	GMT (Day 30)	697	3375.3	(3106.6, 3667.2)	705	2880.1	(2639.9, 3142.2)
	GMFR	663	34.3	(29.6, 39.8)	671	28.8	(25.1, 33.0)
	% ≥ 4-fold rise	663	83.6% (554/663)	(80.5, 86.3)	671	85.4% (573/671)	(82.5, 88.0)
9N	GMT (Day 1)	683	596.1	(528.3, 672.6)	675	520.3	(459.9, 588.8)
	GMT (Day 30)	656	7447.1	(6856.6, 8088.5)	656	6425.2	(5872.9, 7029.5)
	GMFR	611	11.3	(10.0, 12.8)	602	11.4	(10.1, 12.8)_
	% ≥ 4-fold rise	611	72.3% (442/611)	(68.6, 75.9)	602	73.3% (441/602)	(69.5, 76>8)
10A	GMT (Day 1)	668	235.0	(199.4, 277.0)	655	231.6	(196.7, 272.8)
	GMT (Day 30)	678	4394.3	(4024.4, 4798.3)	689	2817.5	(2521.6, 3148.1)
	GMFR	621	16.6	(14.3, 19.1)	618	10.9	(9.5, 12.4)
	% ≥ 4-fold rise	621	74.7% (464/621)	(71.1, 78.1)	618	66.5% (411/618)	(62.6, 70.2)
11A	GMT (Day 1)	679	171.7	(144.8, 203.6)	682	158.9	(133.8, 188.7)
	GMT (Day 30)	679	3733.9	(3455.3, 4034.8)	690	1810.7	(1645.8, 1992.3)
	GMFR	630	18.5	(15.7, 21.7)	643	9.2	(7.9, 10.8)
	% ≥ 4-fold rise	630	72.1% (454/630)	(68.4, 75.5)	643	58.8% (378/643)	(54.9, 62.6)
12F	GMT (Day 1)	703	19.9	(17.6, 22.6)	705	18.8	(16.7, 21.2)
	GMT (Day 30)	692	3093.5	(2819.7, 3393.9)	696	1846.1	(1622.5, 2100.5)
	GMFR	667	89.2	(78.1, 101.8)	669	58.1	(50.5, 66.8)
	% ≥ 4-fold rise	667	93.3% (622/667)	(91.1, 95.0)	669	90.7% (607/669)	(88.3, 92.8)
17F	GMT (Day 1)	675	293.1	(254.3, 337.7)	657	260.3	(225.9, 299.9)
	GMT (Day 30)	639	8221.7	(7524.7, 8983.2)	682	4026.4	(3633.6, 4461.8)
	GMFR	592	25.2	(21.7, 29.3)	609	12.9	(11.3, 14.8)
	% ≥ 4-fold rise	592	84.1% (498/592)	(80.9, 87.0)	609	71.8% (437/609)	(68.0, 75.3)

Serotype	Endpoint	V116 (N = 739)			PPSV23 (N = 741)		
		n	Observed Response	95% CIa	n	Observed Response	95% CI[a]
19A	GMT (Day 1)	710	233.5	(207.0, 263.4)	709	240.7	(214.2, 270.4)
	GMT (Day 30)	695	2672.5	(2461.4, 2901.7)	705	1883.6	(1707.0, 2078.4)
	GMFR	674	10.2	(9.1, 11.4)	682	7.2	(6.5, 8.0)
	% ≥ 4-fold rise	674	70.9% (478/674)	(67.3, 74.3)	682	64.1% (437/682)	(60.3, 67.7)
20A	GMT (Day 1)	717	617.5	(551.6, 691.2)	711	600.5	(535.7, 673.1)
	GMT (Day 30)	693	6954.8	(6362.8, 7601.9)	702	4185.0	(3761.2, 4656.4)
	GMFR	680	10.9	(9.7, 12.2)	680	6.6	(5.9, 7.3)
	% ≥ 4-fold rise	680	71.0% (483/680)	(67.5, 74.4)	680	58.1% (395/680)	(54.3, 61.8)
22F	GMT (Day 1)	655	195.2	(165.3, 230.6)	654	202.4	(171.1, 239.4)
	GMT (Day 30)	673	4717.8	(4320.4, 5151.9)	690	3108.6	(2788.6, 3465.2)
	GMFR	603	20.5	(17.4, 24.1)	616	12.3	(10.5, 14.3)
	% ≥ 4-fold rise	603	76.5% (461/603)	(72.9, 79.8)	616	67.2% (414/616)	(63.3, 70.9)
33F	GMT (Day 1)	699	1771.2	(1611.2, 1947.0)	688	1764.2	(1601.3, 1943.6)
	GMT (Day 30)	625	15753.2	(14065.5, 17643.5)	647	17162.5	(15164.9, 19423.3)
	GMFR	597	8.8	(7.8, 10.0)	604	10.2	(9.0, 11.6)
	% ≥ 4-fold rise	597	66.2% (395/597)	(62.2, 70.0)	604	70.9% (428/604)	(67.1, 74.5)
Unique Serotypes							
6A	GMT (Day 1)	664	123.0	(106.5, 142.1)	674	134.8	(116.6, 156.0)
	GMT (Day 30)	691	3177.2	(2874.3, 3512.1)	682	991.6	(866.9, 1134.2)
	GMFR	626	19.5	(16.9, 22.4)	626	5.5	(4.8, 6.3)
	% ≥ 4-fold rise	626	79.1% (495/626)	(75.7, 82.2)	626	53.0% (332/626)	(49.0, 57.0)
15A	GMT (Day 1)	624	621.9	(546.2, 708.1)	610	619.7	(548.8, 699.6)
	GMT (Day 30)	613	6731.5	(6121.8, 7401.9)	617	1478.5	(1314.6, 1662.8)
	GMFR	522	10.4	(9.0, 12.1)	524	2.4	(2.1, 2.7)
	% ≥ 4-fold rise	522	69.7% (364/522)	(65.6, 73.6)	524	30.3% (159/524)	(26.4, 34.5)
15C	GMT (Day 1)	676	122.0	(104.4, 142.6)	672	111.2	(95.4, 129.6)
	GMT (Day 30)	680	7697.9	(6880.3, 8612.8)	692	2592.9	(2285.7, 2941.4)
	GMFR	627	49.4	(42.4, 57.6)	634	17.3	(15.1, 19.8)
	% ≥ 4-fold rise	627	87.9% (551/627)	(85.1, 90.3)	634	76.2% (483/634)	(72.7, 79.4)
16F	GMT (Day 1)	656	875.2	(788.9, 971.0)	667	769.8	(692.5, 855.8)
	GMT (Day 30)	674	6876.3	(6325.3, 7475.3)	672	1471.0	(1322.1, 1636.5)
	GMFR	604	7.0	(6.3, 7.8)	616	1.8	(1.6, 1.9)
	% ≥ 4-fold rise	604	63.2% (382/604)	(59.3, 67.1)	616	20.3% (125/616)	(17.2, 23.7)
23A	GMT (Day 1)	558	307.1	(257.8, 365.8)	537	294.1	(248.0, 348.7)
	GMT (Day 30)	629	4774.3	(4306.2, 5293.3)	579	853.5	(729.5, 998.5)
	GMFR	476	13.9	(11.7, 16.5)	426	2.7	(2.2, 3.2)
	% ≥ 4-fold rise	476	70.6% (336/476)	(66.3, 74.6)	426	34.7% (148/426)	(30.2, 39.5)
23B	GMT (Day 1)	696	29.7	(25.2, 35.0)	690	23.3	(19.9, 27.3)
	GMT (Day 30)	683	2355.4	(2094.2, 2649.1)	668	130.7	(108.2, 157.8)
	GMFR	649	53.9	(45.9, 63.3)	632	4.5	(3.9, 5.2)
	% ≥ 4-fold rise	649	86.6% (562/649)	(83.7, 89.1)	632	44.1% (279/632)	(40.2, 48.1)
24F	GMT (Day 1)	610	829.4	(734.8, 936.2)	604	792.4	(693.0, 905.9)
	GMT (Day 30)	664	4623.0	(4255.4, 5022.2)	608	1379.6	(1236.1, 1539.7)
	GMFR	551	5.5	(4.8, 6.3)	507	1.6	(1.4, 1.8)
	% ≥ 4-fold rise	551	50.5% (278/551)	(46.2, 54.7)	507	14.6% (74/507)	(11.6, 18.0)
31	GMT (Day 1)	702	212.8	(181.0, 250.2)	703	237.4	(202.4, 278.4)
	GMT (Day 30)	683	4977.5	(4518.2, 5483.5)	680	442.9	(380.2, 515.9)
	GMFR	655	19.5	(16.7, 22.8)	652	1.7	(1.5, 1.9)
	% ≥ 4-fold rise	655	74.4% (487/655)	(70.8, 77.7)	652	18.3% (119/652)	(15.4, 21.4)
35B	GMT (Day 1)	714	1481.1	(1340.6, 1636.2)	712	1528.1	(1385.2, 1685.8)
	GMT (Day 30)	674	10641.2	(9829.3, 11520.2)	698	1759.0	(1595.9, 1938.7)
	GMFR	660	7.0	(6.3, 7.8)	678	1.1	(1.1, 1.2)
	% ≥ 4-fold rise	660	63.8% (421/660)	(60.0, 67.5)	678	5.2% (35/678)	(3.6, 7.1)

[a] For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Day 1 is prevaccination, and Day 30 is 30 days following vaccination.

GMFR and % ≥4-fold rise are calculated from Day 1 to Day 30.

CI=confidence interval; GMFR=geometric mean fold-rise; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Summary of main efficacy results from V116-010

Title: A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 50 Years of Age or Older		
Study identifier	Protocol Number: V116-010 EudraCT: 2022-001785-35 NCT: NCT05569954 EU CT: 2022-503144-40	
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	10 months not applicable not applicable
Hypothesis	Superiority and noninferiority	
Treatment groups	V116	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=741
	PPSV23	Single IM dose of PPSV23 on Day 1 (Visit 1) Randomized N=743
Endpoints and definitions	Primary endpoint: OPA GMTs for common serotypes	To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 versus PPSV23 for the common serotypes in V116 and PPSV23
	Primary endpoint: OPA GMTs for unique serotypes	To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 versus PPSV23 for the unique serotypes in V116
	Primary endpoint: ≥4-fold rise in OPA responses	To compare the proportions of participants with a ≥4-fold rise in serotypes-specific OPA responses form baseline to 30 days postvaccination with V116 versus PPSV23 for the unique serotypes in V116
	Secondary endpoint: ≥4-fold rise in cross-reactive OPA responses	To evaluate serotype-specific cross-reactive OPA responses at 30 days postvaccination for serotypes within a serogroup in V116
	Secondary endpoint: IgG GMCs	To evaluate the serotype specific IgG GMCs at 30 days postvaccination with V116 compared with PPSV23
Database lock	31-OCT-2023	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination	

	The majority of randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint (98.7%) and for both Day 1 and Day 30 timepoints (>93.0%).		
Descriptive statistics and estimate variability	**Primary Endpoint: OPA GMTs for common serotypes**		
	Intervention group	V116	PPSV23
	Number of participants	Refer to Table 24 Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population).	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (V116/PPSV23)	Refer to Table 11 V116 met the predefined criterion for noninferiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >0.5) for each of the 12 common serotypes at 30 days postvaccination	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>0.50 for all common serotypes	
	One-sided p-value	*p*<0.001 for all common serotypes	
Analysis description	**Primary Endpoint: OPA GMTs for unique serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116	PPSV23
	Number of participants	Refer to table 12 V116 met the predefined criterion for superiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >2.0) for each of the 9 serotypes unique to V116 at 30 days postvaccination	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (V116/PPSV23)	Refer to table 12 *V116* met the predefined criterion for superiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >2.0) for each of the 9 serotypes unique to V116 at 30 days postvaccination Table V116 met the predefined criterion for superiority to PPSV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >2.0) for each of the 9 serotypes unique to V116 at 30 days postvaccination	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>2.0 for all unique serotypes	
	One-sided p-value	*p*<0.001 for all unique serotypes	
Analysis description	**Primary Endpoint: ≥4-fold rise in OPA responses for unique serotypes**		
	Intervention group	V116	PPSV23
	Number of participants	Refer to table 13	

Descriptive statistics and estimate variability	Proportion of participants with a ≥4-fold rise in serotype-specific OPA responses	V116 met the predefined criteria for superiority to PPSV23 (lower bound of 95% CI of the differences [V116 - PPSV23] >0.1 [10 percentage points]) for 8 of 9 serotypes unique to V116 based on the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. V116 did not meet the predefined criterion for superiority to PPSV23 for serotype 15C (lower bound of the 95% CI of the percentage point difference [V116 – PPSV23] was 7.5 percentage points)
Effect estimate per comparison	Difference (V116-PPSV23) between the percentages of participants with a ≥4-fold rise	Refer to table 13 V116 met the predefined criteria for superiority to PPSV23 (lower bound of 95% CI of the differences [V116 - PPSV23] >0.1 [10 percentage points]) for 8 of 9 serotypes unique to V116 based on the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. V116 did not meet the predefined criterion for superiority to PPSV23 for serotype 15C (lower bound of the 95% CI of the percentage point difference [V116 – PPSV23] was 7.5 percentage points)
	95% CI	
	Lower bound of the 95% CI for the difference [V116 - PPSV23] between the percentages of participants with a ≥4-fold rise	>0.1 [10 percentage points] (except for serotype 15C, which was 7.5 percentage points)
	One-sided p-value	p<0.001 for all unique serotypes (except for 15C; p=0.214)
Analysis description	**Secondary Endpoint: ≥4-fold rise in cross-reactive OPA responses**	
Descriptive statistics and estimate variability	Intervention group	V116
	Number of participants	Serotype 6C: n=620 Serotype 15B: n=588
	Proportions of participants in V116 with a ≥4-fold rise in OPA responses for serotypes 6C and 15B	Serotype 6C: 52.7% Serotype 15B: 72.6% Among participants vaccinated with V116, the percentage of participants with a ≥4-fold rise in cross-reactive OPA responses from baseline to 30 days postvaccination was 52.7% (95% CI: 48.7, 56.7) for serotype 6C (cross-reactive to serotype 6A) and 72.6% (95% CI: 68.8, 76.2) for serotype 15B (cross-reactive to serotype 15C).

		V116 met the predefined criterion for an acceptable antibody response (lower bound of the 95% CI of the percentage of participants with a ≥4-fold rise in OPA responses >50%) for serotype 15B; V116 did not meet the predefined criterion for an acceptable antibody response for serotype 6C.	
Effect estimate per comparison	95% CI	Serotype 6C: (48.7, 56.7) Serotype 15B: (68.8,76.2)	
	Lower bound of the 95% CI of the proportion of participants with a ≥4-fold rise	Serotype 6C: 48.7 Serotype 15B: >50	
	One-sided p-value	Serotype 6C: 0.093 Serotype 15B: <0.001	
Analysis description	**Secondary Endpoint: IgG GMCs**		
Descriptive statistics and estimate variability	Intervention group	V116	PPSV23
	Number of participants	Refer to table 14 and table 15	
	Serotype-specific IgG GMC	Between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs.	
Effect estimate per comparison	Serotype-specific IgG GMC Ratio (V116/PPSV23)	Refer to table 14 and 15 Between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs.	
	95% CI		

V116-004

Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age

Methods

Design	Number of Participants by Intervention Group[a]	Study Population	Primary Endpoint(s)
Double-blind, randomized, active-comparator study to evaluate the safety, tolerability, and immunogenicity of V116	Randomization ratio V116 Lot 1:V116 Lot 2:V116 Lot 3:PPSV23 = 1:1:1:1 V116 Lot 1: Randomized: 541 Vaccinated: 539 Completed: 521 V116 Lot 2: Randomized: 540 Vaccinated: 538 Completed: 520 V116 Lot 3: Randomized: 541 Vaccinated: 540 Completed: 525 PPSV23: Randomized: 540 Vaccinated: 540 Completed: 526	Pneumococcal vaccine-naïve adults 18 to 49 years of age Sex: 914 M / 1243 F Median age: 35.0 years	• Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs • Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116

Study Participants

Pneumococcal vaccine-naïve adults 18-49 years old.

Clinical investigator study sites were located in 8 countries: Austria, Canada, Denmark, Finland, Israel, Poland, Spain, and the USA.

Treatments

One intramuscular injection with standard dose of 0.5 ml V116 from three different batches or PPSV23.

Objectives and Outcomes/endpoints

Primary immunogenicity objectives and endpoints
Objective: To compare the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination across 3 different lots of V116 for all serotypes included in V116. **Hypothesis:** All 3 lots of V116 are equivalent as assessed by the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in V116. (The statistical criterion for equivalence requires the bounds of the 95% confidence interval [CI] of the OPA GMT ratio for each pairwise V116 lot-to-lot comparison to be within 0.5 to 2.0). **Endpoint:** Serotype-specific OPA responses.
Secondary objectives

Objective: To evaluate the serotype-specific OPA GMTs at 30 days postvaccination in combined lots of V116 compared with PPSV23 for all serotypes included in V116. **Endpoint:** Serotype-specific OPA responses.
Objective: To evaluate the serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination compared across the 3 different lots of V116 and evaluate combined lots of V116 compared with PPSV23 for all serotypes included in V116. **Endpoint:** Serotype-specific IgG responses.
Objective: To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4- fold rise from baseline to 30 days postvaccination for both OPA and IgG responses separately for 3 different lots of V116 for all serotypes included in V116. **Endpoint:** Serotype-specific OPA and IgG responses
Objective: To evaluate the serotype-specific OPA GMTs at 30 days postvaccination separately for 3 different lots of V116 for cross-reactive immune responses to serotypes within a serogroup. **Endpoint:** Serotype-specific OPA responses.
Tertiary/Exploratory Objectives
Objective: To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination. **Endpoint:** Serotype-specific OPA and IgG responses

Sample size

The planned enrollment total was 2040 participants, equally divided into four groups containing 510 in each. This study will randomize approximately 510 participants into each of 3 manufactured lots of V116 (Lot 1, Lot 2, and Lot 3) and 510 participants into the PPSV23 group.

For the primary hypothesis on all serotypes contained in V116, this study had >90% power to demonstrate equivalent immunogenicity across the 3 V116 lots as assessed by the OPA GMTs at 30 days postvaccination at an overall type 1 error = 0.05 (2-sided) level.

Randomisation and blinding (masking)

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented in an IRT.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Statistical methods

Table 16. Analysis strategy for immunogenicity variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
OPA GMTs at 30 days postvaccination for all serotypes included in V116	P	cLDA[b] (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
Secondary Endpoint				
OPA GMTs[c] and IgG GMCs[c] at 30 days postvaccination for all serotypes included in V116	P	cLDA[b] (estimate, 95% CI)	PP	Model-based
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for both OPA and IgG responses for all serotypes included in V116	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
OPA GMTs at 30 days postvaccination for the cross-reactive serotypes	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI = confidence interval; cLDA = constrained longitudinal data analysis; FAS = Full Analysis Set; GMC = Geometric Mean Concentration; GMFR = geometric mean fold rise; GMT = Geometric Mean Titer; IgG = Immunoglobulin G; OPA= opsonophagocytic killing activity; PP = Per-Protocol.

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

[b] cLDA model with terms for vaccination group, time, and the interaction of time-by-vaccination.

[c] Include the following endpoints: serotype-specific OPA GMTs at 30 days postvaccination in combined lots of V116 compared with PPSV23; serotype-specific IgG GMCs at 30 days postvaccination compared across the 3 different lots of V116 and combined lots of V116 compared with PPSV23.

Baseline is the day of vaccination (Day 1); 30 days postvaccination is the day of the Visit 3 blood draw (Day 30).

Multiplicity

The study will be considered to have met the primary objective if success is achieved for all 3 pairwise comparisons for V116 lots for all serotypes contained in V116. Since comparisons are made individually for each serotype and for each pairwise comparison, this approach controls the overall type 1 error rate at 0.05 (2-sided), and no multiplicity adjustment is required.

Results

Participant flow

Of the 2162 randomized participants in V116-004, 2157 were vaccinated, and 2092 (96.8%) completed the study. Most (>98.0%) of the randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint.

As of database lock, 2162 participants were randomized (541 in the V116 Lot 1 group, 540 in the V116 Lot 2 group, 541 in the V116 Lot 3 group, and 540 in the PPSV23 group).

