26 March 2026
EMADOC-1700519818-2976293
Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: CAPVAXIVE

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

Procedure No. EMA/VR/0000294070

Marketing Authorisation Holder (MAH): Merck Sharp & Dohme B.V.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

1. Background information on the procedure 6
1.1. Type II variation 6
1.2. Steps taken for the assessment of the product 6
2. Scientific discussion 7
2.1. Introduction 7
2.1.1. Problem statement 7
2.1.2. About the product 9
2.1.3. The development programme/compliance with CHMP guidance/scientific advice 9
2.1.4. General comments on compliance with GCP 11
2.2. Non-clinical aspects 11
2.3. Clinical aspects 11
2.3.1. Introduction 11
2.3.2. Clinical pharmacology 12
2.4. Clinical efficacy 12
2.4.1. Main study 12
2.4.2. Discussion on clinical efficacy 48
2.4.3. Conclusions on the clinical efficacy 52
2.5. Clinical safety 52
Most Frequently Reported Adverse Event 55
2.5.1. Serious adverse event/deaths/other significant events 69
2.5.2. Discussion on clinical safety 74
2.5.3. Conclusions on clinical safety 78
2.5.4. PSUR cycle 79
2.6. Risk management plan 79
2.7. Update of the Product information 79
2.7.1. User consultation 79
3. Benefit-Risk Balance 80
3.1. Therapeutic Context 80
3.1.1. Disease or condition 80
3.1.2. Available therapies and unmet medical need 80
3.1.3. Main clinical studies 81
3.1.4. Favourable effects 81
3.2. Uncertainties and limitations about favourable effects 81
3.3. Unfavourable effects 83
3.4. Uncertainties and limitations about unfavourable effects 84
3.5. Effects Table 84
3.6. Benefit-risk assessment and discussion 85
3.6.1. Importance of favourable and unfavourable effects 85
3.6.2. Balance of benefits and risks 86
3.6.3. Additional considerations on the benefit-risk balance 87
3.7. Conclusions 87

4. Recommendations 87

List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AOM	acute otitis media
APaT	All Participants as Treated
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
EC	European Commission
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EU	European Union
eVRC	electronic vaccination report card
FDA	Food and Drug Administration
GMC	geometric mean concentration
GMT	geometric mean titres
GMFR	geometric mean fold rise
HIV	human immunodeficiency virus
IPD	invasive pneumococcal disease
IgG	immunoglobulin G
MOPA	multiplexed opsonophagocytic assay
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
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™)
PPSV23	pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23)
PREA	Paediatric Research Equity Act
PT	Preferred Term
Pn ECL	pneumococcal electrochemiluminescence
RMP	Risk Management Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics

SOC System Organ Class

U.S.C. United States Code

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 27 August 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include active immunisation of children and adolescents 2 to less than 18 years of age for CAPVAXIVE, based on final results from study V116-013 (P013V116); this is a phase 3, randomised, double-blind study to evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents with increased risk of pneumococcal disease; a a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 6.6 of the Summary of Product Characteristics (SmPC) are updated. The Package Leaflet (PL) is updated in accordance. Version 1.1 of the risk management plan (RMP) has also been submitted.

The variation requested amendments to the SmPC and PL and to the RMP.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000221419 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000221419 had been completed.

The PDCO issued an opinion on compliance for the PIP EMA/PE/0000221419.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice EMA/SA/0000059363, 24th June 2021. The Scientific Advice covered clinical aspects in relation to paediatric development of the dossier.

1.2. 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

Timetable	Actual dates
Submission date	27 August 2025
Start of procedure:	13 September 2025
CHMP Rapporteur's preliminary assessment report circulated on:	10 November 2025
CHMP Co-Rapporteur's preliminary assessment report circulated on:	13 November 2025
PRAC Rapporteur's preliminary assessment report circulated on:	14 November 2025
CHMP Rapporteur's (joint) updated assessment report circulated on:	5 December 2025
Request for supplementary information adopted by the CHMP on:	11 December 2025
MAH's responses submitted to the CHMP on:	21 January 2026
CHMP Rapporteurs' preliminary assessment report on the MAH 's responses circulated on:	26 February 2026
PRAC Rapporteur's preliminary assessment report circulated on:	27 February 2026
PRAC RMP advice and assessment overview adopted by PRAC	12 March 2026
CHMP Rapporteur's (joint) updated assessment report on the MAH circulated on:	19 March 2026
CHMP opinion:	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Streptococcus pneumoniae is a major cause of vaccine-preventable disease worldwide, leading to significant morbidity and mortality, especially in children under 5 years and adults over 70 years of age. Despite the widespread use of pneumococcal conjugate vaccine (PCVs), individuals with chronic comorbid conditions remain at higher risk for pneumococcal disease. These conditions include chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and chronic kidney disease. The incidence of invasive pneumococcal disease (IPD) is notably higher in children with these conditions, with non-vaccine serotypes causing a significant proportion of cases. Current vaccination guidelines recommend additional pneumococcal vaccinations for at-risk children to broaden serotype coverage.

A retrospective cohort analysis of children <18 years of age during 2007 to 2010 found that the incidence rate ratios for IPD of at-increased-risk children and high-risk children compared to children without risk factors were 1.8 (<5 years of age) and 3.3 (5 to 17 years of age), and compared to children with high risk were 11.2 (<5 years of age) and 40.1 (5 to 17 years of age), respectively. PCVs are commonly used in a 3-dose schedule or 4-dose schedule, where 2 or 3 doses are administered starting as early as 2 months of age, and the last dose administered at 12 to 15 months of age. In addition to routine childhood immunisation with PCVs, there are recommendations to vaccinate

children ≥2 years of age at increased risk for pneumococcal disease due to underlying disease, occupation, or institutionalisation as these individuals are at risk for infections caused by a broader range of serotypes than healthy children.

State the claimed the therapeutic indication

CAPVAXIVE is currently in the EU approved and indicated for active immunization for the prevention of invasive disease and pneumonia caused by *S. 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.

This application proposes to expand the indication to include the following:

Active immunization for the prevention of invasive disease and pneumonia caused by *S. 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 children and adolescents ≥2 to <18 years of age with increased risk of pneumococcal disease.

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 community-acquired pneumonia caused by *S. pneumoniae* requires rapid initiation of appropriate antibiotic therapy and may require additional supportive care such as supplemental O2 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 (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 children currently includes routine childhood vaccination with PCVs and with the addition of pneumococcal polysaccharide vaccine (PPSV) for those at increased risk of pneumococcal disease. 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. There are 2 types of pneumococcal vaccines currently available, the pneumococcal polysaccharide vaccines and PCVs, with the PCVs generally eliciting a more robust immunity. Many

countries have implemented age-based and/or risk-based recommendations for pneumococcal vaccination. More than 140 regions/countries have introduced routine infant PCV immunization programs into their guidelines, with recommendations typically starting at 2 months of age and include 2 or 3 doses of a PCV in infancy (the first year of life), followed by another dose as a toddler (~12 to 15 months of age). In addition to routine childhood immunization with PCVs, there are recommendations to vaccinate children ≥2 years at increased risk for pneumococcal disease due to underlying disease. European national guidelines vary by country in recommendations for at-risk children as well as by age, risk condition, vaccine type and revaccination. A single dose of PPSV23, is the most widely recommended regimen in children ≥2 years of age with increased risk of pneumococcal disease in most EU countries, as well as in the US (alternatively PCV20), Australia, New Zealand, and several South American countries.

Unmet medical need

V116 is intended to complement the existing paediatric vaccination regimen for children and adolescents with chronic medical conditions who are at increased risk for pneumococcal disease and is thus not intended to serve as a primary paediatric regimen. It has 12 shared serotypes with PPSV23. V116 has the potential to broaden protection against pneumococcal disease, addressing the unmet medical need in children and adolescents with chronic medical conditions that confer an increased risk of pneumococcal disease. This broad serotype coverage aims to address the residual burden of pneumococcal disease. As a conjugate vaccine, V116 is expected to provide improved immune and memory responses, longer lasting protection, and better immunogenicity in children and adolescents compared to polysaccharide vaccines such as PPSV23 that are currently used to confer broader coverage for at risk children and adolescents.

2.1.2. About the product

The MAH developed V116, a polyvalent pneumococcal 21-valent conjugate vaccine, for the prevention of pneumococcal disease caused by *S pneumoniae* serotypes 3, 6A, 6C, 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. Serotype 15C represents the immune response to the deOAc15B polysaccharide as the molecular structure for deOAc15B and 15C are similar. V116 (Capvaxive) received a marketing authorisation in adults valid throughout the EU on 24 March 2025.

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

The V116 Phase 3 clinical program included a diverse population of adults ≥18 years of age including those with and without prior pneumococcal vaccination, adults ≥65 years of age, and adults ≥18 years of age with ≥1 chronic medical condition associated with an increased risk of pneumococcal disease. In addition, there was 1 Phase 3 paediatric study (V116-013) conducted in children and adolescents ≥2 to <18 years of age with an increased risk of pneumococcal disease. V116 has the potential to provide broader protection against pneumococcal disease in this population and complement the protection afforded by the primary pneumococcal vaccination regimen.

This application provides safety and immunogenicity data from V116-013.

V116-013 enrolled children and adolescents aged ≥2 to <18 years who had completed a primary pneumococcal vaccination regimen (2+1 or 3+1) and were at increased risk of pneumococcal disease due to chronic conditions (i.e., chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and chronic kidney disease).

PPSV23 is the vaccine included in the majority of guidelines globally in this paediatric increased-risk population and of the currently licensed pneumococcal vaccines, PPSV23 affords the broadest serotype protection and has the most serotypes in common with V116 (12 serotypes); therefore, it was chosen as the comparator in the clinical study V116-013. This was agreed by the CHMP in a Scientific Advice as can be seen in the table below.

The submission of this application addresses paediatric requirements in the EU under Article 22 of Regulation (EC) No 1901/2006 as amended.

The design of study V116-013 was informed by the Agency interactions in support of the FDA agreed initial Paediatric Study Plan and the EMA approved Paediatric Investigation Plan (EMA/PE/0000221419).

Regulatory agency advice was obtained at key points during the development of V116-013.

Table 1 Summary of Key Regulatory-Sponsor Interactions for V116-013

Date	**Type of Meeting / Correspondence**	**Key Outcomes or Recommendations**
17-JUN-2024	CAPVAXIVE™ BL 125814/0 FDA Approval letter	• Paediatric Study Requirement for pneumonia indication waived because necessary studies are impossible or highly impracticable. • Paediatric Study Requirement for IPD indication waived for ages 0 to <2 years because product does not represent a meaningful therapeutic benefit over existing therapies for this age group.
02-DEC-2022	European Medicines Agency Decision P/0485/2022	• Waiver for paediatric population birth to less than 6 months on grounds that the specific medical product is likely to be ineffective. • Waiver for paediatric population 6 months to less than 2 years of age on grounds that the specific medical product does not represent a significant therapeutic benefit as the needs are already covered.
24-JUN-2021	CHMP Initial Scientific Advice EMA/SA/0000059363	• Agreement with design of the pivotal trial with V116 in individuals aged 2 years and older and to less than 18 years who have completed a primary pneumococcal vaccination regimen and are at increased risk of pneumococcal disease. • Agreement with proposal to use PPSV23 as the comparator in the proposed paediatric clinical trial with V116.

2.1.4. General comments on compliance with GCP

The MAH states that V116-013 was conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. V116-013 was conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the study was performed.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the MAH.

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

Table 2 Tabular overview of clinical studies

Summary of V116-013 Clinical Immunogenicity

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design	Number of Participants by Intervention Group	Study Population	Primary Immunogenicity Endpoints/Results
V116-013 Completed [Ref. 5.3.5.1: P013V116] 92 sites in 13 countries (Canada, Chile, Colombia, Finland, France, Israel, Japan, Poland, Spain, Sweden, Thailand, Türkiye, and US)	Randomized, double-blind, active comparator-controlled, parallel-group, multicenter study to evaluate safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years with increased risk of pneumococcal disease. Duration: Single dose at Visit 1 (Day 1)	Randomization ratio V116:PPSV23: 3:2 Total number of participants: 882 V116 group: Randomized: 531 Vaccinated: 528 Completed: 522 Discontinued: 9 PPSV23 group: Randomized: 351 Vaccinated: 348 Completed: 345 Discontinued: 6	Children and adolescents ≥2 to <18 years with increased risk for pneumococcal disease due to chronic conditions Sex: 359 F/515 M Median age: 8.0 years *Stratification Factors:* Number of increased-risk conditions for pneumococcal disease: 1 increased-risk condition: 838 ≥2 increased-risk conditions: 36 Prior pneumococcal vaccination and age: Prior PCV7 alone: 55 Prior PCV7 and 1 prior PPSV23 dose: 4 Prior PCV10 alone and ≥2 to <6 years old: 96 Prior PCV10 alone and ≥6 to <18 years old: 191 Prior PCV10 and 1 prior PPSV23 dose: 6 Prior PCV13 alone and ≥2 to <6 years old: 174 Prior PCV13 alone and ≥6 to <18 years old: 323 Prior PCV13 and 1 prior PPSV23 dose: 9	**Endpoints:** • Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116. **Results:** • 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. • 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.

CI=confidence interval; CTD=Common Technical Document; F=female; GMT=geometric mean titer; M=male; OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23); US=United States; V116=pneumococcal 21-valent conjugate vaccine (CAPVAXIVE™).

2.3.2. Clinical pharmacology

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

2.4. Clinical efficacy

2.4.1. Main study

V116-013

Methods

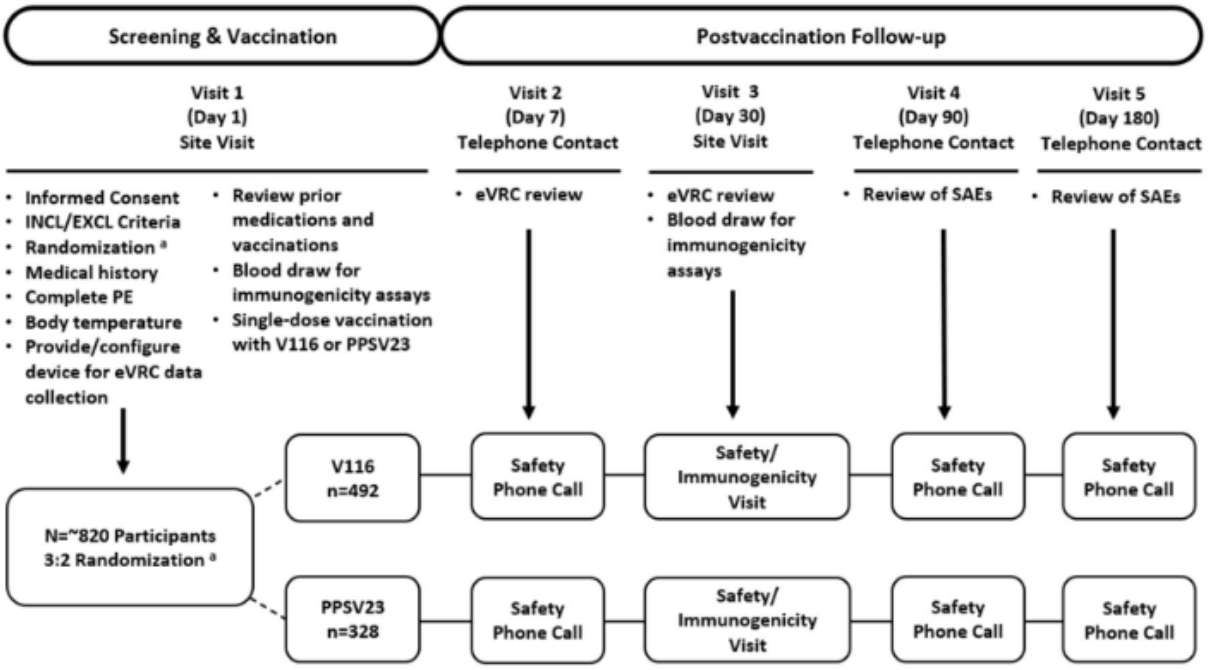
V116-013 was a randomised, double-blind, active comparator-controlled, parallel-group, multisite phase 3 study to investigate the safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years who have completed a primary pneumococcal vaccination regimen and who are at increased risk for pneumococcal disease.