Table 17. Disposition of Participants by Vaccination Groups and Manufacturing Lots (All Randomized Participants)

	V116 Lot 1		V116 Lot 2		V116 Lot 3		V116 (Combined Lots)		PPSV23		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	541		540		541		1,622		540		2,162	
Vaccinated at Visit 1												
V116 Lot 1	538	(99.4)	1	(0.2)	0	(0.0)	539	(33.2)	0	(0.0)	539	(24.9)
V116 Lot 2	0	(0.0)	536	(99.3)	0	(0.0)	536	(33.0)	0	(0.0)	536	(24.8)
V116 Lot 3	1	(0.2)	0	(0.0)	540	(99.8)	541	(33.4)	0	(0.0)	541	(25.0)
PPSV23	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)	540	(100.0)	541	(25.0)
Trial Disposition												
Completed	521	(96.3)	520	(96.3)	525	(97.0)	1,566	(96.5)	526	(97.4)	2,092	(96.8)
Discontinued	20	(3.7)	20	(3.7)	16	(3.0)	56	(3.5)	14	(2.6)	70	(3.2)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Lost To Follow-Up	16	(3.0)	11	(2.0)	11	(2.0)	38	(2.3)	11	(2.0)	49	(2.3)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Withdrawal By Subject	4	(0.7)	8	(1.5)	3	(0.6)	15	(0.9)	1	(0.2)	16	(0.7)
Other	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.1)	1	(0.2)	3	(0.1)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P004V116; adsm.adsl]

Recruitment

First Participant First Visit	12-AUG-2022
Last Participant Last Visit	25-MAY-2023
Last Data Available	03-JUL-2023
Database Lock Date	05-JUL-2023

Conduct of the study

There were no major amendments for study protocol. Important protocol deviations were reported for 164 (7.6%) participants. Of these, 134 participants had important protocol deviations that were considered clinically important.

The most frequently reported clinically important protocol deviations were due to immunogenicity samples drawn outside the protocol-defined window (n=68) and immunogenicity samples not drawn or samples unable to be tested due to an error by the site in processing and/or handling of the sample (n=36). The protocol deviations were comparably distributed between the V116 (combined lots) and the PPSV23 intervention groups.

Baseline data

Among the vaccinated participants (n=2157):

Overall Median Age (Range): 35.0 years (18 to 49 years)

Sex: 914 (42.4%) male, 1243 (57.6%) female

Ethnicity: 1719 (79.7%) not Hispanic or Latino, 422 (19.6%) Hispanic or Latino, 14 (0.6%) not reported, 2 (0.1%) Unknown

Race: 16 (0.7%) American Indian Or Alaska Native, 35 (1.6%) Asian, 194 (9.0%) black or African American, 4 (0.2%) Native Hawaiian or Other Pacific Islander, 3 (0.1%) missing, 81 (3.8%) multiple, 1824 (84.6%) white.

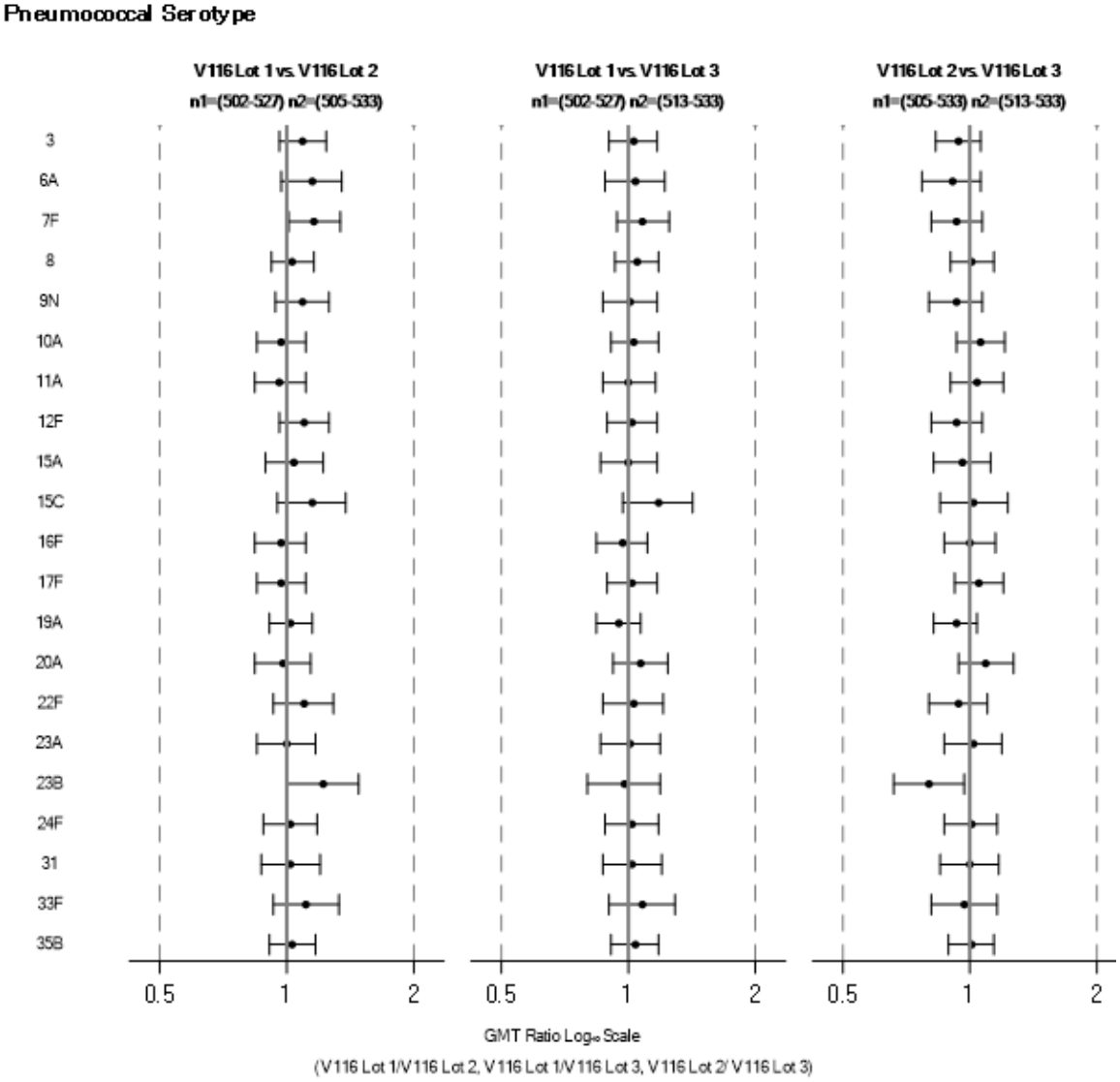
Demographics and baseline characteristics were generally comparable across intervention groups

Numbers analysed

- V116 Lot 1 group: 541 randomized, 539 vaccinated, 521 completed the study, 20 discontinued
- V116 Lot 2 group: 540 randomized, 538 vaccinated, 520 completed the study, 20 discontinued
- V116 Lot 3 group: 541 randomized, 540 vaccinated, 525 completed the study, 16 discontinued
- PPSV23 Group: 540 randomized, 540 vaccinated, 526 completed the study, 14 discontinued

Outcomes and estimation

Figure 1. Forest Plot of Postvaccination OPA GMT Ratios (Comparison Across V116 Lots)(Per-Protocol Population)(V116-004)



n1=Number of participants contributing to analysis from Lot 1, Lot 1, Lot 2 respectively;
n2=Number of participants contributing to analysis from Lot 2, Lot 3, Lot 3 respectively.
Note: The dashed lines indicate the margins for the equivalence test.
Source: [P004V116: adam-adsl; adimm]

Primary Immunogenicity Endpoint

- All 3 lots of V116 met equivalence criteria, as assessed by serotype-specific OPA GMTs at 30 days postvaccination for all 21 serotypes in V116 [Figure 1]. For each pairwise V116 lot-to-lot comparison, the lower and upper limits of the 95% confidence interval of the OPA GMT ratios were within 0.5 and 2.0 for all serotypes in V116.

Key Secondary Immunogenicity Endpoints

- Serotype-specific IgG GMCs at 30 days postvaccination with V116 were generally comparable across the 3 lots, consistent with the results of the primary analysis of OPA GMTs.

- Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination were generally comparable in the V116 (combined lots) and PPSV23 intervention groups for the 12 common serotypes and higher in the V116 (combined lots) group for the 9 serotypes unique to V116

Table 18. Analysis of postvaccination OPA GMTs for common serotypes (comparison between V116 combined lots and PPSV23) (per-protocol population) (V116-004)

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMT Ratio[a] (V116 (Combined Lots) / PPSV23) (95% CI)[a]
	n	GMT[a]	n	GMT[a]	
3	1574	316.5	534	339.8	0.93 (0.84, 1.03)
7F	1580	6702.2	531	5058.1	1.33 (1.18, 1.49)
8	1585	3847.3	537	4543.3	0.85 (0.77, 0.93)
9N	1590	18166.7	533	19031.9	0.95 (0.85, 1.08)
10A	1586	7618.2	534	5763.0	1.32 (1.18, 1.48)
11A	1581	6494.4	534	3728.0	1.74 (1.56, 1.95)
12F	1583	7196.9	534	5207.5	1.38 (1.22, 1.56)
17F	1588	17330.5	536	10159.9	1.71 (1.53, 1.91)
19A	1593	3222.9	533	3474.7	0.93 (0.84, 1.03)
20A	1574	16183.8	533	10994.2	1.47 (1.30, 1.67)
22F	1573	11118.1	530	8308.0	1.34 (1.17, 1.53)
33F	1576	35684.3	533	42515.6	0.84 (0.73, 0.97)

[a] GMTs, GMT ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Table 19. Analysis of Postvaccination OPA GMTs for Unique Serotypes (Comparison between V116 Combined Lots and PPSV23) (Per-Protocol Population) (V116-004)

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMT Ratio[a] (V116 (Combined Lots) / PPSV23) (95% CI)[a]
	n	GMT[a]	n	GMT[a]	
6A	1562	6491.7	529	1866.4	3.48 (3.01, 4.02)
15A	1520	10520.0	512	2608.5	4.03 (3.56, 4.56)
15C	1571	11922.3	529	4112.0	2.90 (2.49, 3.38)
16F	1563	9415.3	527	2532.2	3.72 (3.32, 4.17)
23A	1550	8428.3	519	1056.1	7.98 (6.84, 9.31)
23B	1583	2825.4	533	119.1	23.72 (19.71, 28.55)
24F	1568	4892.9	518	250.3	19.55 (16.70, 22.88)
31	1565	8865.6	531	654.5	13.55 (11.68, 15.71)
35B	1578	12798.6	537	3452.1	3.71 (3.36, 4.09)

[a] GMTs, GMT ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P004V116: adam-adsl; adimm]

Table 20. Analysis of Postvaccination IgG GMCs for Common Serotypes (Comparison between V116 Combined Lots and PPSV23) (Per-Protocol Population)(V116-004)

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMC Ratio[a] (V116 (Combined Lots) / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
3	1603	0.85	539	0.77	1.10 (1.01, 1.21)
7F	1603	5.19	539	3.36	1.54 (1.38, 1.72)
8	1603	10.34	539	12.85	0.81 (0.73, 0.89)
9N	1603	5.51	539	5.41	1.02 (0.91, 1.14)
10A	1603	9.58	539	6.52	1.47 (1.30, 1.66)
11A	1603	6.29	539	4.55	1.38 (1.26, 1.52)
12F	1603	1.69	539	1.20	1.41 (1.23, 1.62)
17F	1603	13.46	539	7.28	1.85 (1.66, 2.07)
19A	1603	8.01	539	7.29	1.10 (0.98, 1.22)
20A	1603	13.82	539	9.03	1.53 (1.37, 1.71)
22F	1603	7.04	539	5.34	1.32 (1.17, 1.49)

33F	1603	8.00	539	9.82	0.81 (0.73, 0.91)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P004V116: adam-adsl; adimm]

Table 21. Analysis of Postvaccination IgG GMCs for Unique Serotypes (Comparison between V116 Combined Lots and PPSV23) (Per-Protocol Population)(V116-004)

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMC Ratio[a] (V116 (Combined Lots) / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
6A	1603	5.67	539	1.45	3.91 (3.43, 4.45)
15A	1603	13.55	539	1.99	6.82 (6.08, 7.65)
15C	1603	13.90	539	4.29	3.24 (2.86, 3.67)
16F	1603	1.91	539	0.30	6.48 (5.83, 7.19)
23A	1603	4.29	539	0.53	8.14 (7.19, 9.23)
23B	1603	6.96	539	1.21	5.74 (5.08, 6.48)
24F	1603	4.44	539	0.31	14.47 (12.77, 16.40)
31	1603	3.62	539	0.38	9.55 (8.61, 10.59)
35B	1603	11.71	539	1.66	7.06 (6.41, 7.77)

[a] GMCs, GMC ratio, and 95% CI are estimated from a cLDA model.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P004V116: adam-adsl; adimm]

Title: A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age		
Study identifier	Protocol Number: V116-004 IND: 19316 EudraCT: 2022-000265-41 NCT: NCT05464420	
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	
	Duration of main phase:	9 months

	Duration of run-in phase: Duration of extension phase:	not applicable not applicable	
Hypothesis	Superiority and noninferiority		
Treatment groups	V116 (Lot 1)	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=541	
	V116 (Lot 2)	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=540	
	V116 (Lot 3)	Single IM dose of V116 on Day 1 (Visit 1) Randomized N=541	
	PPSV23	Single IM dose of PPSV23 on Day 1 (Visit 1) Randomized N=540	
Endpoints and definitions	Primary endpoint: OPA GMTs	To compare the serotype specific OPA GMTs at 30 days postvaccination across 3 different lots of V116 for all serotypes included in V116	
	Secondary endpoint: OPA GMTs	To evaluate the serotype specific OPA GMTs at 30 days postvaccination in combined lots of V116 compared with PPSV23 for all serotypes included in V116	
	Secondary endpoint: IgG GMCs	To evaluate the serotype-specific IgG GMCs at 30 days postvaccination compared across the 3 different lots of V116 and evaluate combined lots of V116 compared with PPSV23 for all serotypes included in V116	
Database lock	05-JUL-2023		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination The majority of randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint (>98%) and for both Day 1 and Day 30 timepoints (>88%).		
Descriptive statistics and estimate variability	**Primary Endpoint: OPA GMTs**		
	Intervention group	V116 (Group A)	V116 (Group B)
	Number of participants	P004V116: Table 14.2-1 Analysis of Postvaccination OPA GMTs Comparison Across V116 Lots) (Per-Protocol Population)	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (Group A/Group B)	Refer to P004V116: Table 14.2-1 Analysis of Postvaccination OPA GMTs Comparison Across V116 Lots) (Per-Protocol Population)	
	95% CI	Figure 1	
	Lower bound of 95% CI for the GMT ratio	Within equivalence margin 0.5 to 2.0 for all serotypes	
	p-value	$p<0.001$ for all serotypes	
Analysis description	**Secondary Endpoint: OPA GMTs (V116 [combined lots] vs. PPSV23)**		
Descriptive statistics and estimate variability	Intervention group	V116 (Combined Lots)	PPSV23
	Number of participants	Refer to Table 18	
	Serotype-specific OPA GMT	Refer to Table 19	

		.
Effect estimate per comparison	Serotype-specific OPA GMT ratio (V116 combined lots/PPSV23)	Refer to Table 18
	95% CI	Refer to Table 19
Analysis description	**Secondary Endpoint: IgG GMCs**	
Descriptive statistics and estimate variability	Intervention group	V116 (Combined Lots) / PPSV23
	Number of participants	Refer to Table 20 and 21
	Serotype-specific IgG GMC	
Effect estimate per comparison	Serotype-specific IgG GMC ratio (V116 (Combined Lots)/PPSV23)	Refer to Table 20 and 21
	95% CI	

2.6.5.3. Clinical studies in special populations

Study V116-007, Adults living with HIV

A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator- Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV

In V116-007 Part A, participants were randomized in a 1:1 ratio to receive either V116 on Day 1 followed by placebo 8 weeks later, or PCV15 on Day 1 followed by PPSV23 8 weeks later.

Of the 313 randomized participants, most (>96%) were vaccinated at both Visit 2 and Visit 5, and the majority (97.1%) completed Part A of the study. Most (>94%) of the randomized participants were included in the IgG and OPA analyses for the PP population.

The majority of participants had CD4+ T-cell counts ≥500 cells/μL at Screening (74.7%) and had undetectable HIV viral load (<20 copies/mL) at Screening (83%).

Primary Immunogenicity Endpoints

- V116 was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V116 (Day 30).
  - V116 elicited immune responses that were generally comparable to PCV15+PPSV23 for the 13 common serotypes and higher for the 8 serotypes unique to V116, as assessed by OPA GMTs at 30 days postvaccination with V116 and at 30 days postvaccination with PCV15+PPSV23 (Week 12).

Table 22. Within Group Analysis of Postvaccination OPA GMTs for 13 Serotypes Common Between V116 and PCV15 + PPSV23 (Per-Protocol Population) (V116-007)

Pneumococcal Serotype	V116 + Placebo (N = 156)			PCV15 + PPSV23 (N = 156)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
3	128	170.7	(132.5, 220.0)	126	172.0	(138.4, 213.7)

6A	131	3896.0	(2929.7, 5181.1)	123	3979.5	(3210.6, 4932.5)
7F	135	3482.3	(2815.8, 4306.6)	126	3275.6	(2658.1, 4036.6)
8	137	1847.5	(1470.9, 2320.6)	129	2262.9	(1776.5, 2882.5)
9N	129	5763.0	(4552.8, 7294.7)	126	5970.0	(4786.9, 7445.6)
10A	137	3693.0	(2870.2, 4751.5)	128	3652.8	(2731.4, 4885.1)
11A	134	3742.5	(3050.7, 4591.1)	123	1722.3	(1277.1, 2322.7)
12F	136	2585.4	(1993.5, 3353.0)	128	2292.4	(1653.2, 3178.8)
17F	135	8698.6	(7046.1, 10738.5)	124	5886.3	(4489.8, 7717.1)
19A	137	2178.9	(1777.1, 2671.7)	130	2667.0	(2193.2, 3243.1)
20A	135	7249.1	(5854.9, 8975.4)	130	5753.3	(4634.0, 7143.0)
22F	129	3622.4	(2902.8, 4520.4)	129	3979.8	(3214.5, 4927.1)
33F	123	14642.5	(11314.9, 18948.6)	123	11864.5	(9283.8, 15162.5)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following V116 [Day 30] for the V116 + Placebo group; 30 days following PPSV23 [Week 12] for the PCV15 + PPSV23 group.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV15=pneumococcal 15-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P007V01V116: adam-adsl; adimm]

Table 23. Within Group Analysis of Postvaccination OPA GMTs for 8 Serotypes Unique to V116 (Per-Protocol Population)(V116-007*)*

Pneumococcal Serotype	V116 + Placebo (N = 156)			PCV15 + PPSV23 (N = 156)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
15A	127	5859.0	(4684.9, 7327.4)	124	1970.5	(1555.1, 2496.8)
15C	131	5613.0	(4136.7, 7616.3)	126	2438.0	(1791.5, 3317.7)
16F	129	6703.0	(5494.0,	127	1839.0	(1474.3,

			8178.1)			2293.9)
23A	130	5053.5	(3781.3, 6753.5)	111	1674.9	(1209.9, 2318.7)
23B	135	1593.8	(1182.7, 2147.9)	125	151.0	(98.1, 232.6)
24F	132	3725.6	(3161.1, 4391.0)	98	567.9	(375.4, 859.1)
31	137	5699.4	(4435.1, 7324.2)	125	530.8	(364.2, 773.7)
35B	135	11306.2	(9364.7, 13650.1)	128	2977.7	(2425.5, 3655.8)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following V116 [Day 30] for the V116 + Placebo group; 30 days following PPSV23 [Week 12] for the PCV15 + PPSV23 group.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV15=pneumococcal 15-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P007V01V116: adam-adsl; adimm]

Key Secondary Immunogenicity Endpoints

- V116 was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific IgG GMCs at Day 30.

  - V116 elicited immune responses that were generally comparable to PCV15+PPSV23 for the 13 common serotypes and higher for the 8 serotypes unique to V116, as assessed by IgG GMCs at 30 days postvaccination with V116 and with PCV15+PPSV23 at Week 12.

Title: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV		
Study identifier	Protocol Number: V116-007 IND: 19316 EudraCT: 2021-006710-36 NCT: NCT05393037	
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	12 months not applicable not applicable
Hypothesis	Descriptive study. No hypothesis testing associated with objectives.	
Treatment groups	V116+Placebo	Single IM dose of V116 on Day 1 (Visit 2); Single IM dose of placebo at Visit 5 (Week 8) Randomized N=156

	PCV15+PPSV23	Single IM dose of PCV15 on Day 1 (Visit 2); Single IM dose of PPSV23 on Visit 5 (Week 8) Randomized N=157	
Endpoints and definitions	Primary endpoint: OPA GMTs for common serotypes	To evaluate the serotype-specific OPA GMTs postvaccination with V116 (30 days postvaccination [Day 30]) and PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12]) within each vaccination group separately	
	Primary endpoint: OPA GMTs for unique serotypes	To evaluate the serotype-specific OPA GMTs postvaccination with V116 (30 days postvaccination [Day 30]) and PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12]) within each vaccination group separately	
	Secondary endpoint: IgG GMCs for common and unique serotypes	To evaluate the serotype specific IgG GMCs postvaccination with V116 (Day 30) and PCV15 + PPSV23 (Week 12) within each vaccination group	
Database lock	11-SEP-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination and Week 12 The majority of randomized participants were included in the OPA and IgG analyses for the PP population for Day 30 (>87%) and for Week 12 (>82%).		
Descriptive statistics and estimate variability	**Primary Endpoint : OPA GMTs for common serotypes**		
	Intervention group	V116+Placebo	PCV15+PPSV23
	Number of participants	Refer to Table 22	
Effect estimate per comparison	Serotype-specific OPA GMT	Refer to Table 22	
	95% CI		
Analysis description	**Primary Endpoint : OPA GMTs for unique serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116+Placebo	PCV15+PPSV23
	Number of participants	Refer to **Error! Reference source not found.** 23	
Effect estimate per comparison	Serotype-specific OPA GMT	Refer to **Error! Reference source not found.** 23	
	95% CI		
Analysis description	**Secondary Endpoint: IgG GMCs for common serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116+Placebo	PCV15+PPSV23
	Number of participants	P007V01V116: Table 14.2-5 Within Group Analysis of Postvaccination IgG GMCs for 13 Serotypes Common Between V116 and PCV15 + PPSV23	

		(Per-Protocol Population)	
Effect estimate per comparison	Serotype-specific IgG GMC	Table 14.2-5 Within Group Analysis of Postvaccination IgG GMCs for 13 Serotypes Common Between V116 and PCV15 + PPSV23 (Per-Protocol Population)	
	95% CI		
Analysis description	**Secondary Endpoint: IgG GMCs for unique serotypes**		
Descriptive statistics and estimate variability	Intervention group	V116+Placebo	PCV15+PPSV23
	Number of participants	Table 14.2-6 Within Group Analysis of Postvaccination IgG GMCs for 8 Serotypes Unique to V116 (Per-Protocol Population)	
Effect estimate per comparison	Serotype-specific IgG GMC	Refer to Table 14.2-6 Within Group Analysis of Postvaccination IgG GMCs for 8 Serotypes Unique to V116 (Per-Protocol Population)	

2.6.5.4. Supportive studies

V116-005, Study With Concomitant Administration of Influenza Vaccine

A Phase 3 Randomized, Double-blind, Placebo- Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older

V116 is immunogenic and can be administered concomitantly with inactivated QIV in adults ≥50 years of age with or without prior pneumococcal vaccination.

Study V116-005

The results of V116-005 showed that V116 administered concomitantly with QIV elicited immune responses that were noninferior to V116 administered sequentially with QIV for 20 of 21 pneumococcal serotypes.

Participants in V116-005 were randomized 1:1 to receive V116 administered concomitantly with QIV or V116 administered sequentially with QIV.

A total of 1080 participants were randomized, 1072 were vaccinated, and 1017 (94.2%) completed the study. Most (>92%) of the randomized participants were included in the OPA, IgG, and HAI analyses for the PP population for at least 1 timepoint.

Primary Immunogenicity Endpoints

- V116 administered concomitantly with QIV met the criterion for noninferiority to V116 administered sequentially with QIV (lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant/sequential] >0.5) for 20 of 21 pneumococcal serotypes in V116 at 30 days postvaccination. Serotype 23B did not meet the prespecified criterion (lower bound of the 2-sided 95% CI of the OPA GMT ratio was 0.44).

- QIV administered concomitantly with V116 met the criterion for noninferiority to QIV administered sequentially with V116 (lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant/sequential] >0.67) for 3 of 4 influenza strains in QIV at 30 days postvaccination. Strain

A/H3N2 did not meet the prespecified criterion (lower bound of the 2-sided 95% CI of the HAI GMT ratio was 0.67).

Table 24. Analysis of postvaccination OPA GMTs (Per-protocol population)(V116-005)

Pneumococcal Serotype	Concomitant Group (N = 536)		Sequential Group (N = 536)		GMT Ratio[a] (Concomitant Group / Sequential Group) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
3	519	209.2	497	250.1	0.84 (0.72, 0.97)	<0.001
6A	521	2056.4	496	2608.2	0.79 (0.66, 0.94)	<0.001
7F	521	2399.2	496	3275.4	0.73 (0.63, 0.85)	<0.001
8	519	1508.9	497	2135.7	0.71 (0.61, 0.82)	<0.001
9N	522	5075.6	499	7566.6	0.67 (0.57, 0.79)	<0.001
10A	524	3033.6	499	3966.2	0.76 (0.65, 0.91)	<0.001
11A	519	2576.3	499	4051.1	0.64 (0.54, 0.75)	0.002
12F	525	1869.9	499	2449.5	0.76 (0.62, 0.94)	<0.001
15A	511	4670.6	458	6559.7	0.71 (0.60, 0.85)	<0.001
15C	522	3426.0	493	4832.6	0.71 (0.58, 0.87)	<0.001
16F	522	5371.5	498	7757.2	0.69 (0.59, 0.81)	<0.001
17F	520	5783.8	497	7924.3	0.73 (0.62, 0.86)	<0.001
19A	524	1830.1	498	2453.3	0.75 (0.65, 0.85)	<0.001
20A	522	5172.8	498	6986.9	0.74 (0.63, 0.87)	<0.001
22F	517	3194.9	490	4158.2	0.77 (0.65, 0.91)	<0.001
23A	511	3358.2	486	4319.9	0.78 (0.63, 0.96)	<0.001
23B	522	934.3	498	1664.5	0.56 (0.44, 0.72)	0.177
24F	517	2996.5	494	4143.1	0.72 (0.61, 0.86)	<0.001
31	522	2997.4	499	4390.6	0.68 (0.56, 0.83)	<0.001
33F	520	9032.5	492	10765.1	0.84 (0.70, 1.01)	<0.001
35B	522	7701.4	495	9940.2	0.77 (0.67, 0.89)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of non-inferiority is based on the lower bound of the 95% CI for the estimated GMT ratio (Concomitant Group/Sequential Group) being > 0.5 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination with V116 (Day 30 for concomitant group and Day 59 for sequential group).

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titers (1/dil); OPA=Opsonophagocytic activity.

Source: [P005V116: adam-adsl; adimm]

Table 25. Analysis of postvaccination HAI GMTs (Per-protocol population)(V116-005)

Influenza Strain	Concomitant Group (N = 536)		Sequential Group (N = 536)		GMT Ratio[a] (Concomitant Group / Sequential Group) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
A/H1N1	526	268.23	526	325.06	0.83 (0.70, 0.97)	0.007
A/H3N2	526	128.07	526	163.06	0.79 (0.67, 0.93)	0.030
B/Victoria	526	70.02	526	85.66	0.82 (0.70, 0.95)	0.005
B/Yamagata	526	31.80	526	35.86	0.89 (0.78, 1.00)	<0.001

[a] GMTs, GMT ratio, 95% CI, and p-value are estimated from a cLDA model.

[b] A conclusion of non-inferiority is based on the lower bound of the 95% CI for the estimated GMT ratio (Concomitant Group/Sequential Group) being > 0.67 (one-sided p-value < 0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination with QIV (Day 30 for both concomitant and sequential group).

A/H1N1=A/Victoria/2570/2019 IVR-215 (H1N1); A/H3N2=A/Darwin/9/2021 SAN-010 (H3N2); B/Victoria=B/Austria/1359417/2021 (B Victoria lineage); B/Yamagata=B/Phuket/3073/2013 (B Yamagata lineage); CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titers (1/dil); HAI=hemagglutination inhibition; QIV=quadrivalent influenza vaccine.

Source: [P005V116: adam-adsl; adimm]

Key Secondary Immunogenicity Endpoint

- Between-group comparisons of IgG GMCs at 30 days postvaccination with V116 were consistent with the results observed for the primary analysis of OPA GMTs.

Title: A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older		
Study identifier	Protocol Number: V116-005 IND: 19316 NCT: NCT05526716	
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator, placebo-controlled	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	9 months not applicable not applicable
Hypothesis	Noninferiority	

Treatment groups	Concomitant Group	Single IM dose of V116 and QIV on Day 1 (Visit 1); single IM dose of placebo on Day 30 (Visit 3) Randomized N=540
	Sequential Group	Single IM dose of QIV and placebo on Day 1 (Visit 1); single IM dose of V116 on Day 30 (Visit 3) Randomized N=540
Endpoints and definitions	Primary endpoint: OPA GMT ratios for each of the 21 serotypes in V116	To compare the serotype specific OPA GMTs at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV
	Primary endpoint: Strain-specific HAI GMT ratios for each of the 4 strains in QIV	To compare the strain-specific HAI GMTs at 30 days postvaccination with QIV administered concomitantly with V116 compared with QIV administered sequentially with V116
	Secondary endpoint: Serotype-specific IgG GMCs for each of the 21 serotypes in V116	To evaluate serotype-specific IgG GMCs at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV
Database lock	03-JUL-2023	
<u>Results and Analysis</u>		
Analysis description	**Primary Analysis**	
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination with V116 or QIV Within both intervention groups, the majority of randomized participants were included in the OPA and IgG analyses for the PP population: • In the concomitant group, >97% participants were included for at least 1 timepoint and >89% participants were included for both baseline (Visit 1) and postvaccination (Visit 3) timepoints. • In the sequential group, >92% participants were included for at least 1 timepoint and >81% participants were included for both baseline (Visit 3) and postvaccination (Visit 5) timepoints. The majority of randomized participants were included in the HAI analyses for at least 1 timepoint (>97%) and for both baseline (Visit 1) and postvaccination (Visit 3) timepoints (>89%). The number of participants excluded from the HAI analyses was generally comparable between the intervention groups.	

Descriptive statistics and estimate variability	**Primary Endpoint: OPA GMT ratios for each of the 21 serotypes in V116**		
	Intervention group	Concomitant Group	Sequential Group
	Number of participants	Refer to table 24	
	Serotype-specific OPA GMT		
Effect estimate per comparison	Serotype-specific OPA GMT ratio (Concomitant Group/Sequential Group)	Refer to table 24	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>0.50 for all serotypes (except serotype 23B, which was 0.44)	
	One-sided p-value	*p*<0.001 for all serotypes (except serotype 23B *p*=0.177 and serotype 11A p=0.002)	
Analysis description	**Primary Endpoint: Strain-specific HAI GMT ratios for each of the 4 strains in QIV**		
Descriptive statistics and estimate variability	Intervention group	Concomitant Group	Sequential Group
	Number of participants	Refer to table 25	
	Strain-specific HAI GMT		
Effect estimate per comparison	Strain-specific HAI GMT ratio (Concomitant Group/Sequential Group)	Refer to table 25	
	95% CI		
	Lower bound of 95% CI for the GMT ratio	>0.67 for 3 of 4 influenza strains (except for strain A/H3N2, which was 0.6659)	
	One-sided p-value	Refer to table 25	

V116-006, Study in Pneumococcal Vaccine-experienced Adults

A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine- Experienced Adults 50 Years of Age or Older

V116 is immunogenic in adults ≥50 years of age who had previously received a pneumococcal vaccine.

Study V116-006

The results of study V116-006 showed that V116 elicited immune responses to all 21 serotypes contained in V116, regardless of pneumococcal vaccination history.

Participants in V116-006 were enrolled into 1 of 3 parallel cohorts based on the participant's prior pneumococcal vaccination history:

- Cohort 1: Participants who were vaccinated with PPSV23 ≥1 year prior to enrollment were randomized 2:1 to receive a single dose of V116 or PCV15 on Day 1.
- Cohort 2: Participants who were vaccinated with PCV13 ≥1 year prior to enrollment were randomized 2:1 to receive a single dose of V116 or PPSV23 on Day 1.

• Cohort 3: Participants who were vaccinated with PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥1 year prior to enrollment received a single dose of open-label V116 on Day 1.

A total of 717 participants were randomized, 712 were vaccinated, and 710 (99.0%) completed the study. Most (>97%) of the randomized participants in each cohort were included in the OPA and IgG analyses for the PP population for at least 1 timepoint.

Primary Immunogenicity Endpoint

• Across all 3 cohorts, V116 was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific OPA GMTs at 30 days postvaccination through.

- In Cohort 1, V116 elicited immune responses that were generally comparable to PCV15 for the 6 common serotypes and higher than PCV15 for the 15 serotypes unique to V116.

- In Cohort 2, V116 elicited immune responses that were generally comparable to PPSV23 for the 12 common serotypes and higher than PPSV23 for the 9 serotypes unique to V116.

Key Secondary Immunogenicity Endpoint

• Across all 3 cohorts, V116 was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific IgG GMCs at 30 days postvaccination.

<table>
<tr><td colspan="3">Title: A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older</td></tr>
<tr><td>Study identifier</td><td colspan="2">Protocol Number: V116-006
IND: 19316
EudraCT: 2021-006679-41
NCT: NCT05420961
JRCT: jRCT2071220025</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2">Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind (Cohorts 1 and 2), open-label (Cohort 3), active comparator</td></tr>
<tr><td>Duration of main phase:
Duration of run-in phase:
Duration of extension phase:</td><td>11 months
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">No hypothesis testing associated with objectives.</td></tr>
<tr><td rowspan="5">Treatment groups</td><td>V116 (Cohort 1)</td><td>Single IM dose of V116 on Day 1 (Visit 1)
Randomized N=231</td></tr>
<tr><td>PCV15 (Cohort 1)</td><td>Single IM dose of PCV15 on Day 1 (Visit 1)
Randomized N=119</td></tr>
<tr><td>V116 (Cohort 2)</td><td>Single IM dose of V116 on Day 1 (Visit 1)
Randomized N=176</td></tr>
<tr><td>PPSV23 (Cohort 2)</td><td>Single IM dose of PPSV23 on Day 1 (Visit 1)
Randomized N=85</td></tr>
<tr><td>V116 (Cohort 3)</td><td>Single IM dose of V116 on Day 1 (Visit 1)
Randomized N=106</td></tr>
</table>

Endpoints and definitions	Primary endpoint: OPA GMTs for all serotypes in V116	To evaluate the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in V116	
	Secondary endpoints: Serotype-specific IgG GMCs for all serotypes in V116	To evaluate the serotype-specific IgG GMCs at 30 days postvaccination for all serotypes included in V116	
Database lock	23-JUN-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PP population: all randomized participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Timepoint: 30 days postvaccination Within each cohort, the majority of randomized participants were included in the OPA and IgG analyses for the PP population for at least 1 timepoint (>97%) and for both Day 1 and 30 timepoints (≥92%). The reasons for exclusion from the PP population were generally comparable between intervention groups.		
Descriptive statistics and estimate variability	**Primary Endpoint: OPA GMTs**		
	Intervention group	V116 (Cohort 1)	PCV15 (Cohort 1)
		V116 (Cohort 2)	PPSV23 (Cohort 2)
		V116 (Cohort 3)	
	Number of participants	See tables 26 to 30 below	
	Serotype-specific OPA GMT		
Effect estimate per comparison	95% CI	See tables 26 to 30 below	

Table 26. Within Group Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population) (Cohort 1)

Pneumococcal Serotype	V116 (N = 229)			PCV15 (N = 119)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
3	197	262.1	(224.0, 306.8)	103	226.3	(182.0, 281.4)
6A	191	1653.5	(1347.2, 2029.4)	94	2076.1	(1571.4, 2742.8)
7F	209	2184.4	(1891.4, 2522.8)	110	1750.3	(1404.7, 2181.0)
19A	204	1513.8	(1318.4, 1738.1)	109	2022.9	(1634.1, 2504.3)
22F	206	1983.8	(1698.3, 2317.4)	108	1595.6	(1227.1, 2074.6)
33F	188	4311.9	(3625.1, 5128.9)	99	3397.2	(2665.3, 4330.0)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV15=pneumococcal 15-valent conjugate vaccine.

Table 27. Within Group Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population) (Cohort 1)

Pneumococcal Serotype	V116 (N = 229)			PCV15 (N = 119)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
8	208	1273.0	(1115.1, 1453.3)	113	345.8	(250.5, 477.5)
9N	191	3805.1	(3324.0, 4356.0)	111	2176.5	(1809.6, 2617.9)
10A	209	1986.2	(1637.7, 2408.9)	112	467.5	(337.0, 648.5)
11A	197	1998.5	(1696.9, 2353.8)	100	335.6	(228.9, 491.8)
12F	212	981.8	(782.4, 1232.1)	114	80.5	(54.0, 120.1)
15A	175	4184.9	(3548.3, 4935.6)	93	877.2	(616.2, 1248.7)
15C	206	2307.8	(1878.4, 2835.4)	110	539.6	(371.1, 784.6)
16F	187	3060.5	(2633.8, 3556.3)	107	392.3	(301.3, 510.8)
17F	194	3599.8	(3134.5, 4134.3)	108	939.6	(693.7, 1272.6)
20A	195	2847.4	(2433.3, 3331.8)	110	1058.9	(829.9, 1351.1)
23A	202	2363.9	(1857.4, 3008.5)	91	310.2	(202.1, 476.0)
23B	197	673.2	(517.1, 876.4)	110	153.0	(98.7, 237.1)
24F	201	1822.6	(1411.6, 2353.3)	97	106.6	(69.7, 162.9)
31	194	3018.4	(2473.6, 3683.3)	108	113.2	(74.5, 172.1)
35B	194	6703.1	(5732.7, 7837.8)	107	1019.1	(739.9, 1403.7)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PCV15=pneumococcal 15-valent conjugate vaccine.