Enrolled participants were randomised in a 3:2 ratio to receive a single dose of V116 or PPSV23 on Day 1.

Randomisation was stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions), by prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and 1 prior PPSV23 dose, prior PCV10 alone, prior PCV10 and 1 prior PPSV23 dose, prior PCV13 alone, or prior PCV13 and 1 prior PPSV23 dose), and age (≥2 to <6 years or ≥6 to <18 years).

The study design is shown in the figure below.

Figure 1 Study design



eVRC = electronic Vaccination Report Card; INCL/EXCL = inclusion/exclusion; PE = physical examination; SAE = serious adverse event

[a] Randomization will be stratified by number of increased-risk conditions for pneumococcal disease and by prior pneumococcal vaccination and age.

Opsonophagocytic antibody titres provide an assessment of functional immune responses as a surrogate marker for vaccine efficacy against pneumococcal disease and have been shown to correlate with vaccine-induced protection. The OPA GMT, IgG GMC, GMFR, and proportion of participants with a 4-fold rise in OPA and IgG responses are acceptable assessments used to evaluate novel PCVs. Several studies have shown a positive correlation between serotype-specific OPA titres and IgG antibody concentrations in children and adults.

In the V116 clinical program, vaccine-induced, serotype-specific OPA and IgG immune responses were measured using validated MOPA and Pn ECL assays, respectively. Evaluation of the serotype-specific OPA responses was the primary objective of V116-013; evaluation of serotype-specific IgG GMCs was a key secondary objective; and evaluation of cross-reactive immune responses to serotypes within a serogroup was an exploratory objective.

The 0.5 margin for the lower bound of the 95% CI of the OPA GMT ratio, translating to 2-fold difference, is based on regulatory precedent for comparing postvaccination antibody levels between licensed and investigational pneumococcal vaccines. This margin, as it relates to the OPA GMT ratio, accounts for the variability of the OPA assay, including the expected variability in antibody titres between pneumococcal serotypes.

Study participants

Inclusion Criteria

Key criteria for inclusion in this study include:

- Children and adolescents ≥2 years to <18 years of age, at the time of providing the informed consent/assent.
- Documented diagnosis of ≥1 of the following risk conditions for pneumococcal disease: diabetes mellitus, chronic liver disease, chronic lung disease, chronic heart disease, or chronic kidney disease.
- Receiving stable medical management for the risk conditions listed above for ≥3 months with no anticipated major change in treatment expected for the duration of the study and with ≤1 hospitalization directly related to the risk condition within 3 months before study vaccination.
- Completed primary PCV regimen with PCV7, PCV10, or PCV13 at least 8 weeks prior to enrolment, with either a 2+1 or 3+1 regimen according to local recommendations; all doses of the primary regimen must be of the same vaccine.
- Was PPSV23 vaccine-naïve or had not received more than 1 dose of PPSV23 ≥5 years before study vaccination.
- POCBP were not pregnant or breastfeeding.

Exclusion Criteria

Key criteria for exclusion in this study include:

- Had a curative procedure/surgery for chronic heart disease and did not require medication, follow-up, additional interventions, or further management per local guidelines.
- Had a history of active hepatitis within 3 months before study vaccination (Day 1).
- Had a history of diabetic ketoacidosis or 2 or more episodes of severe, symptomatic hypoglycaemia within 3 months before study vaccination (Day 1).
- Had a history of severely decreased kidney function, dialysis, autoimmune related chronic kidney disease, nephrotic syndrome of any cause, or an acute/reversible cause of kidney disease.
- Had a history of severe pulmonary hypertension or a history of Eisenmenger syndrome.
- Had a history of IPD or known history of other culture-positive pneumococcal disease within 3 years before study vaccination (Day 1).
- Had a known or suspected impairment of immunological function including congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or autoimmune disease.
- Receipt of systemic corticosteroids or immunosuppressive therapy.

While V116 was only investigated as booster in children and adolescents who have completed a primary pneumococcal vaccination regimen, with the current wording of the therapeutic indication there is a potential for V116 to be perceived as indicated for use also as a primary vaccination regimen in paediatrics. The suitability of a single dose in children who have not previously received a full priming series has not been established. Whilst it may be clear from the information in section 4.2 that V116 is intended for children and adolescents who have previously completed a primary paediatric pneumococcal regimen, ideally this should also be reflected in the indication. The Applicant was asked to either update the indication to reflect this or should justify the suitability of a single dose of V116 in children and adolescents who have not previously received a primary pneumococcal vaccination

regimen. They agreed to include the criteria of primary vaccination in the indication, and the matter was thus resolved.

Furthermore, the CHMP recommended removing the term "at increased risk" from the indication. The study population does not fully represent the entire at risk-population (for instance children with (functional) asplenia, immunocompromising conditions, or following hematopoietic stem cell transplantation) but that the results can be used to show immunogenicity of this vaccine in the extended age group and therefore supports the extension of indication. In the indication wording there is a general statement that the vaccine should be given in accordance with official recommendations – thereby allowing use to be limited to only those who are in need of it as stated in official recommendations. It is acknowledged that the clinical benefit of a "booster" pneumococcal vaccination for healthy children already having received pneumococcal vaccination is less clear compared to children with factors putting them at high risk of severe pneumococcal disease, but this wording allows NITAGs to determine if and how to recommend use in a broader group. The MAH agreed to this change.

Participants with recent (≥5 years before study vaccination) or multiple PPSV23 vaccinations were excluded to mitigate the risk of polysaccharide-induced hypo responsiveness (a transient reduction in antibody responsiveness that can occur following polysaccharide vaccination and gradually resolves over time), and to ensure that observed immune responses reflected the intrinsic immunogenicity of the investigational conjugate vaccine rather than residual immunologic effects of prior vaccination with PPSV23. Hypo responsiveness was for example observed for PCV20 (EMA/12384/2022, p111). To minimize the risk of hypo responsiveness with PCV20 in daily clinical practice, a recommendation was included in the SmPC of PCV20 about the sequence of prior vaccinations and that, if the use of PPSV23 is considered appropriate, PCV20 should be given first (see section 4.2 of the SmPC of PCV20). It was suggested to include such a recommendation in section 4.2 of the SmPC of V116 as well and this was agreed.

Treatments

Table 3 Study interventions

Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
V116	Experimental	Pneumococcal 21-valent conjugate vaccine	Biological/ Vaccine	Injection, Solution	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product	IMP	Central
PPSV23	Active Comparator	Pneumococcal Vaccine, Polyvalent (23-valent)	Biological/ Vaccine	Injection, Solution	25 µg of each PnPs antigen (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Comparator	IMP	Central or local

EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PnPs=pneumococcal polysaccharide; PPSV23=pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23); V116=pneumococcal 21-valent conjugate vaccine.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Objectives and endpoints

The following objectives and endpoints were evaluated in children and adolescents aged ≥2 to <18 years, who were at increased risk for pneumococcal disease due to an underlying medical condition and had completed a primary PCV regimen.

Primary Objectives	**Primary Endpoints**
To evaluate the safety and tolerability of V116 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs Day 1 through Day 5 postvaccination • Solicited systemic AEs Day 1 through Day 5 postvaccination • Vaccine-related serious AEs (SAEs) Day 1 through the duration of participation in the study
To compare the serotype-specific opsonophagocytic (OPA) geometric mean titres (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.)	Serotype-specific OPA responses

Secondary Objectives	**Secondary Endpoints**
To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V116 compared with PPSV23.	Serotype-specific IgG responses
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses and IgG responses	Serotype-specific OPA and IgG responses

from baseline to 30 days postvaccination within each vaccination group.	
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination.	Serotype-specific OPA and IgG responses

Sample size

The planned total enrollment was 820 participants (492/328). As of the study database lock, a total of 882 participants had been randomised (3:2): 531 in the V116 group and 351 in the PPSV23 group.

Primary Immunogenicity Endpoints/Hypotheses (H1 and H2)

For the primary hypotheses, this study had >90% power to declare noninferiority of V116 to PPSV23 for the 12 common serotypes (H1) and superiority of V116 to PPSV23 for the 9 unique serotypes (H2) at an overall 1-sided 2.5% alpha-level.

The statistical criterion for noninferiority required the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PPSV23] to be >0.5.

The statistical criterion for superiority required the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PPSV23] to be >2.0.

The sample size and power calculations were based on the following assumptions:

• For the 12 common serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviation of natural log-transformed OPA results were assumed to be the same as that observed in the V116-004 Phase 3 study. The OPA GMT ratios ranged from 0.84 to 1.74. The standard deviations ranged from 0.93 to 1.43 for V116 and ranged from 0.96 to 1.43 for PPSV23.

• For the 9 unique serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviation of natural log-transformed OPA results were assumed to be the same as that observed in the V116-004 Phase 3 study. The OPA GMT ratios ranged from 2.90 to 23.72. The standard deviations ranged from 1.03 to 1.52 for V116 and ranged from 1.05 to 2.54 for PPSV23.

• 90% evaluability (443 participants in the V116 group and 295 participants in the PPSV23 group).

Sample Size and Power for Safety Analyses

The sample size was further selected to achieve a reasonably sized safety database exposed to V116.

The power calculations assumed that all randomised subjects were to be evaluable for safety analyses.

There was e.g., 80% probability of observing at least 1 SAE among 492 participants in the V116 group if the true incidence rate was 0.33% (1 of every 306 participants receiving the vaccine).

There was a 50% probability of observing at least 1 SAE among 492 participants in the V116 group if the true incidence rate was 0.14% (1 of every 710 participants receiving the vaccine).

If no SAEs were observed among 492 participants, this study was to provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.75% (1 out of every 133 participants) in the V116 group.

Global power for the study was estimated using simulations, with parameters derived from V116-004, a study comparing V116 to PPSV23 in adults. The high-level description of the simulation approach seems adequate, although few details are provided and it is not clear whether covariates were also taken into account for the simulations. The MAH does not justify that parameters in adults (perhaps in particular, the standard deviation of OPA GMTs) can be directly extrapolated to children and adolescents and a slightly more conservative approach (e.g., accounting for potentially larger standard deviations in children and adolescents) might have been preferred. However, as the study has already been completed, this issue was not further pursued.

Randomisation

Eligible subjects were randomised in a 3:2 ratio to receive a single dose of either V116 or PPSV23 on Day 1. Randomisation was made centrally using an IRT system.

Randomisation was stratified by the following factors:

• Prior pneumococcal vaccination and age:

- Prior PCV7 alone
- Prior PCV7 and one prior PPSV23 dose
- Prior PCV10 alone and ≥2 to <6 years old
- Prior PCV10 alone and ≥6 to <18 years old
- Prior PCV10 and one prior PPSV23 dose
- Prior PCV13 alone and ≥2 to <6 years old
- Prior PCV13 alone and ≥6 to <18 years old
- Prior PCV13 and one prior PPSV23 dose

• Number of increased-risk conditions for pneumococcal disease (including chronic heart disease or chronic lung disease or diabetes mellitus or chronic liver disease, and/or chronic kidney disease):

- 1 increased-risk condition
- ≥2 increased-risk conditions*

Randomisation appears to have been unrestricted (i.e., no blocks). This is acceptable. Randomisation was stratified by 2 factors (number of increased risk conditions and a combined age/prior vaccination factor), resulting in a total of 2 x 8 = 16 strata levels. Because all participants who received prior PCV7 or prior PPSV23 were older than 5, these categories were not split by age. While the potential importance of these factors is recognised, the number of strata levels is considered excessive given the study sample size and the skewed distribution of the factors (e.g., very few participants have ≥2 increased-risk conditions, very few participants have received prior PPSV23). This increases the risk of strata levels with only a few participants and of failure to actually achieve balance and might decrease statistical efficiency. As stratification factors also need to be included in the analysis model, the model will have a rather large number of covariates, although this is likely to be less problematic when the outcome is continuous, as in this case. No stratification was performed by center/geographic region. While generally recommended, it is understood that addition of another stratification factor may have been difficult, and it is expected that most relevant variation is captured by age and prior vaccination regimen. Hence the randomisation strategy is considered suboptimal but given the actual results the issue was not further pursued.

Blinding (masking)

A double-blinding technique was used. Study supplies were provided open label. Since V116 and PPSV23 differed in appearance, an unblinded pharmacist (or qualified study-site personnel) was to be responsible for receiving, maintaining, preparing and/or dispensing, and administering the study vaccines.

The participant, participant's legally acceptable representative, the investigator, and Sponsor personnel or delegate(s) who were involved in the study intervention administration or clinical evaluation of the participants were unaware of the intervention assignments.

To avoid bias, contact between the unblinded study-site personnel and study participants and their legally acceptable representatives was strictly prohibited for any study-related procedures/assessments other than administration of study vaccines.

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

For emergency situations where the investigator or medically qualified designee needed to identify the intervention used by a participant and/or the dosage administered, he/she was to contact the emergency unblinding call centre by telephone and make a request for emergency unblinding.

No confirmed events of premature unblinding were reported.

Statistical methods

Section 9 of the study protocol ("Key statistical considerations") provided the principal features of the confirmatory analyses. The separate statistical analysis plan (SAP) was to serve as a companion document to provide additional statistical analysis details or data derivations.

The official final database was not to be unblinded until medical/scientific review had been performed, protocol deviations had been identified, and data had been declared final and complete.

Database lock date was 18-Mar-2025.

Immunogenicity analysis sets

The per-protocol (PP) population served as the primary population for the immunogenicity endpoint(s).

The PP population was to exclude subjects due to important protocol deviations. Predefined potential deviations that may have led to exclusion from the PP population included:

- Failure to receive study vaccine at Visit 1 (Day 1)
- Failure to receive correct clinical material as per randomisation schedule
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination

Additional potential deviations identified for specific immunogenicity analyses (depending on the time point) were:

- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside the prespecified window

The final determination on important protocol deviations, and thereby the composition of the PP population, was to be made prior to the final unblinding of the database and was to be documented in a separate memo.

A supportive analysis using the FAS population was to be performed for the primary immunogenicity endpoint. The FAS population consisted of all randomised participants who had received at least 1 study vaccination and had at least 1 serology result.