Table 28. Within Group Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population) (Cohort 2)

Pneumococcal Serotype	V116 (N = 174)			PPSV23 (N = 85)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
3	149	391.1	(332.8, 459.6)	75	583.1	(453.5, 749.6)
7F	150	3129.8	(2609.9, 3753.3)	70	4057.0	(3211.2, 5125.6)
8	161	2320.1	(1987.3, 2708.7)	75	2723.2	(2197.4, 3374.8)
9N	143	7214.4	(6062.9, 8584.6)	58	6482.5	(4908.9, 8560.7)
10A	155	3976.8	(3360.7, 4705.8)	73	1797.6	(1136.2, 2843.9)
11A	142	2846.6	(2411.0, 3360.8)	71	1736.6	(1367.1, 2206.0)
12F	160	2552.6	(2120.5, 3072.9)	73	1402.5	(912.2, 2156.4)
17F	125	5963.8	(5036.6, 7061.7)	67	4367.3	(3372.5, 5655.7)
19A	158	2528.9	(2201.7, 2904.9)	74	3241.5	(2646.0, 3971.0)
20A	138	6005.5	(4919.8, 7330.8)	72	3393.9	(2536.9, 4540.5)
22F	143	4389.2	(3541.1, 5440.3)	71	2524.0	(1834.5, 3472.5)

33F	131	8162.9	(6407.2, 10399.7)	59	8761.9	(6157.4, 12468.1)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Table 29. Within Group Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population) (Cohort 2)

Pneumococcal Serotype	V116 (N = 174)			PPSV23 (N = 85)		
	n	Observed GMT	95% CI[a]	n	Observed GMT	95% CI[a]
6A	152	3624.0	(3099.2, 4237.7)	74	1812.3	(1226.6, 2677.6)
15A	134	6185.2	(5179.3, 7386.6)	63	1668.2	(1234.4, 2254.5)
15C	152	4334.4	(3563.8, 5271.5)	72	1470.4	(978.6, 2209.3)
16F	146	4626.5	(3861.8, 5542.6)	74	832.8	(604.3, 1147.6)
23A	156	4253.4	(3417.6, 5293.5)	60	433.6	(247.5, 759.5)
23B	160	1530.7	(1196.5, 1958.3)	75	203.9	(127.6, 325.6)
24F	151	2746.1	(2257.9, 3339.9)	63	48.5	(28.6, 82.1)
31	146	4413.5	(3530.2, 5517.7)	68	171.8	(99.9, 295.6)
35B	148	8143.5	(6761.4, 9808.1)	76	1527.7	(1169.5, 1995.5)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

CI=confidence interval; GMT=geometric mean titer (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Table 30. Within Group Analysis of Postvaccination OPA GMTs for 21 Serotypes in V116 (Per-Protocol Population) (Cohort 3)

Pneumococcal Serotype	V116 (N = 105)		
	n	Observed GMT	95% CI[a]
3	85	318.3	(250.0, 405.3)
6A	93	2097.3	(1693.4, 2597.6)
7F	96	2051.3	(1630.2, 2581.0)
8	98	1486.8	(1230.5, 1796.6)
9N	90	4054.5	(3389.4, 4850.2)
10A	96	2564.0	(1959.1, 3355.6)
11A	87	2373.0	(1905.4, 2955.4)
12F	99	1235.3	(948.3, 1609.2)
15A	86	4328.6	(3378.7, 5545.7)
15C	89	2191.9	(1573.2, 3053.9)
16F	89	2477.0	(1887.2, 3251.2)

17F	82	3836.7	(3063.4, 4805.1)
19A	93	1533.8	(1272.4, 1848.9)
20A	88	2433.4	(1880.5, 3148.9)
22F	99	1913.5	(1453.5, 2519.0)
23A	86	3967.2	(2764.8, 5692.7)
23B	97	844.0	(608.2, 1171.4)
24F	90	2041.5	(1500.8, 2777.1)
31	90	3285.5	(2485.0, 4343.8)
33F	88	4654.3	(3532.1, 6133.1)
35B	90	5836.8	(4693.6, 7258.6)

[a] The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Postvaccination=30 days following vaccination.

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

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has in support of this application submitted data from seven clinical studies: one Phase 1/2 study (which included a dose response-study) and six Phase 3 studies. Two the Phase 3 studies, V116-003 and V116-010 can be regarded as pivotal, with the other studies focusing on particular aspects of the product (V116-004: lot-to-lot consistency, V116-007: investigation of the vaccine in adults living with HIV, V116-005: concomitant administration with QIV, and V116-006: investigation of the vaccine in pneumococcal vaccine-experienced adults).

Both pivotal studies were designed to show non-inferiority of the immune response between V116 and the comparator vaccine for the serotypes that were shared between the 2 vaccines and superiority of the serotypes unique to V116. Furthermore, the serotype specific cross-reactive OPA responses (6C and 15B) at 30 days post-vaccination were evaluated. Due to the lack of an established threshold value associated with clinical benefit, interpretation of the outcome of non-inferiority, and especially superiority testing for the unique serotypes, is difficult. Superiority testing will only indicate that an immune response is elicited and the observed differences between groups are unlikely due to chance. Whether this immune response is sufficient to offer protection cannot be determined within an immunogenicity study. As a consequence of the testing strategy, to control type I error, the studies will only have met the primary objectives in case non-inferiority is shown with respect to the OPA GMTs for the common serotypes, and superiority with respect to both OPA GMTs and the proportions of participants with ≥4-fold rises in OPA responses for the unique serotypes. However, as the clinical importance of the margins is unknown, the totality of evidence including OPA GMTs, percentage of participants achieving a 4-fold rise, geometric mean fold rise and reverse cumulative distribution curves (RCDCs) for all serotypes will be taken into consideration.

The designs of the studies were generally adequate, with some exceptions. The CHMP had in a previous SA (EMEA/H/SA/4272/1/2019/III) advised against using 18–49-year-olds subjects for the dose response-study as it is well-known that the immune system of elderly adults, which are the main target population for V116, is typically weaker and may require a stronger dose for a potent response

as compared to 18–49-year-olds. The lack of a dose response-study in a more appropriate age cohort was a weakness for the overall clinical development program, but is not considered a major deficiency.

The patient populations used in the studies are generally regarded as adequate and relevant for the indication. V116-003 and V116-010 both enrolled adults ≥50 years of age, which is a group considered to be the primary target population for the vaccine. Studies V116-003 and V116-004 also enrolled 18–49-year-olds, which supports the sought indication, for adults 18 years of age and above. The randomization, blinding, inclusion/exclusion criteria, baseline data and participant flows are regarded as appropriate for the purpose of the studies.

Study assessment methods were all considered appropriate and previously approved for pneumococcal vaccines (MOPA and PnECL were updated versions of previously used assays).

The choice of comparator also deserves discussion. The applicant has sought the indication "prevention of IPD and pneumococcal pneumonia". For one the comparators, PPSV23, used in the main studies V116-010 and V116-004, as well as in V116-006, there is no proven efficacy for pneumococcal pneumonia. If the applicant had only immunobridged V116 to PPSV23, the indication would have to be limited to IPD. For the comparator in the other pivotal study V116-003, PCV20, efficacy is based on immunobridging to PCV13, meaning that using PCV20 as a comparator constitutes a bridge-to-bridge exercise. The CHMP cautioned that should PCV20 be used a comparator in pivotal clinical trials for V116, the applicant would need to use a stringent NI criterion (for instance: the lower bound of the two-sided 95% CI >0.67 for the OPA GMT ratios). However, the applicant chose to proceed with the NI criteria that the lower bound of the two-sided 95% CI >0.5 for the OPA GMT ratios. This allows for instances of biocreep with regard to immunobridging the efficacy of V116.

The use of analgesic or antipyretic medication that occurs on the day of vaccination is recorded in both pivotal studies, as this might impact reactogenicity events seen during/directly after administration of the vaccination and also potentially immunogenicity. The applicant was requested to clarify whether use of analgesic or antipyretic medication on Day 2-5, during which solicited adverse events (AEs) are documented, was recorded and provide an overview of analgesic or antipyretic medication use over the study arms for the recorded period. The requested information was provided by the applicant. The only difference in use of analgesic/antipyretic medication use was observed in the younger cohort of study V116-003 (Cohort 2), with a higher percentage in the V116 group compared to PCV20, which was not observed in study V116-004. The data indicated that the difference in use of analgesic or antipyretic medications anytime through Day 5 postvaccination, did not substantially impact the immune response and the CHMP considers the issue resolved.

Immunogenicity data and additional analyses

V116 met the formal criterion for NI to PCV20 for the common serotypes in V116-003 and would also have met a more stringent criteria of, for instance, the lower bound of the two-sided 95% CI >0.67 for the OPA GMT ratios. V116 was also shown to be NI to PPSV23 in the pivotal study V116-010 with regard to the shared serotypes.

V116 did not formally meet the superiority criterion set for its unique serotypes in either study, which were primary immunogenicity endpoints.

In study V116-003, V116 (Capvaxive) met the predefined superiority criterion compared to PCV20 for all but one (15C) of the 11 additional serotypes to Capvaxive as assessed by the GMT ratio (Capvaxive/PCV20) and as assessed by the proportion of individuals who achieved a ≥ 4-fold rise from prevaccination to 1-month postvaccination for OPA responses.

In study V116-010, V116 (Capvaxive) met the predefined superiority criterion compared to PPSV23 for all the 9 additional serotypes to Capvaxive as assessed by the GMT ratio (Capvaxive/PPSV23) but

failed to meet the superiority criterion compared to PPSV23 for all but one (also 15C) of the 9 additional serotypes in Capvaxive as assessed by the proportion of individuals who achieved a ≥ 4-fold rise from prevaccination to 1-month postvaccination for OPA responses.

Given that the testing strategy required both non-inferiority and superiority to be positive, a type I error controlled claim that V116 was proven non-inferior to PCV20 or PPSV23 cannot be made. The study results are discussed in detail below. Overall, they indicate that V116 is immunogenic in all subgroups tested

The results from Study V116-003 indicate that a substantial immune response is generated by V116 which is largely comparable to PCV20. However, for 2 serotypes, 6A and 19A, shared between V116 and PCV20, a slightly lower immune response was observed, which is noteworthy given that the response to these serotypes was also lower after vaccination with PCV20 compared to PCV13 for which efficacy has been shown. The applicant was requested to discuss the potential consequences of the observed reduced response to serotypes 6A and 19A. The applicant responded that the impact of the slightly lower immune response in PCV20 compared to PCV13 is currently unknown, as effectiveness of PCV20 is not yet known. Therefore, the impact of the lower response for serotypes 6A and 19A in participants receiving V116 compared to PCV20, which was already lower compared to the response to the vaccine for which effectiveness was shown, cannot be easily determined. Although, it is not possible to assess the effect size, based on knowledge obtained in the field it is reasonable to assume that the immune response generated by V116 could provide protection against pneumococcal disease. The CHMP finds this acceptable.

Overall, the immune response elicited by V116 was comparable to the active comparators PCV20 and PPSV23 for the respective shared serotypes as measured by OPA GMTs, IgG GMCs, GMFR, the proportion of participants with ≥4-fold rise in OPA or IgG titre and RCDC. The immune response against the unique serotypes targeted by V116 was via the same methods shown to be superior for all but one serotype (15C). It is likely that serotype 15C did not meet the superiority margin due to cross-reactive response to serotype 15B present in PCV20 and PPSV23, considering that the 2 serotypes contain a similar polysaccharide capsule structure that only differs in O-acetylation and the serotype de-O-acetylated 15B included in V116 is essentially serotype 15C .

The immune response to 15B generated by V116 was comparable to the immune response generated by both PCV20 and PPSV23. Consequently, a protective effect of V116 against 15B can reasonably be assumed. However, the immune response to 6C was not considered acceptable as predefined by the applicant and the response was comparable to the response seen as generated by PCV20 which does not claim any protective effect against 6C. Therefore, any claim for a protective effect against serotype 6C should be removed from the SmPC. This request was agreed to by the applicant.

As the studies formally failed their primary objectives, as significance was not reached for all individual comparisons (~32 for study V116-003), no formal claim of statistical significance can be made. Given the many comparisons of individual serotypes, upon request the applicant provided more insight into type I error control by generating 10,000 trials using a bootstrap method to estimate the chance of multiple false-positive conclusions taking into account the correlation between serotypes within the study. The findings support a conclusion that the chance of a large number of false-positive results is low (chance of at least 5 positive results of individual tests around 1%).

The studies were conducted in different geographical locations and primarily in elderly cohorts, thus they are considered clinically relevant for the intended target population.

Consistently throughout the dossier, there was a noticeable variation in observation numbers for each serotype in the OPA analysis. For example, the PP population should be n=1179 for V116 arm in study V116-003, but none of the serotype's analyses had this number of datapoints. The highest n = 1161

for 10A and the lowest N= 1107 for 15A. An explanation was requested of why and how the immunogenicity results were removed. It had been noted, that in IgG testing, the observation numbers were equal for each serotype, suggesting that this phenomenon was MOPA related. The applicant has provided a sufficient explanation, namely that the samples from participants were excluded due to the intrinsic variability of the MOPA as well due to positive or missing intrinsic killing test, which is acceptable.

In study V116-003 and study V116-010, the handling of missing data was either according to the analysis model or by excluding subjects in that missing was not imputed. The latter concerned the analysis of the proportion of subjects with a ≥4-fold rise in serotype-specific OPA responses. For study V116-003, the lowest number of subjects contributing with data in the superiority analysis of proportion of subjects with a ≥4-fold rise in OPA responses for unique serotypes based on FAS was for 15A: 719/1179 (61%): V116 and 742/1177 (63%): PCV20. The highest number of subjects in the analysis was for serotype 23B: 1056/1179 (90%): V116 and 1068/117 (91%): PCV20. The proportion of subjects excluded were not fully explained by subjects not contributing with data both on day 1 and day 30. New analyses appeared not to be meaningful for neither the statistical nor the clinical interpretation, but the applicant was requested to clarify. In response the applicant explained that the number of participants included in the analysis for each serotype was impacted by serotype-specific missingness resulting from MOPA testing and samples with a positive or missing Intrinsic Killing (IK) test.

For study V116-003 the repeated measures cLDA model as proposed by Liang and Zeger was used for the primary analysis, which will allow for different baseline means for each age stratum, but restrict the baseline mean within each age stratum to be the same for all vaccination groups to allow the inclusion of participants who are missing either the baseline or postbaseline measurements. The applicant was requested to also provide as sensitivity analyses the unadjusted analysis for those with both baseline and postbaseline measurement available, which showed results in line with the primary analysis.

The baseline GMT data showed that seropositivity was common in the pneumococcal vaccine-naïve population. Importantly, comparable baseline GMTs were observed in both arms. The baseline antibody titers were already considerable for multiple serotypes and vaccination with both vaccines elicited an immune response.

The results of secondary endpoints supported the results of the primary endpoints in both pivotal studies.

We note that it is stated in the study protocol of V116-010 that immunogenicity samples will be collected up to 24 months post-vaccination. Considering that there currently is no data in the dossier regarding the durability of the immune response (all immunogenicity data is based on the 30-days post-vaccination samples), the CHMP requested to see any data regarding the follow-up of the immunity that is currently available, and a commitment to provide the final data when available. The applicant provided an approximate date for when the long-term immunogenicity data will become available to the CHMP (end of 2025). There are no interim analyses planned. This is considered acceptable.

Study V116-004, all three lots of V116 met the equivalence criteria as assessed by serotype-specific OPA GMTs at 30 days postvaccination for all 21 serotypes in V116, which was the sole primary immunogenicity endpoint. However, the immune response against serotype 23B fluctuated much more compared to the other serotypes. The applicant was asked to explain this discrepancy and discuss if it can entail any problems for efficacy during industrial scale production of V116. The applicant provided a sufficient response as to the control of the manufacturing process. Albeit the point estimate of the

OPA GMT ratios for serotype 23B has a considerably larger variation compared to the other serotypes, it is not expected to drop below a protective level of immunogenicity.

Study V116-007 did not have any formal immunogenicity criterion but V116 was seen to elicit an immune response in adults living with HIV for all 21 serotypes targeted by the vaccine as assessed by OPA GMTs, and that the immune response for the 13 serotypes common with PCV15+PPSV23 were generally comparable. However, it should be noted that HIV-patients receiving ART and with having CD4+ T-cell counts within the normal range are not regarded as immunosuppressed by the CHMP.

Concomitant administration of V116 with QIV affects both the immune response to V116 and QIV, with immune responses being lower in the concomitant group compared to the sequential group. However, for both V116 and QIV a substantial immune response was still observed after concomitant administration. The percentage of participants achieving a 4-fold rise in OPA GMTs was >50% for all serotypes, except 19A (39.7% in the concomitant group vs 50.5% in the sequential group). In addition, 95% CI of the percentage of participants achieving a 4-fold rise in OPA GMTs overlapped for 17 out of 21 serotypes, with only 9N, 17F, 19A and 20A missing this. For influenza vaccine, the percentage of participants achieving HAI titers ≥1:40 were comparable between the concomitant and sequential groups (A/H1N1: 92.9% vs 93.7%; A/H3N2: 84.2% vs 85.5%; B/Victoria: 75.6% vs 76.3% and B/Yamagata: 52.3% vs 55.1%). In addition, the RCDCs show a similar pattern between the 2 groups for both OPA GMTs and HAI titers. Therefore, although the GMTs 30 days postvaccination are numerically lower in the concomitant group compared to the sequential group, the response in the concomitant group does appear to be substantial for both vaccines. Therefore, the benefit of the option of giving the 2 vaccines together outweighs the potential risk of a somewhat reduced response with an unknown clinical impact.

In study V116-005, V116 did not meet the formal NI criterion for concomitant administration with QIV as compared to sequential administration, as the lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant/sequential] did not exceed 0.5 for one serotype (23B). For the remaining 20 serotypes, as well as for NI immune response against influenza virus, concomitant administration of V116 met the predefined NI criterion. The applicant was requested to justify why concomitant administration should be endorsed for V116 with QIV given the formal failure of the study. The applicant argued that while the criterion was not met for one serotype, the totality of immunogenicity data including OPA GMTs, IgG GMCs, OPA and IgG GMFR, and the proportion of participants with a ≥4-fold increase for both OPA and IgG responses supports concomitant administration of V116 and QIV. Considering the totality of the data and the real-life settings concerning patient compliance for multiple vaccinations during the same season, it is agreed that concomitant vaccination with V116 and QIV can be endorsed. The SmPC is updated in section 4.5 according to the new guidelines.

In study V116-006 investigating the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-experienced adults ≥50 years of age, there were no formal immunogenicity criteria. The data showed that regardless of prior pneumococcal vaccine received, V116 was immunogenic for all 21 serotypes contained in the vaccine as evaluated by OPA GMTs. In cohort 1, the immune response elicited by V116 was generally comparable to PCV15 for the five common serotypes. In cohort 2, the immune response elicited by V116 was generally comparable to that of PPSV23 for the 12 common serotypes. The immune responses elicited against V116-unique serotypes were generally higher compared to the different comparators.

Of note, in an exploratory analysis it was seen that there were no notable numerical differences within the cohorts with regard to time since last pneumococcal vaccination and prior pneumococcal vaccination history, suggesting that V116 can efficacy-wise be given to pneumococcal-experienced people. However, since there were no formal hypothesis testing for efficacy, we suggested to remove

the descriptive efficacy information from the SmPC, or at least, keep it very short. The applicant agreed to this request.

The submission currently does not contain any information regarding long-term persistence of the immune response to V116. However, study V116-010 is ongoing and does include an immunogenicity sub-study, which will investigate immunogenicity up to 24 months after vaccination with V116. This is especially relevant as it is not ensured that the kinetics of the response generated with V116 (which does not include an adjuvant) are comparable to other conjugated vaccines which included aluminium as an adjuvant. The applicant was requested to submit data on the persistence of the immune response up to 24 months once available. The applicant provided an approximate date for when the long-term immunogenicity data will become available to the CHMP (end of 2025). There are no interim analyses planned. This is considered acceptable.

No information regarding need for revaccination is currently available. In addition, sequential vaccination with a conjugated vaccine first, followed by PPSV23 (e.g. one year thereafter) is widely recommended by NITAGS in the EU, but has not been investigated with V116.

Considering that as the immunogenicity data were convincing, it can reasonably likely be assumed that V116 confers protection against clinical manifestations of pneumococcal pneumonia and IPD. However, the level of clinical efficacy remains unknown, especially regarding the unique serotypes in V116, for which efficacy cannot be bridged to a licenced product. For this purpose, the applicant has stated that they intend to follow up vaccine impact/effectiveness post-marketing via two strategies. For IPD, the applicant plans to monitor IPD surveillance data in countries (US and EU) where V116 will be recommended and used. For pneumococcal pneumonia, the applicant has submitted a draft protocol for a test-negative case-control study to evaluate the effectiveness of V116 in older adults. This will be an observational hybrid study using both primary and secondary data collection with a test-negative case-control design. The primary objective of the study is to assess the effectiveness of V116 in preventing hospitalized confirmed community acquired pneumonia (CAP, invasive and non-invasive) caused by *S. pneumoniae* serotypes contained in V116 in adults ≥65 years of age. The company has chosen this particular study design as a randomized, active-controlled efficacy trial of V116 compared to a currently licensed pneumococcal vaccine is not considered feasible due to the sample size required. Moreover, the population willing to enrol in a randomized study may be small and not representative of the larger vaccinated population due to the large uptake of already licensed pneumococcal vaccines in the elderly population in the US and EU.

The study is planned to start after licensure, recommendation, introduction, and adequate uptake of V116 into the market in older adults and ends when the number of cases required to test the primary hypothesis of the study are accrued (expected to be 5 years following study start). Approximately 15 000 subjects with CAP are expected to be evaluated to reach the sample size calculated to power the study.