Safety analysis sets

Safety analyses were to be conducted in the All-Participants-as-Treated population (APaT), which was to consist of all randomised participants who received one dose of study intervention. Participants were to be included in the vaccination group corresponding to the study vaccination they actually received.

To be included in the analysis of body temperature, at least 1 temperature measurement obtained subsequent to study intervention was required. The participant/participant's legally acceptable representative was to record body temperature measurements from day 1 to day 5 after vaccination using an electronic vaccination report card.

Immunogenicity hypotheses and analyses methods

For the 12 common serotypes, the primary noninferiority hypothesis (H1) regarding OPA GMT levels between recipients of V116 and PPSV23 was:

H0: GMT1/GMT2 ≤0.50 versus

H1: GMT1/GMT2 >0.50

For the 9 serotypes that are unique to V116, the primary superiority hypothesis (H2) regarding OPA GMT levels between recipients of V116 and PPSV23 was:

H0: GMT1/GMT2 ≤2.0 versus

H1: GMT1/GMT2 >2.0

For each of the hypothesis, H1 and H2, GMT1 was the serotype-specific OPA GMT for the V116 group, and GMT2 was the serotype-specific OPA GMT for the PPSV23 group.

The GMT ratio estimation, 95% CI, and the hypothesis test (using a one-sided p-value) was to be calculated using a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] using data from both vaccination groups. In this model, the response vector consists of the log-transformed antibody titres at baseline and 30 days postvaccination. This model allowed the inclusion of participants who were missing either the baseline or postbaseline measurements.

A similar statistical model as used for the first primary objective was to be used to address the secondary objective that compares the serotype-specific IgG GMCs at 30 days-postvaccination with V116 compared with PPSV23.

The analysis strategy for the immunogenicity endpoints is shown below:

Endpoint/Variable (Description, Time Point)	**Primary vs Supportive Approach***	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Primary Endpoints				
	P		PP	

OPA GMTs at 30 days postvaccination for the 12 common serotypes in V116 and PPSV23	S	cLDA (estimate, 95% CI, p-values)	FAS	Model-based
OPA GMTs at 30 days postvaccination for the 9 unique serotypes in V116	P	cLDA (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
Secondary Endpoints				
IgG GMCs at 30 days post vaccination for the 12 common serotypes between V116 and PPSV23 & 9 unique serotypes in V116	P	cLDA (estimate, 95% CI)	PP	Model-based
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for 1) serotype-specific OPA responses and 2) serotype-specific IgG responses within each vaccination group	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 activity; PP=per-protocol. P=Primary approach; S=Supportive approach.				

Multiplicity

Study 013-01 was to have met its primary immunogenicity objectives if noninferiority was demonstrated with respect to the OPA GMTs for each of the 12 common serotypes (via H1), and superiority was demonstrated with respect to OPA GMTs for each of the 9 unique serotypes (via H2).

All hypotheses were to be tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach controlled the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was considered required.

Analysis of safety endpoints

Safety endpoints were to be analysed using descriptive statistics.

The overall safety evaluation was to include a summary by vaccination group of the number and percentage of participants with any AEs, any unsolicited AEs, any vaccine-related AEs, any SAEs, any vaccine-related SAEs, and any AEs resulting in death after vaccination. Point estimates and 95% CIs

for the between-group differences (V116 compared with PPSV23) in the percentages of participants with the event were to be provided.

The number and percentage of participants with specific AEs was to be presented. Point estimates and 95% CIs for the differences between vaccination groups in the percentages of participants with specific AEs were to be provided for solicited AEs and AEs that occurred in ≥2% of participants in the V116 group or PPSV23 group.

The number and percentage of participants with maximum temperature measurements meeting the Brighton Collaboration cut points [Marcy, S. M., et al 2004] were to be presented along with point estimates and 95% CIs of between-group differences.

Confidence intervals (CIs) for between-group differences were to be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Rainfall plots with point estimates and 95% CIs were to be displayed for AEs that occurred in ≥5% of participants in the V116 group or PPSV23 group.

Interim Analyses

A periodic review of safety and tolerability data from the V116 paediatric study 013-01 was to be conducted by an independent, unblinded, external DMC.

Participant-level unblinding was to be restricted to an external unblinded statistician performing ongoing safety reviews. Intervention-level ongoing safety reviews were to be provided by the external unblinded statistician to the DMC. Prior to final study unblinding, the external unblinded statistician was not to be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the safety reviews.

The MAH aimed to investigate the safety, tolerability, and immunogenicity of V116 (currently indicated in adults ≥18 years of age for the prevention of invasive disease and pneumonia caused by the 21 *S. pneumoniae* serotypes covered by the vaccine) in children and adolescents aged ≥2 to <18 years, which have completed a primary pneumococcal vaccination regimen and are at increased risk for pneumococcal disease. These children, on top of their primary vaccination with conjugate pneumococcal vaccines, receive in most EU countries a shot of PPSV23 between the ages of 2-18 years to enhance their protection against pneumococcal disease. This treatment broadens the immunity against serotypes exclusive to the PPSV23, as well as boosts immunity against serotypes included in PPSV23 and PCVs. The aim of the MAH is to provide a conjugate vaccine alternative to the PPSV23 "booster" administered to these at risk-children and adolescents (that is, V116 is in this study not investigated for primary vaccination against pneumococcal disease). Methodologically, the MAH aimed to via functional immunogenicity immunobridge V116 to PPSV23 for the shared serotypes, and to demonstrate superiority for the unique serotypes only included in V116.

The overall study design, endpoints and objectives to achieve these aims are according to established precedent and regarded as acceptable by the CHMP but a point for clarification was raised.

The primary analysis was performed using constrained LDA. This is less commonly seen than ANCOVA, but cLDA and ANCOVA perform comparably in the absence of missing data (Wan, 2021, BMC Medical Research Methodology). In the presence of missing data, cLDA is more efficient than ANCOVA, although multiple imputation followed by ANCOVA would be expected to be about as efficient, possibly more so given the large number of parameters in the cLDA model due to interactions with time. Missing data is assumed to be missing at random, which may or may not be a reasonable assumption depending on the reason for missing data. Given the results (see section 10.2) and given that a number of reasons for missingness appear likely to be (completely) at random (e.g., lost or damaged serum sample, see section 10.2), and given that a comparison is made between two active vaccine for

a similar indication, it is not expected that any missingness-not-at-random will have a large impact on the conclusions and no issues with regard to missing data are pursued.

If the cLDA model did not converge, the intercept was excluded from the cLDA model. This changes the parameterization (from a global intercept with estimated deviations for each cell, to cell-specific means) but does not change the number of estimated parameters. The MAH clarified that nonconvergence did not occur in the primary analyses and only occurred for two serotypes in the supportive analysis of OPA GMTs in the FAS and one serotype in the secondary analysis of IgG GMTs. In all cases, convergence was achieved after exclusion of the intercept. Alternative model specifications (with a global intercept, but other covariance structures) yielded nearly identical results. Therefore, while exclusion of the intercept was not prespecified in the SAP as an approach for resolving nonconvergence, the approach is considered acceptable.

The cLDA model includes terms for stratum (prior vaccination + age, number of increased risk conditions). Inclusion of stratification factor in the analysis model is recommended, but there is concern about the stability of the estimates due to inclusion of separate terms for PCV7 + PPSV23, PCV10 + PPSV23, PCV13 + PPSV23, since prior PPSV23 vaccination was very rare (with only 0.5 – 1.0% of participants in each of the three levels). The SAP specifies that strata with small numbers of participants may be combined for analysis, and the MAH clarified that combining of very small strata was in fact done. The MAH also provided both model-based results and observed GMTs. As these are similar and there are no other indications that model estimates are unstable (e.g., very wide confidence intervals), this issue was not further pursued.

Results

Participant flow

The disposition of participants was generally comparable between intervention groups (Table 4). Overall, a total of 882 participants were randomised, and 876 received study intervention. The majority (98.3%) of participants in both groups completed the study. Two participants were vaccinated without documented initial consent and/or assent, and they were excluded from the All Vaccinated Participants, PP, APaT, and FAS populations.

The percentage of participants who discontinued the study was comparable between intervention groups. The most frequent reason for study discontinuation in both groups was withdrawal by parent/guardian (Table 4).

All (n=39) nonrandomised participants were screen failures who did not satisfy the inclusion or who met the exclusion criteria.

Table 4 Disposition of Participants (All Randomised Participants)

Disposition of Participants
(All Randomized Participants)

	V116		PPSV23		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	531		351		882	
Vaccinated at Visit 1						
V116	528	(99.4)	0	(0.0)	528	(59.9)
PPSV23	0	(0.0)	348	(99.1)	348	(39.5)
Trial Disposition						
Completed	522	(98.3)	345	(98.3)	867	(98.3)
Discontinued	9	(1.7)	6	(1.7)	15	(1.7)
Death	0	(0.0)	2	(0.6)	2	(0.2)
Lost To Follow-Up	2	(0.4)	0	(0.0)	2	(0.2)
Randomized By Mistake Without Study Treatment	1	(0.2)	1	(0.3)	2	(0.2)
Withdrawal By Parent/Guardian	5	(0.9)	3	(0.9)	8	(0.9)
Other	1	(0.2)	0	(0.0)	1	(0.1)

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

Source: [P013V116: adam-adsl; adex]

Clinical investigator study sites were located in 13 countries: Canada, Chile, Colombia, Finland, France, Israel, Japan, Poland, Spain, Sweden, Thailand, Türkiye, and the US.

Baseline data

Participant demographic and baseline characteristics were generally comparable between intervention groups.

The majority (59.6%) of participants were White, 14.6% were multiple races, and 10.4% were American Indian or Alaska Native. Most (58.9%) participants were male, and 44.4% of participants were of Hispanic or Latino ethnicity. The median age was 8.0 years (range: 2 to 18 years), and 68.8% of participants were ≥6 to <18 years of age.

Enrolment included 1 participant who was 18 years and 3 months of age. This participant was included in both the immunogenicity and safety analyses populations, as a deviation of 3 months was not expected to have a substantial effect on the primary immunogenicity and safety endpoints.

The majority (95.9%) of participants had a single increased-risk condition.

Approximately 57% of participants received prior PCV13 vaccination alone, approximately 6% of participants received prior PCV7 alone, and approximately 33% received prior PCV10 alone. All participants in the prior PCV7 alone group were in the older age group (≥6 to <18 years) (Table 5) as PCV7 was introduced in the US in 2000 and in the EU in 2001 and subsequently adopted in NIPs for children globally. In the prior PCV10 alone, and prior PCV13 alone groups, participants were in both the younger (≥2 to <6 years) and older (≥6 to <18 years) age groups (Table 5) because PCV10 and PCV13 were licensed 2009 to 2010, replacing PCV7 in NIPs. Additionally, there was 1 participant with missing information regarding the type of prior pneumococcal vaccine and regimen, as the investigator could not confirm this information from the medical and vaccine records.

A total of 56.3% of participants received a 2+1 regimen and 39.0% of participants received a 3+1 regimen.

Table 5 Participants by Prior Pneumococcal Vaccination Status and Age Category (All Vaccinated Participants)

	≥2 to <6 Years		≥6 to <18 Years		≥18 Years[a]		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	272		601		1		874	
Prior pneumococcal vaccination status								
Prior PCV7 alone	0	(0.0)	54	(9.0)	1	(100.0)	55	(6.3)
Prior PCV7 and one prior PPSV23 dose	0	(0.0)	4	(0.7)	0	(0.0)	4	(0.5)
Prior PCV10 alone	96	(35.3)	191	(31.8)	0	(0.0)	287	(32.8)
Prior PCV10 and one prior PPSV23 dose	0	(0.0)	6	(1.0)	0	(0.0)	6	(0.7)
Prior PCV13 alone	174	(64.0)	323	(53.7)	0	(0.0)	497	(56.9)
Prior PCV13 and one prior PPSV23 dose	0	(0.0)	9	(1.5)	0	(0.0)	9	(1.0)
Others[b]	2	(0.7)	13	(2.2)	0	(0.0)	15	(1.7)
Missing	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

For eligible pneumococcal vaccine regimens, participants must have received one or more doses of the same prior vaccine.
[a] Includes a participant who is 18 years and 3 months of age.
[b] Includes any combinations of prior pneumococcal vaccines, other than the 2+1 or 3+1 primary regimens, in which all doses of the primary regimen consist of the same pneumococcal vaccine (PCV7, PCV10, or PCV13), followed by one dose of the PPSV23 vaccine.
PCV7= pneumococcal 7-valent conjugate vaccine; PCV10= pneumococcal 10-valent conjugate vaccine; PCV13= pneumococcal 13-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl]

Medical history conditions were generally comparable between intervention groups. The 5 most common prespecified single increased-risk conditions were asthma (50.5%), diabetes mellitus (15.4%), heart disease congenital (10.3%), chronic kidney disease (8.7%), and chronic lung disease (8.1%). The proportions of participants with prespecified increased-risk conditions for pneumococcal disease at randomization were comparable between intervention groups.

Prior and Concomitant Medications/Treatments/Vaccines

Reported prior and concomitant medications and non-study vaccines were generally comparable between intervention groups.

Numbers analysed

Immunogenicity analyses were based on the PP population.

The overall percentage of randomised subjects included in the PP population for the OPA analyses for at least 1 timepoint was 91.0% (803/882), and for both Day 1 and Day 30 timepoints 81.0% (714/882).

Table 6 Number of subjects included in the OPA analyses based on the PP population (CSR P013V116)

	V116		PPSV23		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	531		351		882	
Participants included in analyses by timepoint						
Day 1	468	(88.1)	307	(87.5)	775	(87.9)
Day 30	451	(84.9)	291	(82.9)	742	(84.1)
At least one timepoint	488	(91.9)	315	(89.7)	803	(91.0)
Both Day 1 and Day 30 timepoints	431	(81.2)	283	(80.6)	714	(81.0)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	**40**	**(7.5)**	**33**	**(9.4)**	**73**	**(8.3)**
No consent	1	(0.2)	1	(0.3)	2	(0.2)
Impairment of immune function due to medical condition	0	(0.0)	1	(0.3)	1	(0.1)
Did not meet criteria related to risk condition	9	(1.7)	4	(1.1)	13	(1.5)
Prohibited prior therapy, medication, or vaccination	4	(0.8)	4	(1.1)	8	(0.9)
Pneumococcal vaccine naive or prior pneumococcal vaccination prohibited by protocol	25	(4.7)	20	(5.7)	45	(5.1)
Randomized but not treated	3	(0.6)	3	(0.9)	6	(0.7)
Visit-level exclusions - Day 1	**27**	**(5.1)**	**14**	**(4.0)**	**41**	**(4.6)**
Missing serology results[b]	19	(3.6)	14	(4.0)	33	(3.7)
Positive results for intrinsic killing test	7	(1.3)	0	(0.0)	7	(0.8)
Missing results for intrinsic killing test	20	(3.8)	14	(4.0)	34	(3.9)
Visit-level exclusions - Day 30	**49**	**(9.2)**	**36**	**(10.3)**	**85**	**(9.6)**
Blood draw out of window	11	(2.1)	16	(4.6)	27	(3.1)
Missing serology results[b]	23	(4.3)	17	(4.8)	40	(4.5)
Positive results for intrinsic killing test	13	(2.4)	2	(0.6)	15	(1.7)
Missing results for intrinsic killing test	23	(4.3)	17	(4.8)	40	(4.5)
Prohibited concomitant therapy, medication, or vaccination	3	(0.6)	1	(0.3)	4	(0.5)

Percentages are calculated based on the number of participants randomized.