However, although a test-negative design is an acceptable design to study VE, due to potential bias the estimate of the magnitude of VE may remain uncertain. The applicant is recommended to take into account the following comments.
First, an important source of potential bias is selection of subjects who are and who are not offered V116. The applicant plans to start the test-negative design if uptake of V116 is at least 20%, so effect of selection will not be too severe. However, there is already a high uptake of licensed pneumococcal vaccines making it important to provide insight into the reasons for being offered V116 or an alternative pneumococcal vaccine and the potential to properly adjust for this in the analysis.
Second, demonstration of validity of classifying vaccination status is also considered of importance.
Third, the proposed test negative case-control study plans to include approximately 15 000 subjects with CAP. The study will be sufficiently powered to confirm effectiveness, if the true VE is at least 52%,

which may be considered still optimistic, also considering the potential for bias, and may lead to absence of confirmation of a smaller however potentially still relevant effect size (REC). This study is requested as a Recommendation and not as a condition for the marketing authorisation as it is not considered key for the Benefit/Risk. The Benefit/Risk balance for Capvaxive is considered positive.

Considering the knowledge obtained in the field with other pneumococcal vaccines, it is likely that the response seen offers protection against the serotypes included in V116. The effect size of the protection is however unknown. In addition, as serotype replacement is an issue, it is unknown how long any benefit of the additional serotypes included in this vaccine compared to other vaccines will remain. As with all pneumococcal vaccines, epidemiological surveillance is necessary to ensure early detection of breakthrough disease caused by potential vaccine failure or reduced vaccine effectiveness. The applicant is expected to collect and report information on breakthrough disease and serotypes replacement (**REC**). The CHMP agreed to request it as a Recommendation.

2.6.7. Conclusions on the clinical efficacy

Overall, the results indicate that V116 is immunogenic in all subgroups tested. For the shared serotypes, a largely comparable immune response is observed between V116 and the comparator vaccines, therefore a level of protection can be inferred. For the unique serotypes, a substantial immune response is generated, with overall the majority of participants achieving a 4-fold rise in OPA antibodies 30 days after vaccination. Based on knowledge obtained in the field, it can be assumed that this immune response will likely translate into some level of protection. However, it is not possible to determine the exact level of protection, as there is no correlate of protection.

As expected, a trend towards a lower immune response is seen with increasing age.

2.6.8. Clinical safety

The clinical safety data base constitutes of data from seven clinical trials including subjects ≥18 years; one Phase 2 study (V116-001), and six Phase 3 studies (V116-003 (pivotal), V116-004, V116-005, V116-006, V116-007, and V116-010).

An Integrated Safety Summary (ISS) from the six Phase 3 studies was available by pooling 4,914 participants who received V116 into one group (003, 004, 006, 010, the sequential groups in 005, and 007) and by pooling 2,914 participants who received PCV15, PCV20, and/or PPSV23 into one combined control group.

The ISS includes subgroup summaries by age categories 18 to 49 years, and 50 years of age and older. In addition, subgroup summaries for the additional age categories of 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years of age, are available.

Key criteria for inclusion were male or female from 18 years of age. Any underlying chronic conditions were assessed to be stable per the investigator’s judgment. Women of childbearing potential were not pregnant or breastfeeding.

The primary safety endpoints in all six phase 3 studies were solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs. The methods used for safety evaluation were consistent across all Phase 3 studies in the V116 clinical program. Participants used an electronic vaccination card to report safety information.

All participants were observed for at least 30 minutes after administration of study intervention for any immediate reactions. Reactogenicity was followed for 5 days. Non-serious, unsolicited AEs were followed for 30 days while SAEs were collected up to 6 months.

2.6.8.1. Patient exposure

The participants were randomized to either receive the study vaccine (V116), active comparator (PCV20, PCV15 or PPSV23) or placebo. In the phase 3 studies a total of 5,450 adults received V116, and 2,919 received active comparator vaccines. The active comparator PCV20 was included in the pivotal study 003, while in studies 004, 006, 007 and 010, PCV15 or PPSV23 was used as active comparator. One study compared V116 when given concomitantly or sequentially with quadrivalent influenza vaccine (QIV) (study 005).

Overall, among the participants in the V116 group, 3,531 were ≥50 years and 1,919 participants were 18 to 49-year-old (Table 31). In the age group 65 to 74 years old, 1,276 participants received V116, and corresponding numbers of participants, 311, and 39 received V116 in the age groups 75 to 84 years, and ≥85 years of age, respectively.

A slightly higher share of the subjects was female (55-57%) in both the younger and older adult group in the integrated safety population. The main study population constitutes of white subjects from North America. Overall, demographic characteristics within age subgroup (18 to 49 and ≥50 years of age) in the integrated safety population were generally comparable between the V116 and combined control groups. The median age was 35 years in the younger age group and 65 years in the older age group.

Overall, 97-99% of the subjects completed the study. Discontinuation of study intervention due to AE was only evaluated in studies 005 and 007 as these concerned studies in which participants received more than 1 study vaccination. The most common reason for discontinuation was lost to follow-up (1-2%). There was no difference in participants completing the studies between the younger and older adult population or between the study vaccine and active comparator. In study 007, 155 HIV infected participants received V116. In the younger age group, 18 to 49 years, almost all were pneumococcal vaccine naïve, and in the older age group above 50 years of age, approximately one third of the participants had a previous history of pneumococcal vaccination(s). In total 878 participants receiving V116 and 261 participants in the control group had previous exposure to pneumococcal vaccine(s).

The size and composition of the safety database is considered sufficient for the assessment of the safety profile of V116. Post-marketing routine pharmacovigilance will continuously monitor safety for the detection of rare adverse events.

Table 31. Number of participants who received V116 or control in phase 3 clinical studies, (V116-003, V116-004, V116-005, V116-006, V116-007, V116-010).

Population	Study Number	Number of Participants in 6 Phase 3 Studies		Number of Participants in Integrated Analysis	
		V116	Control[a]	V116	Control[a]
Pneumococcal vaccine-naïve adults 18 to 49	V116-003	200	100	200	100
	V116-004	1616	541	1616	541
	V116-007	80	66	80	65[b]
Total		**1896**	**707**	**1896**	**706**
Pneumococcal vaccine-experienced adults 18 to 49	V116-007	23	23	23	23
Total		**23**	**23**	**23**	**23**
Pneumococcal vaccine-naïve adults ≥50	V116-003	1179	1177	1177[b]	1175[b]
	V116-005	738	N/A	364[c]	N/A
	V116-007	20	33	20	33
	V116-010	739	741	739	741
Total		**2676**	**1951**	**2300**	**1949**
Pneumococcal vaccine-experienced adults ≥50	V116-005	314	N/A	154[c]	N/A
	V116-006	509	203	509	202[b]
	V116-007	32	35	32	34[b]
Total		**855**	**238**	**695**	**236**
Overall population in Phase 3		5450	2919		
		8369			
Overall population in Integrated Analysis				4914	2914
				7828	

N/A=not applicable; PCV15=pneumococcal 15-valent conjugate vaccine (VAXNEUVANCE™); PCV20=pneumococcal 20-valent conjugate vaccine (Prevnar 20™ / APEXXNAR™); PPSV23=pneumococcal vaccine, polyvalent (23 valent) (PNEUMOVAX™23)

[a] Control included participants in V116-003 who received PCV20, participants in V116-004 who received PPSV23, participants in V116-006 who received PPSV23 or PCV15, participants in V116-007 who received PCV15 and PPSV23, and participants in V116-010 who received PPSV23.

[b] Participants excluded from the integrated analysis: 2 participants in Study V116-003 who received 1 dose each of V116 and PCV20, and 1 participant in Study V116-006 and 2 participants in V116-007 who received the incorrect study intervention.

[c] Only participants from V116-005 in the sequential group vaccinated with V116 were included in the V116 group in the integrated analysis.

Sources: [Ref. 5.3.5.1: P003V116: Table 14.1-4, 14.1-5] [Ref. 5.3.5.1: P003V116: 10.1] [Ref. 5.3.5.1: P004V116: Table 10-1] [Ref. 5.3.5.1: P005V116: Table 14.1-17] [Ref. 5.3.5.1: P006V116: Table 10-1] [Ref. 5.3.5.1: P006V116: 10.3.2] [Ref. 5.3.5.1: P007V01V116: Table 14.1-2] [Ref. 5.3.5.1: P007V01V116: Table 10-1] [Ref. 5.3.5.1: P010V116: Table 14.1-9] [Ref. 5.3.5.1: P010V116: Table 10-1] [Ref. 5.3.5.3: 08FL2C].

2.6.8.2. Adverse events

Any AE in the ISS within 30 days after vaccination with V116 or active control occurred at a higher frequency among the subjects aged 18 to 49 years, 80% (control 75%) compared to the subjects aged 50 years and older, 57% (control 62%), in both intervention groups. Most AEs were solicited AEs in both age groups and in both intervention groups.

Overall, the frequency of SAEs was low (<3%) and no clear difference was noted between interventions or between age groups (table 32).

Table 32. Summary of AEs by age, from 18 to 49 years of age and ≥50 years of age, for the integrated safety population ((V116-003, V116-004, V116-005, V116-006, V116-007, V116-010), integrated summary of safety).

	18 to 49 Years				50 Years and Older			
	V116		Control[a]		V116		Control[a]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,919		729		2,995		2,185	
with adverse events from Day 1 through Day 30 postvaccination	1,530	(79.7)	544	(74.6)	1,709	(57.1)	1,365	(62.5)
solicited[b]	1,488	(77.5)	522	(71.6)	1,512	(50.5)	1,230	(56.3)
unsolicited[c]	516	(26.9)	177	(24.3)	621	(20.7)	478	(21.9)
with vaccine-related adverse events from Day 1 through Day 30 postvaccination	1,491	(77.7)	522	(71.6)	1,546	(51.6)	1,233	(56.4)
solicited[b]	1,481	(77.2)	519	(71.2)	1,485	(49.6)	1,213	(55.5)
unsolicited[c]	206	(10.7)	47	(6.4)	190	(6.3)	112	(5.1)
with serious adverse events from Day 1 through Day 30 postvaccination	3	(0.2)	1	(0.1)	16	(0.5)	10	(0.5)
with serious adverse events from Day 1 through Month 6 postvaccination	17	(0.9)	13	(1.8)	65	(2.2)	51	(2.3)
with serious vaccine-related adverse events from Day 1 through Day 30 postvaccination	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
with serious vaccine-related adverse events from Day 1 through Month 6 postvaccination	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
with serious adverse events within 30 minutes postvaccination	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
with adverse events resulting in death	1	(0.1)	1	(0.1)	6	(0.2)	2	(0.1)

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

Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.

Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.

For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.

[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.

[b] Includes the predefined terms of injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, and pyrexia solicited from Day 1 through Day 5 postvaccination.

[c] Events include nonserious and serious adverse events reported within 30 days of vaccination, excluding predefined adverse event terms injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, and pyrexia solicited Day 1 through Day 5 postvaccination.

PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [ISS: adam-adsl; adaece]

Table 33. Summary of AEs in the integrated safety population (all ages) (V116-003, V116-004, V116-005, V116-006, V116-007, V116-010**).**

	V116			Control[a]		
	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]
Participants in population	4,914			2,914		
with adverse events from Day 1 through Day 30 postvaccination	3,239	(65.9)	(64.6, 67.2)	1,909	(65.5)	(63.8, 67.2)
solicited[c]	3,000	(61.1)	(59.7, 62.4)	1,752	(60.1)	(58.3, 61.9)
unsolicited[d]	1,137	(23.1)	(22.0, 24.3)	655	(22.5)	(21.0, 24.0)
with vaccine-related adverse events from Day 1 through Day 30 postvaccination	3,037	(61.8)	(60.4, 63.2)	1,755	(60.2)	(58.4, 62.0)
solicited[c]	2,966	(60.4)	(59.0, 61.7)	1,732	(59.4)	(57.6, 61.2)
unsolicited[d]	396	(8.1)	(7.3, 8.9)	159	(5.5)	(4.7, 6.3)
with serious adverse events from Day 1 through Day 30 postvaccination	19	(0.4)	(0.2, 0.6)	11	(0.4)	(0.2, 0.7)
with serious adverse events from Day 1 through Month 6 postvaccination	82	(1.7)	(1.3, 2.1)	64	(2.2)	(1.7, 2.8)
with serious vaccine-related adverse events from Day 1 through Day 30 postvaccination	2	(0.0)	(0.0, 0.1)	0	(0.0)	(0.0, 0.1)
with serious vaccine-related adverse events from Day 1 through Month 6 postvaccination	2	(0.0)	(0.0, 0.1)	0	(0.0)	(0.0, 0.1)
with serious adverse events within 30 minutes postvaccination	1	(0.0)	(0.0, 0.1)	0	(0.0)	(0.0, 0.1)

	V116			Control[a]		
	n	(%)	(95% CI)[b]	n	(%)	(95% CI)[b]
with adverse events resulting in death	7	(0.1)	(0.1, 0.3)	3	(0.1)	(0.0, 0.3)

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

Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.

Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.

For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.

[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.

[b] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with

the integrated statistical analysis plan.

[c] Includes the predefined terms of injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, and pyrexia solicited from Day 1 through Day 5 postvaccination.

[d] Events include nonserious and serious adverse events reported within 30 days of vaccination, excluding predefined adverse event terms injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, and pyrexia solicited Day 1 through Day 5 postvaccination.

CI=confidence interval; PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Solicited Adverse Events

Solicited AEs was reported at a higher frequency in both intervention groups in the 18- to 49-year-old age group, 78% (control 72%) compared with 50% (control 56%) in the age group ≥ 50 years of age (Table 34)

The most reported solicited AEs in individuals 18 to 49 years of age who received V116 were; injection-site pain (72%), fatigue (35%), headache (27%), myalgia (16%), injection-site erythema (13%), and injection site swelling (13%). Pyrexia was reported in 2.9% of the participants. The reported solicited injection site AEs were somewhat lower for the combined control group compared to the V116 group, but the difference is assessed to be of no clinical importance and there was no difference regarding systemic solicited AEs between intervention groups.

The most reported solicited AEs in individuals in individuals 50 years of age and older who received V116 were; injection site pain (41%), fatigue (19%), headache (12%), whereas injection site erythema, injection site swelling, and myalgia were below 7%, and pyrexia was reported in 1.4% of the participants.

As expected, overall, there were more participants with one or more AEs in the 50 to 64-year-old population compared to the older age groups (65 to 74, 75 to 84, and ≥ 85 years of age), with same age dependent pattern for active comparators. Increasing age led to a decrease in reactogenicity and this trend was especially seen for injection-site pain. The age dependent decrease was not as clear for systemic AEs and very few participants were reported with pyrexia in all age groups above 50 years of age.

Overall, in the separate studies it has been described that most participants with solicited AEs had events of short duration (≤3 days) and with a maximum intensity grade of mild (Grade 1) or moderate (Grade 2). The proportions of participants with solicited AEs that were severe in maximum intensity grade were low.

Table 34. Solicited AEs in the integrated safety population by age group ((V116-003, V116-004, V116-005, V116-006, V116-007, V116-010), Integrated Summary of Safety).

	18 to 49 Years				50 Years and Older			
	V116		Control[a]		V116		Control[a]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,919		729		2,995		2,185	
with one or more solicited adverse events	1,488	(77.5)	522	(71.6)	1,512	(50.5)	1,230	(56.3)
with no solicited adverse events	431	(22.5)	207	(28.4)	1,483	(49.5)	955	(43.7)
Solicited injection site adverse event	**1,399**	**(72.9)**	**464**	**(63.6)**	**1,276**	**(42.6)**	**1,052**	**(48.1)**
Injection site erythema	252	(13.1)	57	(7.8)	183	(6.1)	139	(6.4)
Injection site pain	1,383	(72.1)	456	(62.6)	1,216	(40.6)	998	(45.7)
Injection site swelling	248	(12.9)	62	(8.5)	190	(6.3)	160	(7.3)
Solicited systemic adverse event	**921**	**(48.0)**	**303**	**(41.6)**	**799**	**(26.7)**	**572**	**(26.2)**
Fatigue	676	(35.2)	237	(32.5)	567	(18.9)	390	(17.8)
Headache	521	(27.1)	154	(21.1)	347	(11.6)	269	(12.3)
Myalgia	309	(16.1)	67	(9.2)	200	(6.7)	140	(6.4)
Pyrexia	56	(2.9)	13	(1.8)	41	(1.4)	32	(1.5)

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

Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.

Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.

For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.

[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination. Pyrexia was defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination.

Adverse event terms are reported using MedDRA version 26.1.

PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Table 35. Participants with solicited AEs by age group in participants 50 years and older ((V116-003 Cohort 1, V116-005, V116-006, V116-007, V116-010), V116 Statistical Report).

	50 to 64 Years				65 to 74 Years				75 to 84 Years				85 Years and Older			
	V116		Control[a]		V116		Control[a]		V116		Control[a]		V116		Control[a]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,369		1,046		1,276		912		311		205		39		22	
with one or more solicited adverse events	783	(57.2)	672	(64.2)	588	(46.1)	463	(50.8)	124	(39.9)	88	(42.9)	17	(43.6)	7	(31.8)
with no solicited adverse events	586	(42.8)	374	(35.8)	688	(53.9)	449	(49.2)	187	(60.1)	117	(57.1)	22	(56.4)	15	(68.2)
Solicited injection site adverse event	**686**	**(50.1)**	**601**	**(57.5)**	**489**	**(38.3)**	**382**	**(41.9)**	**92**	**(29.6)**	**63**	**(30.7)**	**9**	**(23.1)**	**6**	**(27.3)**
Injection site erythema	88	(6.4)	73	(7.0)	72	(5.6)	54	(5.9)	20	(6.4)	11	(5.4)	3	(7.7)	1	(4.5)
Injection site pain	673	(49.2)	575	(55.0)	456	(35.7)	361	(39.6)	79	(25.4)	56	(27.3)	8	(20.5)	6	(27.3)
Injection site swelling	102	(7.5)	95	(9.1)	77	(6.0)	57	(6.3)	11	(3.5)	7	(3.4)	0	(0.0)	1	(4.5)
Solicited systemic adverse event	**429**	**(31.3)**	**318**	**(30.4)**	**293**	**(23.0)**	**207**	**(22.7)**	**63**	**(20.3)**	**42**	**(20.5)**	**14**	**(35.9)**	**5**	**(22.7)**
Fatigue	304	(22.2)	219	(20.9)	203	(15.9)	140	(15.4)	48	(15.4)	26	(12.7)	12	(30.8)	5	(22.7)
Headache	209	(15.3)	160	(15.3)	120	(9.4)	89	(9.8)	16	(5.1)	19	(9.3)	2	(5.1)	1	(4.5)
Myalgia	123	(9.0)	73	(7.0)	58	(4.5)	57	(6.3)	16	(5.1)	9	(4.4)	3	(7.7)	1	(4.5)
Solicited systemic adverse event	**429**	**(31.3)**	**318**	**(30.4)**	**293**	**(23.0)**	**207**	**(22.7)**	**63**	**(20.3)**	**42**	**(20.5)**	**14**	**(35.9)**	**5**	**(22.7)**
Pyrexia	16	(1.2)	14	(1.3)	20	(1.6)	14	(1.5)	4	(1.3)	4	(2.0)	1	(2.6)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.
Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.
For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.
[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.
Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination. Pyrexia was defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination.
Adverse event terms are reported using MedDRA version 26.1.
PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Unsolicited Adverse Events

Overall, in both age groups, 18 to 49 years, and 50 years of age and older, there were less than 9% who reported unsolicited AEs by SOC. The occurrence of unsolicited AEs mostly appeared balanced between V116 and active controls. The most reported unsolicited AEs by SOC until 30 days postvaccination was *Infections and Infestations* followed by *General disorders and administration site conditions* with no relevant difference between intervention groups or between age groups. Most unsolicited AEs with frequency above 1% were associated with reactogenicity.

Related Adverse Events

Among the AEs that were considered related to study intervention, the most reported SOC was *General disorders and administration site disorders* followed by *Nervous system disorders.*

All injection site AEs were considered related to vaccination.

There was no relevant difference in the frequency of participants with one or more vaccine related AEs in the integrated safety population (all ages) in the V116 group (62%) compared with combined control group (60%). The most frequently vaccine-related AEs in the integrated safety population were solicited AEs of injection-site pain 53% (control 50%), fatigue 24% (control 20%), headache 16.9% (control 14%), myalgia 10% (control 7%), injection-site erythema 10% (control 7%), and injection-site swelling 9% (control 8%).