[a] Participants may have more than one reason for exclusion.

[b] Missing serology results for all serotypes, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, and serum sample lost, damaged, or unable to generate valid results.

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

Source: [P013V116: adam-adsl; adpdev; adimm]

The overall percentage of randomised subjects included in the PP population for the IgG analyses for at least 1 timepoint was 86.3% (761/882). A total of 66.8% of subjects (589/882) were included in the IgG analyses for both Day 1 and Day 30 timepoints.

Table 7 Number of subjects included in the IgG analyses based on the PP population (CSR P013V116)

	V116		PPSV23		Total	
	n	(%)	n	(%)	n	(%)
Participants randomized	531		351		882	
Participants included in analyses by timepoint						
Day 1	413	(77.8)	276	(78.6)	689	(78.1)
Day 30	408	(76.8)	253	(72.1)	661	(74.9)
At least one timepoint	462	(87.0)	299	(85.2)	761	(86.3)
Both Day 1 and Day 30 timepoints	359	(67.6)	230	(65.5)	589	(66.8)
Reasons for exclusions from analyses[a]						
Participant-level exclusions	**40**	**(7.5)**	**33**	**(9.4)**	**73**	**(8.3)**
No consent	1	(0.2)	1	(0.3)	2	(0.2)
Impairment of immune function due to medical condition	0	(0.0)	1	(0.3)	1	(0.1)
Did not meet criteria related to risk condition	9	(1.7)	4	(1.1)	13	(1.5)
Prohibited prior therapy, medication, or vaccination	4	(0.8)	4	(1.1)	8	(0.9)
Pneumococcal vaccine naive or prior pneumococcal vaccination prohibited by protocol	25	(4.7)	20	(5.7)	45	(5.1)
Randomized but not treated	3	(0.6)	3	(0.9)	6	(0.7)
Visit-level exclusions - Day 1	**85**	**(16.0)**	**49**	**(14.0)**	**134**	**(15.2)**
Missing serology results[b]	85	(16.0)	49	(14.0)	134	(15.2)
Visit-level exclusions - Day 30	**91**	**(17.1)**	**77**	**(21.9)**	**168**	**(19.0)**
Blood draw out of window	11	(2.1)	16	(4.6)	27	(3.1)
Missing serology results[b]	80	(15.1)	62	(17.7)	142	(16.1)
Prohibited concomitant therapy, medication, or vaccination	1	(0.2)	1	(0.3)	2	(0.2)

Percentages are calculated based on the number of participants randomized.

[a] Participants may have more than one reason for exclusion.

[b] Missing serology results for all serotypes, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, and serum sample lost, damaged, or unable to generate valid results.

IgG=immunoglobulin G; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116. adam-adsl; adpdev; adimm]

Safety analyses were based on an analysis set including a total of 874 subjects, 527 in the V116 arm and 347 in the PPSV23 arm, who had received study intervention and had documented initial consent. The participant flow was satisfactory. 882 participants were randomised, of which 876 received study intervention. The percentage of participants who discontinued the study was comparable between the study arms. Both study arms were well-balanced in terms of sex, age, race, ethnicity, country, prior pneumococcal vaccination (primary as well as PPSV23 "boosting") and number of increased risk-conditions for pneumococcal disease. The overall percentage of randomised subjects included in the per protocol population for the OPA analyses for at least 1 timepoint was 91.0% (803/882), and for both Day 1 and Day 30 timepoints 81.0% (714/882). The overall percentage of randomised subjects included in the per protocol population for the IgG analyses for at least 1 timepoint was 86.3% (761/882). A total of 66.8% of subjects (589/882) were included in the IgG analyses for both Day 1 and Day 30 timepoints. The reasons for exclusion from the analyses was generally comparable between the two study arms.

Outcomes and estimation

The results of the immunogenicity analyses are summarised by:

- Common serotypes: The 12 serotypes included in both V116 and PPSV23 (3, 7F, 8, 9N, 10A, 11A, 12F, 17F, 19A, 20A, 22F, and 33F serotypes).
- Unique serotypes: The 9 serotypes included in V116 but not in PPSV23 (6A, 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B serotypes).
- Cross-reactive serotypes: serotype 6C (cross-reactive to serotype 6A) and serotype 15B (cross-reactive to serotype 15C).

Immunogenicity Results

Primary Immunogenicity Endpoints

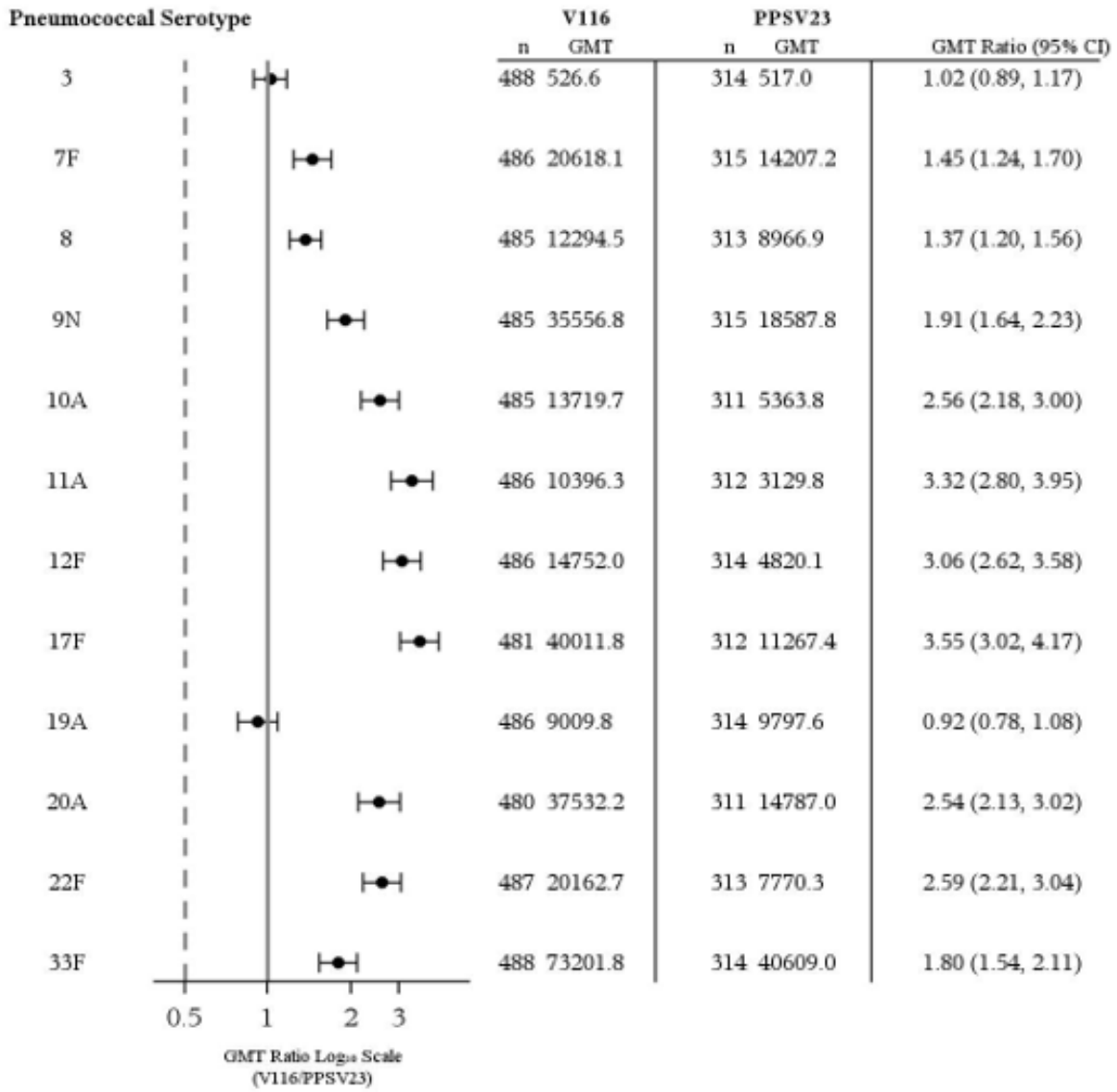
Comparison of Serotype-Specific OPA GMTs for Common Serotypes