As expected, the frequency of participants with one or more vaccine-related AEs was higher in the age group 18 to 49 years (78%) compared to age group 50 years and older (52%).

Participants with vaccine-related AEs, both solicited and unsolicited was higher in the younger age group (18 to 49 years of age); solicited AEs 77% (control: 71%), unsolicited AEs 11% (control 6%)

compared with the older age group (≥50 years of age); solicited AEs 50% (control 56%), unsolicited AEs 6% (control 5%), but with no relevant difference between V116 group and combined control group.

In the V116-010 study, there were a total of 5 events of urticaria reported, 3 of which occurred in the V116 group (2 non-serious AEs, and 1 SAE). The event of urticaria assessed by the investigator as an SAE occurred in a participant who had a history of urticaria (last time 10 years ago). On Day 22 the participant went to the ED twice due to rash and itching. Treatment included fexofenadine hydrochloride, hydrocortisone, promethazine, metamizole sodium, and prednisone. On Day 24, the participant went to the ED due to rash that worsened to scattered urticarial lesions on the skin all over the body and were itchy. Lab. test results: CRP of 43.5 mg/L (NR: 0-5), WBC count of 12240 × 10^9/L (NR: 4500-11500). On the same day, the participant was hospitalized with a diagnosis of urticaria. Treatment with prednisone and fexofenadine hydrochloride were continued. The participant reported no travel history and the etiology of urticaria could not be determined and no testing for hypersensitivity was performed. On Day 25 CRP was 23.9 mg/L and WBC count on Day 25 and 26 was WNL. On Day 26 the participant was discharged with the diagnosis of urticaria. On Day 28 urticaria resolved. In the opinion of the investigator, urticaria was not related to the study vaccination. As of Day 168, the last known date of contact, the participant had completed the study.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

The proportion of participants with SAEs was ≤3% and generally comparable for the V116 group and the combined control group in the integrated safety population from day 1 through month 6. No specific pattern of SAEs was identified.

Subjects with onset of SAEs showed a wide spectrum of diagnosis and occurred in an overall low frequency in both V116 group and in the combined control group. Cardiac disorders were reported in 7 (0.1%) participants in the V166 group and in 9 (0.3%) participants in the combined control group with no report of myocarditis or pericarditis. Nervous system disorders were reported in 9 (0.2%) participants in the V116 group and in 6 (0.2%) participants in the combined control group, with no reports of neurological inflammatory diseases (Table 5.3.5.3.3-AdultPCV:16).

As expected, the frequency of participants who reported SAEs were higher in the longer time follow-up period compared to the shorter time follow-up period, but there was no relevant difference between intervention groups. During follow-up period Day 1 through 6 months postvaccination in the V116 group, 82 cases (1.7%) with SAEs was reported, compared to 19 cases (0.4%) during the shorter follow-up period Day 1 through Day 30 postvaccination.

The frequency of vaccine-related SAEs was ≤0,1%. SAEs that were considered to be vaccine related by the investigator were reported for 2 participants in the V116 group. One participant in the sequential group of study 005 reported an SAE of bronchospasm. The event occurred within 30 minutes following vaccination with V116, and required medical intervention, and was assessed by the investigator as a SAE/other important medical event (medically significant, but not life-threatening or requiring hospitalization). The event resolved after approximately 24 hours. Bronchospasm is listed in SmPC Table 1. One Participant in study 006 in the V116 group was reported with injection-site cellulitis assessed by the investigator as vaccine-related SAE with onset on Day 5 postvaccination with V116 and required hospitalization and resolved on Day 16. As this concerns a single case it is acknowledged that other factors may have contributed/led to the adverse event, and therefore this AE does not need to be labelled. However, the applicant was requested to commit to follow-up injection-site cellulitis in PSURs via routine pharmacovigilance (please see section Discussion on clinical safety).

Table 36. Participants with SAEs from Day 1 through Month 6 Postvaccination ((V116-003, V116-004, V116-005, V116-006, V116-007, V116-010), Integrated Summary of Safety).

	V116		Control[a]	
	n	(%)	n	(%)
Participants in population	4,914		2,914	
with one or more serious adverse events from day 1 through month 6 postvaccination	82	(1.7)	64	(2.2)
with no serious adverse events from day 1 through month 6 postvaccination	4,832	(98.3)	2,850	(97.8)
Cardiac disorders	**7**	**(0.1)**	**9**	**(0.3)**
Acute myocardial infarction	0	(0.0)	1	(0.0)
Atrial fibrillation	1	(0.0)	0	(0.0)
Cardiac arrest	1	(0.0)	1	(0.0)
Cardiac failure	0	(0.0)	1	(0.0)
Cardiac failure congestive	2	(0.0)	0	(0.0)
Coronary artery embolism	0	(0.0)	1	(0.0)
Extrasystoles	1	(0.0)	0	(0.0)
Mitral valve incompetence	1	(0.0)	0	(0.0)
Myocardial infarction	1	(0.0)	4	(0.1)
Myocardial ischaemia	0	(0.0)	1	(0.0)
Sinus bradycardia	1	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**2**	**(0.1)**
Vertigo	0	(0.0)	2	(0.1)
Endocrine disorders	**1**	**(0.0)**	**1**	**(0.0)**
Thyroid mass	1	(0.0)	1	(0.0)
Eye disorders	**1**	**(0.0)**	**0**	**(0.0)**
Retinal detachment	1	(0.0)	0	(0.0)
Gastrointestinal disorders	**9**	**(0.2)**	**7**	**(0.2)**
Abdominal pain	0	(0.0)	1	(0.0)
Abdominal pain upper	1	(0.0)	0	(0.0)
Abdominal wall haematoma	1	(0.0)	0	(0.0)
Anal fissure	1	(0.0)	0	(0.0)
Aortoenteric fistula	0	(0.0)	1	(0.0)
Colitis	0	(0.0)	1	(0.0)

Duodenal ulcer perforation	1	(0.0)	0	(0.0)
Inguinal hernia	1	(0.0)	0	(0.0)
Intestinal perforation	1	(0.0)	0	(0.0)
Jejunal perforation	0	(0.0)	1	(0.0)
Mallory-Weiss syndrome	0	(0.0)	1	(0.0)
Oral mucosa erosion	1	(0.0)	0	(0.0)
Small intestinal obstruction	1	(0.0)	1	(0.0)
Small intestinal perforation	0	(0.0)	1	(0.0)
Small intestinal ulcer haemorrhage	1	(0.0)	0	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.0)
General disorders and administration site conditions	**5**	**(0.1)**	**2**	**(0.1)**
Chest discomfort	2	(0.0)	0	(0.0)
Chest pain	2	(0.0)	1	(0.0)
Death	1	(0.0)	0	(0.0)
Non-cardiac chest pain	0	(0.0)	1	(0.0)
Hepatobiliary disorders	**4**	**(0.1)**	**2**	**(0.1)**
Cholangitis	0	(0.0)	1	(0.0)
Cholecystitis	1	(0.0)	0	(0.0)
Cholelithiasis	1	(0.0)	1	(0.0)
Hepatic cirrhosis	1	(0.0)	0	(0.0)
Hepatic necrosis	1	(0.0)	0	(0.0)
Subcapsular hepatic haematoma	1	(0.0)	0	(0.0)
Immune system disorders	**0**	**(0.0)**	**1**	**(0.0)**
Drug hypersensitivity	0	(0.0)	1	(0.0)
Infections and infestations	**21**	**(0.4)**	**18**	**(0.6)**
Abdominal abscess	1	(0.0)	1	(0.0)
Abdominal infection	1	(0.0)	0	(0.0)
Abdominal wall abscess	1	(0.0)	0	(0.0)
Appendicitis	1	(0.0)	0	(0.0)
Arthritis bacterial	0	(0.0)	1	(0.0)
COVID-19	0	(0.0)	1	(0.0)
Cellulitis	0	(0.0)	1	(0.0)
Complicated appendicitis	1	(0.0)	0	(0.0)
Diverticulitis	1	(0.0)	0	(0.0)
Douglas' abscess	1	(0.0)	0	(0.0)
Encephalitis viral	0	(0.0)	1	(0.0)
Gastroenteritis	0	(0.0)	3	(0.1)
Infectious mononucleosis	0	(0.0)	1	(0.0)
Influenza	1	(0.0)	0	(0.0)
Injection site cellulitis	1	(0.0)	0	(0.0)
Neurosyphilis	0	(0.0)	1	(0.0)
Osteomyelitis chronic	1	(0.0)	0	(0.0)
Pelvic abscess	0	(0.0)	1	(0.0)
Peritonitis	1	(0.0)	0	(0.0)
Pneumonia	1	(0.0)	5	(0.2)
Pneumonia aspiration	1	(0.0)	0	(0.0)
Pyelonephritis	1	(0.0)	0	(0.0)
Respiratory tract infection	0	(0.0)	1	(0.0)
Sepsis	3	(0.1)	1	(0.0)
Septic shock	2	(0.0)	0	(0.0)
Tooth abscess	1	(0.0)	0	(0.0)
Urinary tract infection	2	(0.0)	0	(0.0)
Urosepsis	1	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**6**	**(0.1)**	**5**	**(0.2)**
Ankle fracture	1	(0.0)	0	(0.0)
Brain contusion	0	(0.0)	1	(0.0)
Concussion	1	(0.0)	0	(0.0)
Hip fracture	1	(0.0)	1	(0.0)
Lower limb fracture	0	(0.0)	1	(0.0)
Procedural pain	1	(0.0)	0	(0.0)
Rib fracture	0	(0.0)	1	(0.0)
Road traffic accident	0	(0.0)	1	(0.0)
Traumatic fracture	1	(0.0)	0	(0.0)

Upper limb fracture	2	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**3**	**(0.1)**	**0**	**(0.0)**
Diabetes mellitus inadequate control	1	(0.0)	0	(0.0)
Hyponatraemia	2	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(0.1)**	**4**	**(0.1)**
Chondrocalcinosis	0	(0.0)	1	(0.0)
Intervertebral disc protrusion	0	(0.0)	1	(0.0)
Lumbar spinal stenosis	0	(0.0)	1	(0.0)
Osteoarthritis	2	(0.0)	0	(0.0)
Spinal osteoarthritis	1	(0.0)	0	(0.0)
Systemic lupus erythematosus	0	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10**	**(0.2)**	**6**	**(0.2)**
Adenocarcinoma gastric	0	(0.0)	1	(0.0)
Benign fallopian tube neoplasm	1	(0.0)	0	(0.0)
Breast cancer	1	(0.0)	0	(0.0)
Clear cell renal cell carcinoma	1	(0.0)	0	(0.0)
Diffuse large B-cell lymphoma	0	(0.0)	1	(0.0)
Endometrial cancer	1	(0.0)	0	(0.0)
Gastric cancer	1	(0.0)	0	(0.0)
Invasive ductal breast carcinoma	1	(0.0)	0	(0.0)
Malignant melanoma	1	(0.0)	0	(0.0)
Metastases to meninges	0	(0.0)	1	(0.0)
Oligodendroglioma	1	(0.0)	0	(0.0)
Plasma cell myeloma	0	(0.0)	1	(0.0)
Prostate cancer	0	(0.0)	1	(0.0)
Rectal adenocarcinoma	1	(0.0)	0	(0.0)
Squamous cell carcinoma	0	(0.0)	1	(0.0)
Squamous cell carcinoma of skin	1	(0.0)	0	(0.0)
Nervous system disorders	**9**	**(0.2)**	**6**	**(0.2)**
Aphasia	1	(0.0)	0	(0.0)
Cerebrovascular accident	3	(0.1)	0	(0.0)
Dizziness	1	(0.0)	0	(0.0)
Encephalopathy	0	(0.0)	1	(0.0)
Haemorrhage intracranial	1	(0.0)	0	(0.0)
Hepatic encephalopathy	1	(0.0)	0	(0.0)
Ischaemic stroke	0	(0.0)	2	(0.1)
Metabolic encephalopathy	0	(0.0)	1	(0.0)
Paraesthesia	1	(0.0)	0	(0.0)
Peroneal nerve palsy	1	(0.0)	0	(0.0)
Radial nerve palsy	0	(0.0)	1	(0.0)
Seizure	0	(0.0)	1	(0.0)
Syncope	1	(0.0)	0	(0.0)
Product issues	**1**	**(0.0)**	**0**	**(0.0)**
Device occlusion	1	(0.0)	0	(0.0)
Psychiatric disorders	**7**	**(0.1)**	**1**	**(0.0)**
Alcohol withdrawal syndrome	1	(0.0)	1	(0.0)
Alcoholism	1	(0.0)	0	(0.0)
Bipolar disorder	2	(0.0)	0	(0.0)
Delirium tremens	1	(0.0)	0	(0.0)
Depression	1	(0.0)	0	(0.0)
Major depression	1	(0.0)	0	(0.0)
Psychotic disorder	1	(0.0)	0	(0.0)
Renal and urinary disorders	**2**	**(0.0)**	**2**	**(0.1)**
Acute kidney injury	1	(0.0)	1	(0.0)
Nephrolithiasis	1	(0.0)	1	(0.0)
Reproductive system and breast disorders	**1**	**(0.0)**	**0**	**(0.0)**
Testicular pain	1	(0.0)	0	(0.0)

Respiratory, thoracic and mediastinal disorders	**6**	**(0.1)**	**1**	**(0.0)**
Acute respiratory failure	1	(0.0)	0	(0.0)
Bronchospasm	1	(0.0)	0	(0.0)
Chronic obstructive pulmonary disease	1	(0.0)	1	(0.0)
Dyspnoea	1	(0.0)	0	(0.0)
Pneumothorax	1	(0.0)	0	(0.0)
Pulmonary embolism	1	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.0)**	**0**	**(0.0)**
Urticaria	1	(0.0)	0	(0.0)
Social circumstances	**1**	**(0.0)**	**0**	**(0.0)**
Victim of homicide	1	(0.0)	0	(0.0)
Vascular disorders	**1**	**(0.0)**	**2**	**(0.1)**
Deep vein thrombosis	0	(0.0)	1	(0.0)
Hypotension	0	(0.0)	1	(0.0)
Orthostatic hypotension	1	(0.0)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.
Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.
For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.
[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.
Adverse event terms are reported using MedDRA version 26.1.
PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Deaths

Over the course of these six clinical Phase 3 studies, 11 deaths were reported. Eight deaths (0.1%) were reported in the V116 group: myocardial infarction (n=1), death (unknown cause) (n=1), hepatic cirrhosis (n=1), hepatic encephalopathy (n=1), sepsis (n=1), septic shock (n=1), cerebrovascular accident (n=1), victim of homicide (n=1).
• Three deaths (0.1%) in the combined control group: cardiac arrest (n=1), abdominal abscess (n=1), road traffic accident (n=1).

In addition to those described above, one death occurred in the concomitant group (V116+QIV) in study-005 (metastatic malignant melanoma).

None of the deaths in either treatment group were considered by the investigator to be related to the study treatment. Narratives of all cases (except victim of homicide) characterize multi-morbid patients with a complex history, and other underlying conditions as causal factor cannot be safely excluded in these cases. Thus, a conclusion on a clear causality with vaccination cannot be drawn in these cases.

2.6.8.4. Safety in special populations

Age

Any adverse event within 30 days after vaccination with V116 or active control occurred at a higher frequency among the subjects aged 18 to 49 years of age 80% (control 75%) compared to the subjects aged 50 years and older 57% (control 63%). Solicited AEs was also reported at a higher frequency in both intervention groups in the younger age group, 78% (control 72%) compared with 50% (control 56%) in the older age group. The same pattern was noted for the vaccine related AEs.

As expected, overall, there were more participants with one or more AEs in the 50 to 64-year-old population compared to the older age groups (65 to 74, 75 to 84, and ≥ 85 years of age), with same age dependent pattern for active comparators. Increasing age led to a decrease in reactogenicity and this trend was especially seen for injection-site pain. The age dependent increase was not as clear for systemic AEs and very few participants were reported with pyrexia in all age groups.

HIV infected individuals

The safety of V116 was evaluated in HIV-1 infected individuals in study 007, in which 313 adults 8 weeks apart received V116 followed by placebo, or PCV15 followed by PPSV23. All participants included in the study received antiretroviral therapy, the majority did not have a detectable viral load and 74.7% had a CD4+ T-cell counts >200 cells/µL, which suggests that most participants were not immunocompromised.

The proportion of participants with solicited injection-site AEs was lower in the V116+Placebo group compared with the PCV15+PPSV23 group, both when following any vaccination or following each vaccination. Reported solicited systemic AEs was generally comparable in participants receiving V116 (32%) compared with PCV15 (29%) or PPSV23 (30%). Very few participants in both intervention groups experienced pyrexia postvaccination. Overall, the safety profile in well-controlled HIV-1 infected individuals was similar to the safety profile in immunocompetent adults.

Prior pneumococcal vaccination

Across studies, the safety profile was generally comparable in each intervention group, regardless of prior pneumococcal vaccination status or prior pneumococcal vaccine received.

Sex, Race and Ethnicity

Overall, the safety profile in the different subgroups (age, sex, race and ethnicity) was similar to the safety profile in the overall population, and no new safety signals are observed.

Male participants reported fewer AEs than female participants regardless of intervention group. These patterns have also been observed for previous pneumococcal conjugate vaccines and do not have clinical implications. No clear trends were observed with respect to reactogenicity between race or ethnic subgroups. Overall, the safety profile in the different subgroups of sex, race and ethnicity was as for the entire population.

Number of Risk Factors for Pneumococcal Disease

In studies with subgroup analyses by number of risk factors, safety results observed in participants by number of risk factors were generally consistent with those in the overall study population.

Table 37. Participants with Adverse Events by Age Group (Incidence > 0% in One or More Vaccination Groups)(All Participants as Treated Population)(V116-003, V116-004, V116-005, V116-006, V116-007, V116-010)

	18 to 64 Years		65 to 74 Years		75 to 84 Years		85 Years and Older	
MedDRA Terms	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)
Participants in population	3,288	1,775	1,276	912	311	205	39	22
Total AEs	2,384 (72.5)	1,274 (71.8)	701 (54.9)	532 (58.3)	156 (50.2)	109 (53.2)	22 (56.4)	8 (36.4)
Serious AEs - Total	39 (1.2)	32 (1.8)	33 (2.6)	26 (2.9)	7 (2.3)	6 (2.9)	3 (7.7)	0 (0.0)
– Fatal	4 (0.1)	1 (0.1)	3 (0.2)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
– Hospitalization/prolong existing hospitalization	29 (0.9)	29 (1.6)	30 (2.4)	23 (2.5)	6 (1.9)	5 (2.4)	3 (7.7)	0 (0.0)
– Life-threatening	11 (0.3)	4 (0.2)	7 (0.5)	8 (0.9)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)
– Disability/incapacity	2 (0.1)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Other (medically significant)	5 (0.2)	2 (0.1)	2 (0.2)	3 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	25 (0.8)	13 (0.7)	2 (0.2)	7 (0.8)	0 (0.0)	1 (0.5)	1 (2.6)	0 (0.0)
Nervous system disorders	829 (25.2)	370 (20.8)	152 (11.9)	114 (12.5)	21 (6.8)	22 (10.7)	3 (7.7)	2 (9.1)
Accidents and injuries	27 (0.8)	17 (1.0)	12 (0.9)	9 (1.0)	4 (1.3)	1 (0.5)	0 (0.0)	0 (0.0)
Cardiac disorders	3 (0.1)	5 (0.3)	4 (0.3)	5 (0.5)	2 (0.6)	2 (1.0)	0 (0.0)	0 (0.0)
Vascular disorders	7 (0.2)	13 (0.7)	5 (0.4)	4 (0.4)	1 (0.3)	2 (1.0)	0 (0.0)	0 (0.0)
Cerebrovascular disorders	1 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	246 (7.5)	163 (9.2)	101 (7.9)	66 (7.2)	27 (8.7)	11 (5.4)	4 (10.3)	0 (0.0)
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	41 (1.2)	15 (0.8)	11 (0.9)	12 (1.3)	3 (1.0)	2 (1.0)	1 (2.6)	1 (4.5)

Every participant is counted a single time for each applicable row and column; Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.

Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group; For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.

[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.

Adverse event terms are reported using MedDRA version 26.1.

Psychiatric disorders, Nervous system disorders, Cardiac disorders, Infections and infestations, Vascular disorders were defined by the respective MedDRA 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 CMQ and included the following PTs: Quality of life decreased, Impaired quality of life; Sum of postural hypotension, falls, black out, syncope, dizziness, ataxia, fractures was defined by a CMQ and included the following PTs: MedDRA 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.

CMQ=Custom MedDRA Query; HLGT=High Level Group Term; PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); PT=Preferred Term; SMQ=standardized MedDRA Query; SOC= System Organ Class.

Table 38. Participants With Adverse Events Related to Study Vaccine by Age Group (Incidence >0% in One or More Vaccination Groups)

MedDRA Terms	18 to 64 Years		65 to 74 Years		75 to 84 Years		85 Years and Older	
	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)
Participants in population	3,288	1,775	1,276	912	311	205	39	22
Total AEs	2,281 (69.4)	1,188 (66.9)	614 (48.1)	472 (51.8)	128 (41.2)	87 (42.4)	14 (35.9)	8 (36.4)
Serious AEs - Total	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Hospitalization/prolong existing hospitalization	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Other (medically significant)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	5 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	715 (21.7)	308 (17.4)	119 (9.3)	85 (9.3)	16 (5.1)	18 (8.8)	2 (5.1)	1 (4.5)
Accidents and injuries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	13 (0.4)	5 (0.3)	3 (0.2)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	18 to 64 Years		65 to 74 Years		75 to 84 Years		85 Years and Older	
MedDRA Terms	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)	V116 n (%)	Control[a] n (%)
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	26 (0.8)	5 (0.3)	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Every participant is counted a single time for each applicable row and column; Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.

Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group; For V116-007, reported events include nonserious adverse events within 30 days postvaccination with V116 or PCV15 and serious adverse events within 180 days postvaccination with V116 or PCV15.

[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.

Adverse event terms are reported using MedDRA version 26.1.

Psychiatric disorders, Nervous system disorders, Cardiac disorders, Infections and infestations, Vascular disorders were defined by the respective MedDRA 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 CMQ and included the following PTs: Quality of life decreased, Impaired quality of life; Sum of postural hypotension, falls, black out, syncope, dizziness, ataxia, fractures was defined by a CMQ and included the following PTs: MedDRA 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.

CMQ=Custom MedDRA Query; HLGT=High Level Group Term; PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); PT=Preferred Term; SMQ=standardized MedDRA Query; SOC= System Organ Class.

Source: [ISS: adam.adsl;adaece]

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

In study 005 safety profile was generally similar between the concomitant and sequential intervention groups. In this separate study, some differences are noted for local and systemic AEs (except pyrexia) in both intervention groups when compared to the V116 group in the integrated safety population (≥50 years of age).

2.6.8.6. Discontinuation due to adverse events

Discontinuation of study intervention due to AE was only evaluated in studies 005 and 007 as these concerned studies in which participants received more than 1 study vaccination.

In study 005, 2 of 534 (0.4%) participants in the concomitant group and 1 of 535 (0.2%) participants in the sequential group had AEs leading to study vaccine discontinuation. In study 007, no participants discontinued study intervention due to AEs. Participants in studies 003, 004, 006, and 010 received a single dose of V116 or control and, therefore, could not discontinue study intervention.

Overall, 97-99% of the subjects completed the study. The most common reason for discontinuation was lost to follow-up (1-2%). There was no difference in participants completing the studies between the younger and older adult population or between the study vaccine and active comparator (Table 39).

Table 39. Disposition of participants included in the integrated safety analysis ((study V116-003, V116-004, V116-005, V116-006, V116-007 and study V116-010), Integrated Summary of Safety)

	18 to 49 Years						50 Years and Older					
	V116		Control[a]		Total		V116		Control[a]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,919		729		2,648		2,995		2,185		5,180	
Vaccination With												
V116	1,919	(100.0)	0	(0.0)	1,919	(72.5)	2,995	(100.0)	0	(0.0)	2,995	(57.8)
PCV15	0	(0.0)	88	(12.1)	88	(3.3)	0	(0.0)	184	(8.4)	184	(3.6)
PCV20	0	(0.0)	100	(13.7)	100	(3.8)	0	(0.0)	1,175	(53.8)	1,175	(22.7)
PPSV23	0	(0.0)	541	(74.2)	541	(20.4)	0	(0.0)	826	(37.8)	826	(15.9)
Trial Disposition												
Completed	1,859	(96.9)	709	(97.3)	2,568	(97.0)	2,956	(98.7)	2,151	(98.4)	5,107	(98.6)
Discontinued	60	(3.1)	20	(2.7)	80	(3.0)	39	(1.3)	34	(1.6)	73	(1.4)
Death	1	(0.1)	1	(0.1)	2	(0.1)	6	(0.2)	2	(0.1)	8	(0.2)
Lost To Follow-Up	43	(2.2)	14	(1.9)	57	(2.2)	22	(0.7)	20	(0.9)	42	(0.8)
Physician Decision	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Withdrawal By Subject	14	(0.7)	4	(0.5)	18	(0.7)	10	(0.3)	11	(0.5)	21	(0.4)
Trial Disposition												
Other	2	(0.1)	1	(0.1)	3	(0.1)	1	(0.0)	0	(0.0)	1	(0.0)

Each participant is counted once for Trial Disposition based on the latest corresponding disposition record.
Only participants from V116-005 in the sequential group vaccinated with V116 are included in the V116 group.
Participants from V116-007 who were randomized to V116+Placebo are included in the V116 group; participants from V116-007 who were randomized to PCV15+PPSV23 are included in the control group.
Participants from V116-007 who received PCV15+PPSV23 are included in the vaccinated with PCV15 counts.
[a] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23.
PCV15=pneumococcal 15-valent conjugate vaccine; PCV20=pneumococcal 20-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

2.6.9. Discussion on clinical safety

The main evidence for the clinical safety of V116 was based on six Phase 3 clinical trials which included subjects ≥18 years who were randomized to either receive the study vaccine (V116), active comparator (PCV20, PCV15 or PPSV23) or placebo. In total, 5,450 adults received V116, and 2,919 received active comparator vaccines in the Phase 3 studies. The active comparator PCV20 was included in the pivotal study 003, while in studies 004, 006, 007 and 010, PCV15 or PPSV23 was used as active comparator. One study compared V116 when given concomitantly or sequentially with quadrivalent influenza vaccine (QIV) (study 005).

The primary safety endpoints in all six Phase 3 studies were solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs. The methods used for safety evaluation were consistent across all Phase 3 studies in the V116 clinical program. Participants used an electronic vaccination card to report safety information. All participants were observed for at least 30 minutes after administration of study intervention for any immediate reactions. Solicited AEs were followed for 5 days. Unsolicited reactogenicity reactions were monitored for 30 days. For severe adverse events, subjects were followed for 6 months, which is considered a sufficient period of time to collect relevant (serious) adverse events and is in accordance with the Guideline on clinical evaluation of vaccines.

An Integrated Safety Summary (ISS) from the six Phase 3 studies was available by pooling 4,914 participants who received V116 into one group (003, 004, 006, 010, the sequential groups in 005, and 007) and by pooling 2,914 participants who received PCV15, PCV20, and/or PPSV23 into one combined control group. The ISS includes subgroup summaries by age categories 18 to 49 years, and 50 years of age and older. In addition, subgroup summaries for the additional age categories of 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years of age, are available.

Based on the reactogenicity data of the individual comparator vaccines and the observed trends between age groups, the pooling strategy of the applicant is considered acceptable.

Safety data from the Phase 2 study is not included in the ISS, and therefore only presented as separate data.

Exposure

Overall, 5,450 participants received V116, of which 3,531 were ≥50 years old and 1,919 participants were 18 to 49 years old. In age group 65 to 74 years old, 1,369 participants received V116, and corresponding numbers of participants 1,276, 311, and 39 received V116 in the age groups 65 to 74 years, 75 to 84 years, and ≥85 years, respectively. The median age was 35 years in the younger age group 18 to 49 years, and 65 years in the age group 50 years and older.

In total 878 participants receiving V116 had previous exposure to a pneumococcal vaccine.

In study 007, 155 HIV infected participants received V116.

In study 005, 1,052 participants either received V116 concomitantly with QIV or sequentially.

Overall, 97-99% of the subjects completed the study. The most common reason for discontinuation was lost to follow-up (1-2%).

Adverse Events

Overall, the majority of participants experienced vaccine-related AEs in both V116 and the combined control groups. The proportion of participants experiencing vaccine-related AEs are generally similar for

all intervention groups and no clinically significant differences can be observed between V116 and the combined control group in the integrated safety analysis.

Across studies, observations about AEs were consistent, with most participants experiencing one or more solicited AEs, and injection-site pain being the most frequently reported solicited AE, followed by fatigue and headache. and most AEs were mild to moderate in intensity, and of short duration (≤3 days).

All injection-site AEs and pyrexia solicited from day 1 through day 5 postvaccination were considered to be vaccine-related and this can be agreed.

In the ISS and across all studies the proportions of participants with solicited AEs were generally comparable between the V116 group and the group receiving control.

In the ISS analysed for the individuals 18 to 49 years of age, AEs was reported in 78% of the V116 group and 72% in the control group. The most reported solicited AEs in the V116 group were injection-site pain (72%), fatigue (35%), headache (27%), myalgia (16%), injection-site erythema (13%), and injection site swelling (13%). Pyrexia was reported in 2.9% of the participants.

In the ISS, the proportion of individuals 50 years of age or older reporting at least one solicited AEs was 50% in the V116 group and 56% in the control group. The most reported solicited AEs in V116 group were injection-site pain (41%), fatigue (19%), headache (12%), whereas injection site erythema, injection site swelling, and myalgia were below 7%, and pyrexia was reported in 1.4% of the participants.

As expected, increasing age led to a decrease in reactogenicity. Participant above 50 years of age generally reported fewer AEs than participants 18 to 49 years of age, regardless of intervention group. The same pattern was noted for the vaccine related AEs.

There were more participants 50 years and older with AEs in the 50 to 64-year-old population compared to the older age groups (65 to 74, 75 to 84, and ≥ 85 years of age), with same age dependent pattern for active comparators. In these older age groups increasing age led to a decrease in reactogenicity and this trend was especially seen for injection-site pain. The age dependent decrease was not as clear for systemic AEs and very few participants were reported with pyrexia in all age groups. The applicant was requested that this difference should be reflected in the SmPC. In line with the differences in frequencies of local injection site reactions in the older age groups this has been accurately reflected in the SmPC section 4.8. For AEs not related to reactogenicity there was no clinical meaningful difference, and this is also accurately reflected in the SmPC.

Overall, <9% reported unsolicited AEs by SOC. The occurrence of unsolicited AEs mostly appeared balanced between V116 and active controls. Most unsolicited AEs with frequency above 1% were associated with reactogenicity.

The most frequently reported (≥5%) vaccine-related AEs in the integrated safety population were the solicited AEs of injection-site pain, fatigue, headache, myalgia, injection-site erythema, and injection-site swelling.

There was no relevant difference in the frequency of participants with one or more vaccine related AEs in the integrated safety population (all ages) in the V116 group (62%) compared with combined control group (60%). The most frequently vaccine-related AEs in the integrated safety population were solicited AEs of injection-site pain 53% (control 50%), fatigue 24% (control 20%), headache 17% (control 14%), myalgia 10% (control 7%), injection-site erythema 10% (control 7%), and injection-site swelling 9% (control 8%).

As expected, the frequency of participants with one or more vaccine-related AEs was higher in the age group 18 to 49 years (78%) compared to age group 50 years and older (52%).

Based on the general statement of the applicant, potential relatedness of the different AEs considered related to the vaccine by the investigator could not be established. The applicant was asked to further analyse and evaluate causality for AEs that have been observed with this product. AEs that have been reported for V116 and at a similar or higher frequency compared to the Comparator and listed as ADRs for the other recently approved PCV vaccines (for adults) were analysed and presented. The same analysis was executed for the AEs that are not reported as ADRs for the other recently approved PCV vaccines but reported at a higher frequency compared to the Comparator and not already listed as ADRs for V116 in SmPC 4.8, Table 1. Following this analysis, the applicant responded that AEs not labelled in 4.8, were urticaria, decreased appetite, vomiting, dyspnoea, injection site bruising and seasonal allergy. The applicant did not identify any additional terms relevant for inclusion in section 4.8 of the proposed V116 SmPC. There were no AEs categorized as Adverse Events of Special Interest (AESIs) in the V116 clinical development program.

Based on time to onset and presence of confounding factors, it is agreed that there is insufficient evidence to support a causal association between V116 and urticaria, decreased appetite, dyspnoea and seasonal allergy. However, the conclusion of the applicant that causality between vomiting and injection-site bruising and V116 cannot be concluded, is not agreed, and vomiting and injection-site bruising with frequency uncommon is added to Section 4.8 of the SmPC.

Serious adverse events and death

The reported frequency of SAEs in the integrated safety population was low (≤3%) and generally comparable between interventions. The frequency of vaccine-related SAEs was low (≤0,1%), in total 2 cases in the V116 group. These 2 vaccine-related SAEs were bronchospasm within 30 minutes postvaccination, and injection-site cellulitis with onset Day 5 postvaccination. Bronchospasm has been incorporated in section 4.8 of the SmPC as ADR, and this is considered adequate since this is a hypersensitivity reaction, which are known to occur in rare instances after vaccination. The applicant was requested to commit to report on all hypersensitivity events, but also other rare adverse events in future Periodic Update Safety Reports (PSURs). The applicant committed to monitor and report rare adverse reactions and allergic reactions via routine pharmacovigilance.

Injection-site cellulitis, which occurred on Day 5 post-vaccination at the site of injection has not been included in section 4.8 of the SmPC. As this concerns a single case where other factors may have contributed/led to the adverse event it is not proposed to label injection site cellulitis at this stage, however the applicant was requested to commit to follow-up injection-site cellulitis in PSURs. The applicant has acknowledged the request and agreed to monitor injection-site cellulitis events via routine pharmacovigilance and to discuss in future PSURs.

An SAE of urticaria with onset D22 postvaccination was observed, for which a causal relationship with V116 cannot be excluded in the opinion of the assessor. This SAE occurred in a participant with a history of urticaria. Three additional cases of vaccine-related urticaria occurred in the V116 group. Together this raises questions concerning possible exacerbation of (pre-existing) immune-mediated diseases after vaccine administration, which cannot be excluded. The applicant was requested to provide a tabulated overview of any immune-mediated illnesses and their frequencies of occurrence that may have worsened after V116/comparator vaccine administration and discuss their relatedness. In case a causal relationship between exacerbation of illness and V116 administration seems probable, these should be labelled accordingly in section 4.8 of the SmPC. As evident from data provided by the applicant, no patients with pre-existing urticaria experienced worsening of their condition following

vaccination with V116 and only 2 other cases experienced exacerbation of their medical history condition after vaccination, each with a different type of condition. These 3 different cases do not provide strong evidence for a causal relationship between vaccination and exacerbation of pre-existing medical condition. Furthermore, no differences are evident between the V116 and control groups.

Based on narrative information provided by the applicant, none of the vaccine-related urticaria cases are evaluated as causality associated with vaccination.

No specific pattern of SAEs was identified.

In the six Phase 3 studies, eight deaths were reported among participants receiving V116, none of them was considered related to vaccination.

Discontinuation due to AE

As vaccination with V116 only requires a single dose, participants could only discontinue the intervention in studies in which V116 was combined with a different intervention. A low number of discontinuations were reported in study V116-005 (3 in total), in which V116 was combined with concomitant or sequential QIV. One case was considered potentially related to V116 with AEs leading to discontinuation being injection-site pain, malaise, injection-site swelling and injection-site erythema. The reported AEs injection-site pain and swelling were moderate in intensity, whilst the AE injection-site erythema was reported as severe in intensity. All AEs were resolved 19 days postvaccination and are labelled in 4.8 of the SmPC. Consequently, no new safety signals are observed.

Concomitant vaccination with QIV

The safety profile was generally similar between the concomitant and sequential intervention groups. In this separate study, some differences are noted for local and systemic AEs (except pyrexia) in both intervention groups when compared to the V116 group in the integrated safety population (≥50 years of age). The applicant was requested to discuss possible explanations for this difference and update the SmPC accordingly. Applicant provided a discussion based on clinical data from study V116-005. Based upon comparison between events following second vaccination in the sequential group, where participants received a single vaccination of V116, and events following first vaccination in the concomitant group where participants received QIV concomitantly with V116, it is agreed that the SmPC text accurately reflects the clinical trial data.

HIV infected individuals

The safety of V116 was evaluated in HIV-1 infected individuals in study 007, in which 313 adults eight weeks apart received V116 followed by placebo, or PCV15 followed by PPSV23.

The proportion of participants with solicited injection-site AEs was lower in the V116+Placebo group compared with the PCV15+PPSV23 group, both when following any vaccination or following each vaccination. Reported solicited systemic AEs was generally comparable in participants receiving V116 (32%) compared with PCV15 (29%) or PPSV23 (30%). Very few participants in both intervention groups experienced pyrexia postvaccination. Overall, the safety profile in well-controlled HIV-1 infected individuals was similar to the safety profile in immunocompetent adults.

All participants included in the study received antiretroviral therapy, the majority did not have a detectable viral load and 74.7% had a CD4+ T-cell counts >500 cells/µL, and that most participants were not immunocompromised and thereby not relevant information for immunocompromised individuals. The applicant was therefore requested to remove the information in section 4.8 regarding HIV-subjects**.** Although it should be noted that all participants included in the study received antiretroviral therapy, the majority did not have a detectable viral load and 74.7% had a CD4+ T-cell counts >500 cells/µL, and that most participants were not immunocompromised and thereby not

relevant information for immunocompromised individuals. However, as the information on this study included in section 4.8 only states that no safety signals have been observed in participants living with HIV without claiming immunocompromised status for these participants, this statement can be accepted. Furthermore, the SmPC text is in accordance with recently approved SmPC for PCV vaccines and is considered as relevant for the prescriber.

Prior pneumococcal vaccination

Across studies, the safety profile was generally comparable in each intervention group, regardless of prior pneumococcal vaccination status or prior pneumococcal vaccine received. The applicant was requested to present an integrated safety summary by vaccination status (pneumococcal vaccine naïve compared with pneumococcal vaccine experienced). The applicant presented complementary analysis according to the request. It is agreed that the safety profile of V116 was generally comparable to control within the vaccine-naïve group and the vaccine-experienced group and that the safety evaluation of the integrated population by vaccination status is generally consistent with the overall integrated safety analysis.

Sex, Race and Ethnicity

Overall, the safety profile in the different subgroups (age, sex, race and ethnicity) was similar to the safety profile in the overall population, and no new safety signals are observed.

Male participants reported fewer AEs than female participants regardless of intervention group. These patterns have also been observed for previous pneumococcal conjugate vaccines and do not have clinical implications. Overall, these observed trends do not impact the use of the vaccine.

Pregnancy

Across all 6 phase 3 clinical trials, there was one report of a pregnancy in the V116 intervention group (vaccinated 21 days prior to the last reported menstruated period). Considering the lack of experience with V116 during pregnancy, the applicant was requested to discuss these outcomes in the yearly PSURs within the context of routine pharmacovigilance and the responses was acknowledged. The commitment to monitor pregnancy outcomes via routine pharmacovigilance is agreed.

2.6.10. Conclusions on the clinical safety

The safety profile of V116 was generally comparable to comparator pneumococcal vaccines.

Even though many participants reported AEs, these were mostly related to reactogenicity, mild or moderate in intensity, and of short duration.

The most frequently reported AEs were injection-site pain, fatigue, headache, myalgia, and injection-site erythema. Pyrexia was reported at a low frequency (<3%). In line with expectations, for this type of vaccines reactogenicity decreased with age.

Two SAEs occurred that was considered related to V116 (bronchospasm, injection-site cellulitis), both were resolved. Bronchospasm has been labelled in the product information. Injection-site cellulitis concerns a single case, and other factors may have contributed/led to the adverse event, and the event was therefore not labelled. The applicant has agreed to monitor injection-site cellulitis events via routine pharmacovigilance and to discuss in future PSURs.

No deaths occurred that were considered potentially related to V116.

In conclusion, V116 is well tolerated in adults ≥18 YOA.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 40. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

No safety concerns that require follow up through the risk management plan have been identified with the proposed regimen.
The applicant has not included any important identified risks, important potential risks or missing information. Based on the evaluation of safety data outlined of this AR, this can be agreed.

2.7.2. Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for Pneumococcal 21-valent Conjugate Vaccine.

2.7.3. Risk minimisation measures

No additional risk minimisation measures are needed. There are not routine risk minimisation activities.

2.7.4. Conclusion

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

2.8. Pharmacovigilance

2.8.1. 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.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure

2.8.2. 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 17-Jun-2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The applicant submitted a bridging test as a full user test was not considered necessary. This is considered acceptable. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Capvaxive (Pneumococcal polysaccharide conjugate vaccine (21-valent)) is included in the additional monitoring list as it is a biological and contains new active substances which, on 1 January 2011, were not contained in any medicinal product authorised in the EU. Those are pneumococcal polysaccharides of serotypes 9N, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 20A, 23A, 23B, 24F, 31 and 35B conjugated to CRM_{197} carrier, and can therefore be considered New Active Substances.

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

Streptococcus pneumoniae causes pneumococcal disease (PD). Clinical manifestations of pneumococcal disease include invasive pneumococcal disease (IPD) and non-invasive disease. Invasive pneumococcal disease can lead to meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis. The non-invasive disease can present as, e.g., otitis media, sinusitis and non-bacteraemic pneumonia.

3.1.2. Available therapies and unmet medical need

Treatment options:

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data. For the outpatient treatment of healthy patients without comorbidities, recommended antibiotic therapy includes amoxicillin, doxycycline, or a macrolide. For outpatients with comorbidities (e.g., 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.

Unmet medical need

V116 is being developed to provide significantly broader pneumococcal disease coverage in adults compared with currently licensed pneumococcal vaccines. V116 specifically targets residual disease in adults with the inclusion of key serotypes common to licensed vaccines and 8 unique serotypes not contained in any currently licensed vaccine.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is two pivotal, randomized, active comparator-controlled, parallel-group, multisite, double-blind phase 3 studies of V116 in pneumococcal vaccine-naïve adults ≥18 years of age (the large majority of participants were ≥50 years of age, matching the target population). In study V116-003 *n* = 2656 participants received study intervention. Cohort 1, comprising of participants 50 years and older, were randomized 1:1 to receive either V116 or active comparator PCV20. Cohort 2 (*n* = 300), comprising of participants 18-49 years of age, were randomized 2:1 to receive either V116 or active comparator PCV20. In study V116-010 *n* = 1480 participants ≥50 years of age received study intervention, randomized 1:1 to receive either V116 or active comparator PPSV23.

3.2. Favourable effects

Immunogenicity. Functional antibodies as measured by OPA can be regarded a proxy for clinical efficacy. V116 was compared in pivotal trials with licensed pneumococcal vaccines PCV20 and PPSV23. OPA GMTs increased post-vaccination for all serotypes in V116 in study participants.

V116 compared to PCV20 (Study V116-003): V116 met the predefined criterion for noninferiority to PCV20 for the 10 serotypes shared. For 10 of 11 serotypes unique to V116, the predefined criteria for superiority to PCV20 was met. V116 met the predefined superiority criterion compared to PCV20 for all but one (15C) of the 11 additional serotypes to V116 as assessed by the GMT ratio (Capvaxive/PCV20) and as assessed by the proportion of individuals who achieved a ≥ 4-fold rise from prevaccination to 1-month postvaccination for OPA responses. V116 successfully immunobridged serotype-specific immune responses to each of the 21 vaccine serotypes in individuals 18 to 49 years of age to individuals 50 to 64 years of age.

The primary immunogenicity endpoints were supported by the secondary analyses.

V116 compared to PPSV23 (Study V116-010): V116 met the predefined criterion for noninferiority to PPSV23 for each of the 12 common serotypes at 30 days postvaccination and also met the predefined criterion for superiority to PPSV23 for each of the 9 serotypes unique to V116 at 30 days postvaccination. See table below. In this study, V116 met the predefined superiority criterion compared to PPSV23 for all the 9 additional serotypes to Capvaxive as assessed by the GMT ratio (Capvaxive/PPSV23) but failed to meet the superiority criterion compared to PPSV23 for all but one (also 15C) of the 9 additional serotypes in Capvaxive as assessed by the proportion of individuals who achieved a ≥ 4-fold rise from prevaccination to 1-month postvaccination for OPA responses.

The primary immunogenicity endpoints were supported by the secondary analyses.

In summary, V116 was shown to be NI with regard to eliciting an immune response against shared serotypes compared to both active comparators. V116 also met the statistical criterion for superiority in eliciting an immune response for all the unique serotypes but one.

Elderly. V116 targets the pneumococcal serotypes epidemiologically identified as the most prevalent disease-causing in the elderly population. V116 would thus be the first PCV specifically designed to counter the disease-burden afflicting this vulnerable population and can be considered to address an unmet medical need. V116 was immunogenic in all age categories investigated. Although the immune response declined with age, a notable immune response was still present in participants ≥75-year-old.

Cross-reactivity to serotype 15B. A comparable immune response to 15B was observed after vaccination with V116 (which does not contain 15B) and either PCV20 and PPSV23 (which contain 15B), based on GMTs, percentage of participants achieving a 4-fold rise and reverse cumulative distribution curves. Consequently, a protective effect of V116 against 15B can be assumed, even though this serotype is not contained within the vaccine itself.

3.3. Uncertainties and limitations about favourable effects

Immunogenicity. There are no vaccine efficacy data reported for V116 in any of the clinical studies. Efficacy is instead extrapolated from immunogenicity data, using functional antibodies as measured per OPA as a proxy for vaccine efficacy. This approach is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

The usage of immunogenicity data instead of vaccine efficacy entails two main uncertainties. 1) The efficacy against pneumococcal pneumonia is extrapolated from bridging V116 to PCV20, which in turn was bridged to PCV13. This bridge-to-bridge exercise introduces a risk for biocreep. However, the

immunogenicity data was convincing and the risk for biocreep is regarded as low. It should nonetheless be noted that bridging was only possible for the 10 serotypes that were common in both V116 and PCV20, which brings us to point 2). The efficacy against the unique serotypes in V116 is based on statistical superiority against "the lack of response" elicited by V116. The clinical relevance of these findings can be reasonably assumed to be positive based on prior knowledge of immune response against other pneumococcal serotypes, but post-marketing epidemiological surveillances will be desirable to monitor vaccine effectiveness against all serotypes included in V116.

To this end, the applicant has provided a draft protocol for a post-marketing effectiveness study investigating the effectiveness of V116 in preventing IPD and pneumococcal pneumonia. This strategy is endorsed and the CHMP has agreed this study to be requested as a Recommendation.

Type I error not controlled. Noninferiority criteria were met for all shared serotypes in both studies. Superiority criteria were met for all the unique serotypes, except for serotype 15C. The fact that superiority is not met is likely due to the fact that 15B present in PCV20 and PPSV23 leads to increased levels of OPA antibodies that cross react to 15C, as the 2 serotypes have similar polysaccharide capsule structures that only differ in O-acetylation. However, as a consequence of the testing strategy, the studies will only have met the primary objectives in case both non-inferiority was shown for all common serotypes and superiority was shown for all unique serotypes. Therefore, the studies both formally failed their primary endpoints and no type-I error controlled claims regarding non-inferiority or superiority can be made.

Reduced response to certain serotypes. The immunogenicity results obtained during the pivotal study V116-003 showed a numerically lower immune response to V116 compared to PCV20 for 4 serotypes: 6A, 10A, 19A and 22F. For these 4 serotypes, the 95%-CIs of the vaccine specific OPA GMTs were non-overlapping between both vaccines. As the response to serotypes 6A and 19A was already lower after vaccination with PCV20 compared to PCV13, the potential consequences of the observed reduced response are unknown as effectiveness of PCV20 is not yet known. Therefore, the impact of the lower response for serotypes 6A and 19A in participants receiving V116 compared to PCV20, which was already lower compared to the response to the vaccine for which effectiveness was shown, cannot be easily determined. Although, it is not possible to assess the effect size, based on knowledge obtained in the field it is reasonable to assume that the immune response generated by V116 could provide protection against pneumococcal disease.

Immunocompromised patients. Another limitation about favourable effects of V116 is its effect in immunocompromised patients. Study V116-007 conducted in adults living with HIV is as mentioned not regarded as a study of immunocompromised patients as many of the participants had CD4+ T-cell counts within the normal range due to anti-retroviral therapy. The effect of V116 in immunocompromised people remains thus mainly unknown. This is reflected in the SmPC, the safety and immunogenicity data on Capvaxive are not available for individuals in immunocompromised groups. Vaccination should be considered on an individual basis. It is also reflected that based on experience with pneumococcal vaccines, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response to Capvaxive.

Concomitant administration with QIV. Study V116-005 investigated the concomitant administration of V116 and QIV. In addition to a generally weaker response against all Pn serotypes and influenza strains tested, co-administration of the two vaccines failed to meet the statistical NI-criterion for 1 of 21 Pn serotypes and one of four influenza strains. For the remaining 20 serotypes, as well as for NI immune response against influenza virus, concomitant administration of V116 met the predefined NI criterion. While the criterion was not met for one serotype, the totality of immunogenicity data including OPA GMTs, IgG GMCs, OPA and IgG GMFR, and the proportion of

participants with a ≥4-fold increase for both OPA and IgG responses supports concomitant administration of V116 and QIV.

Persistence of immune response. The last uncertainty with regard to the favourable effect of V116 is the durability of the immune response and the potential need of boosting. All immunogenicity analyses in the pivotal studies were conducted 30 days post-vaccination and the persistence of the immune response beyond that is currently unknown. The applicant has stated in the protocol for the pivotal studies that 24-month immunogenicity evaluation will be conducted. The applicant indicated that the results from the immunogenicity sub-study will be summarised in a report which will be available for submission by the end of 2025.

3.4. Unfavourable effects

Adverse events

The safety profile of V116 was comparable to the safety profile of PCV20, PCV 15 and PPSV23. For all interventions, most participants experienced 1 or more AEs in all studies and the most reported AEs were solicited AEs.

In participants 18 to 49 years of age, 78% of participants experienced AEs. The most reported AEs were solicited AEs: injection-site pain (72%), fatigue (35%), headache (27%), myalgia (16%), injection-site erythema (13%), and injection site swelling (13%). Pyrexia was reported in 2.9% of the participants.

In participants ≥50 years of age, 50% of participants experienced AEs. The most reported AEs were solicited AEs: injection site pain (41%), fatigue (19%), headache (12%), whereas injection site erythema, injection site swelling, and myalgia were below 7%, and pyrexia was reported in 1.4% of the participants.

As expected, increasing age led to a decrease in reactogenicity and this trend was especially seen for injection-site pain. The age dependent decrease was not as clear for systemic AEs and very few participants were reported with pyrexia in all age groups.

All injection site related AEs were considered related to vaccination. The most frequently reported (≥5%) vaccine-related AEs in the integrated safety population (all ages) were the solicited AEs of injection-site pain, fatigue, headache, myalgia, injection-site erythema, and injection-site swelling. There was no relevant difference in the frequency of participants with one or more vaccine related AEs in the integrated safety population (all ages) in the V116 group (62%) compared with combined control group (60%). As expected, the frequency of participants with one or more vaccine-related AEs was lower the in the age group 18 to 49 years (78%) compared to age group 50 years and older (52%).

Across all studies most AEs were mild to moderate in intensity, and of short duration (≤3 days).

The number of SAEs was low (≤3%). Two were considered related to V116 administration (bronchospasm and injection-site cellulitis) and were resolved at the end of the study.

Discontinuations due to AE. In study 005, 2 of 534 (0.4%) participants in the concomitant group and 1 of 535 (0.2%) participants in the sequential group had AEs leading to study vaccine discontinuation. In study 007, no participants discontinued study intervention due to AEs. Participants in studies 003, 004, 006, and 010 received a single dose of V116 or control and, therefore, could not discontinue study intervention.

3.5. Uncertainties and limitations about unfavourable effects

Safety has not been assessed in pregnant women, which has been addressed in section 4.6 in the SmPC. Safety of exposure of pregnant women to V116 will need to be systematically collected post-licensure via routine pharmacovigilance.

In total, 5,450 participants received V116, of which 3,531 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. Information on hypersensitivity reactions after vaccination with V116 is limited in the dossier. One serious incidence of a hypersensitivity reaction (SAE bronchospasm within 30 minutes post vaccination) occurred. Hypersensitivity reactions are a known risk for vaccines, and these should be systematically collected post licensure.

Information on safety of V116 in high-risk immunocompromised populations is currently lacking. The dossier submitted only included 1 study enrolling people living with HIV, however, based on baseline characteristics, the participants included in the study still had a functioning immune system.

3.6. Effects table

Effect	Short Description	Unit	V116	Comparator	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Non-inferiority of 10 shared serotypes	OPA GMT ratio	PCV20 was the comparator. Lowest 95 % CI lower bound 0.68. [1]			V116-003
	Superiority of 11 unique serotypes	OPA GMT ratio	Lowest 95 % CI lower bound 1.8 for serotype 15C.[2]			
	Superiority of 11 unique serotypes	% OPA responders	Lowest 95%CI lower bound was 5.6% for serotype 15C.			
Primary endpoint	Non-inferiority of 12 shared serotypes	OPA GMT ratio	**PPSV23** was the comparator. Lowest 95 % CI lower bound 0.76. [1]			V116-010
	Superiority of 9 unique serotypes	OPA GMT ratio	**PPSV23** was the comparator. Lowest 95 % CI lower bound 2.5. [2]			
	Superiority of 9 unique serotypes	% OPA responders	Lowest 95%CI lower bound was 7.5% for serotype 15C.			
Unfavourable Effects						
Injection-site AE	Injection-site pain	%	52.9	49.9	Overall, across studies and in the ISS, these were the most reported AEs in participants of ≥50 years	Integrated Summary of Safety (ISS),
Systemic AE	Fatigue	%	25.3	21.5		

Effect	Short Description	Unit	V116	Comparator	Uncertainties/ Strength of evidence	References
	Headache	%	17.7	14.5	of age and in participants of 18-49 years of age with and without risk factors for pneumococcal disease. As expected, increasing age led to a decrease in reactogenicity.	(all ages)

[1] A conclusion of non-inferiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/comparator) being > 0.5 (one-sided p-value < 0.025).
[2] A conclusion of superiority is based on the lower bound of the 95% CI for the estimated GMT ratio (V116/comparator) being > 2.0 (one-sided p-value < 0.025).
[3]The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the differences [V116 – comparator] between the proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination to be >10%

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The application is based on clinical studies comparing the functional antibody responses to Capvaxive to PCV20 and PPSV23 respectively, which is an acceptable and previously established strategy and in line with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

Overall, the immunogenicity data showed that the immune response to Capvaxive was generally comparable to the response to PCV20 and PPSV23 for all shared serotypes, with non-inferiority criteria being met for all comparisons for the shared serotypes (LL of the 95%CI of the GMT ratio>0.67). In both pivotal studies, the immune response to serotypes unique to Capvaxive was higher compared to the comparator vaccine and superiority criteria were met for all serotypes, except for 15C. A likely explanation is the fact that serotype 15B is present in PCV20 and PPSV23 and 15C and 15B have a similar polysaccharide capsule structure that only differs in O-acetylation. This notion is further substantiated by the fact that a substantial cross-reactive immune response was generated against 15B by vaccination with Capvaxive.

As the study formally failed its primary objective - significance was not reached for all individual comparisons (32 for V116-003 and 30 for V116-010) - no formal claim of statistical significance can be made as the chance of finding at least one false positive statistically significant test is not controlled at 5%. Upon request the applicant provided more insight into type I error control by generating 10,000 trials using a bootstrap method to estimate the chance of multiple false-positive conclusions taking into account the correlation between serotypes within the study. The findings support a conclusion that the chance of a large number of false-positive results is low (chance of at least 5 positive results of individual tests around 1%). In addition, results between both main studies were consistent. However, as type I error is not controlled in the strong sense and the chance of at least one false-positive conclusion is high, reflection of p-values or statistical claims in the SmPC is not considered appropriate.

The comparators in the pivotal studies were PCV20 and PPSV23. Both have the common advantage of maximising the number of common serotypes, but also have drawbacks. PCV20 was approved based on immunobridging to PCV13, and thus the comparison constitutes a bridge to a bridge. PPSV23 is only approved for prevention of IPD, not the additional indications sought for Capvaxive. Taken together the

choice of comparators is acceptable. The studies were conducted in different geographical locations and primarily in elderly cohorts, thus they are considered clinically relevant for the intended target population.

Capvaxive did not only meet the formal criterion for NI to PCV20 for the common serotypes in V116-003 but would also have met a more stringent criteria of the lower bound of the two-sided 95% CI >0.67 for the OPA GMT ratios, as discussed in a previous CHMP scientific advice. A substantial immune response was generated by Capvaxive for all serotypes, with the majority of participants achieving at least a 4-fold rise in OPA antibodies. Furthermore, the reverse cumulative distribution curves are comparable between Capvaxive and the comparator vaccines, indicating that the immune response over the group was comparable for the shared serotypes. Therefore, it is likely that the immune response generated will translate into protection against the serotypes included in Capvaxive. However, the effect size of the induced protection cannot be determined especially regarding the unique serotypes in Capvaxive, for which efficacy cannot be bridged to a licenced product.

The applicant plans to investigate vaccine effectiveness for all serotypes in post-marketing studies, which is agreed. Furthermore, as serotype replacement is known to occur, no prediction can be made about the longevity of any additional benefit of the serotypes included in this vaccine compared to other pneumococcal vaccines. Epidemiological surveillance monitoring will be necessary, and is proposed, to ensure early detection of breakthrough disease caused by potential vaccine failure or reduced vaccine effectiveness and impact of serotype replacement.

The safety profile of Capvaxive was comparable to the safety profile of the comparator pneumococcal vaccines. In the phase 1/2 clinical study and 6 phase 3 clinical studies submitted in the dossier, no new safety signals were observed for Capvaxive compared to PCV20, PPSV23 and PCV15. Capvaxive was slightly more reactogenic than the control vaccines, although for both intervention groups the majority of participants experienced 1 or more AEs. Capvaxive is well-tolerated in adults ≥18 YOA since the majority of AEs were mild in intensity and of short duration. Additionally, the discontinuations due to adverse events were low.

The documented safety exposure is considered sufficient for adequate assessment of the safety profile of Capvaxive. 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 via routine pharmacovigilance.

Information on safety and efficacy of Capvaxive in high-risk immunocompromised populations is currently lacking. Immunocompromised individuals are at risk of developing pneumococcal disease and are therefore likely to be vaccinated. The dossier submitted only included 1 study enrolling people living with HIV, however, based on baseline characteristics, the participants included in the study still had a functioning immune system.

3.7.2. Balance of benefits and risks

Capvaxive elicits a robust immune response against all 21 serotypes contained withing the vaccine and 1 cross-reactive serotype (15B), as measured by the rise in functional antibodies using OPA. Although it is not possible to assess the effect size, the provided data and prior knowledge in the field it is considered reasonable to conclude that Capvaxive could provide protection against pneumococcal disease. Therefore, it is considered a relevant vaccine as an immune response is generated to a broader spectrum of serotypes. Especially in locations where increased emergence of non-vaccine serotypes causing pneumococcal disease is likely or is occurring.

The safety profile of Capvaxive is characterised by injection-site pain, fatigue, headache, and myalgia and is comparable to the safety profile of PCV20, PCV15 and PPSV23. As the reported AEs are mainly mild or moderate in intensity and of short duration, the beneficial effect associated with Capvaxive outweighs the risks.

Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive. Therefore, Capvaxive is considered approvable.

3.8. Conclusions

The overall benefit/risk balance of Capvaxive 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 Capvaxive is favourable in the following indication:

Capvaxive 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 Capvaxive 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 pneumococcal polysaccharide serotype 9N, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B conjugated to CRM_{197} contained in Capvaxive (pneumococcal polysaccharide conjugate vaccine (21-valent)) are to be qualified as a new active substances in themselves as they are not a constituent of a medicinal product previously authorised within the European Union.