V116 met the predefined criterion for noninferiority compared 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 (Figure 2 Forest Plot of Postvaccination OPA GMT ratios for common serotypes (per-protocol population)Figure 2 & Table 8).

Results for serotype-specific OPA GMTs at 30 days postvaccination in the FAS population were consistent with those observed in the PP population.

The distribution of serotype-specific OPA titres at 30 days postvaccination was generally comparable between the intervention groups for the common serotypes as shown by RCDCs.

Figure 2 Forest Plot of Postvaccination OPA GMT ratios for common serotypes (per-protocol population)



Note: The dashed line indicates the margin for the non-inferiority test.
Source: [P013V116: adam-adsl; adimm]

Table 8 Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population)

Pneumococcal Serotype	V116 (N = 527)		PPSV23 (N = 347)		GMT Ratio[a] (V116 / PPSV23) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
3	488	526.6	314	517.0	1.02 (0.89, 1.17)	<0.001
7F	486	20618.1	315	14207.2	1.45 (1.24, 1.70)	<0.001
8	485	12294.5	313	8966.9	1.37 (1.20, 1.56)	<0.001
9N	485	35556.8	315	18587.8	1.91 (1.64, 2.23)	<0.001
10A	485	13719.7	311	5363.8	2.56 (2.18, 3.00)	<0.001
11A	486	10396.3	312	3129.8	3.32 (2.80, 3.95)	<0.001
12F	486	14752.0	314	4820.1	3.06 (2.62, 3.58)	<0.001
17F	481	40011.8	312	11267.4	3.55 (3.02, 4.17)	<0.001
19A	486	9009.8	314	9797.6	0.92 (0.78, 1.08)	<0.001
20A	480	37532.2	311	14787.0	2.54 (2.13, 3.02)	<0.001
22F	487	20162.7	313	7770.3	2.59 (2.21, 3.04)	<0.001
33F	488	73201.8	314	40609.0	1.80 (1.54, 2.11)	<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: [P013V116: adam-adsl; adimm]

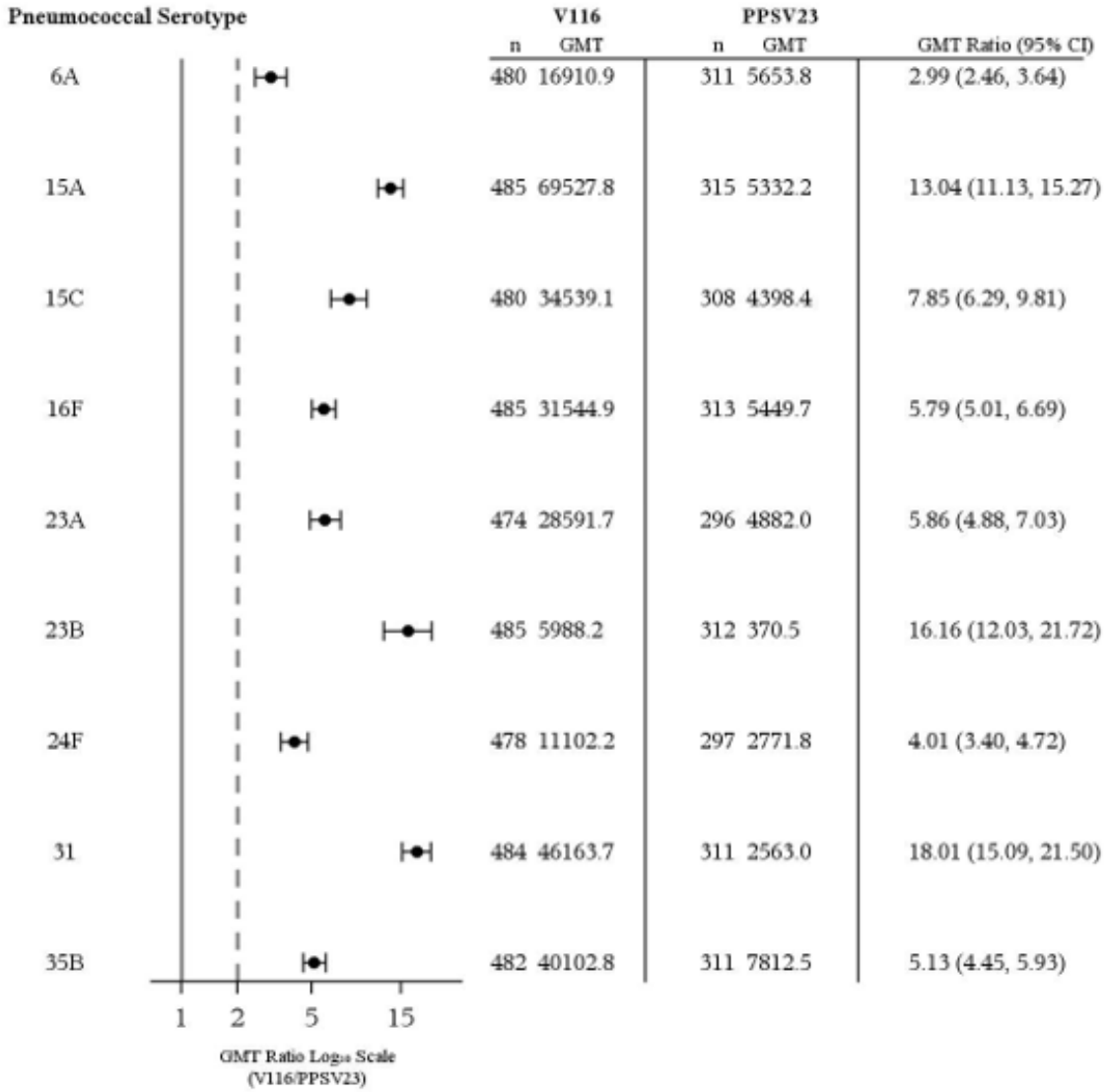
Comparison of Serotype-Specific OPA GMTs for Unique Serotypes

V116 met the predefined criterion for superiority compared 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 (Figure 3 & Table 9).

Results for serotype-specific OPA GMTs at 30 days postvaccination in the FAS population were consistent with those observed in the PP population.

The distribution of serotype-specific OPA titres at 30 days postvaccination was higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116 as shown by RCDCs.

Figure 3 Forest Plot of Postvaccination OPA GMT Ratios for Unique Serotypes (Per-Protocol Population)



Note: The dashed line indicates the margin for the superiority test.
Source: [P013V116: adam-adsl; adimm]

Table 9 Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population)

Pneumococcal Serotype	V116 (N = 527)		PPSV23 (N = 347)		GMT Ratio[a] (V116 / PPSV23) (95% CI)[ab]	p-Value[ab] (1-sided)
	n	GMT[a]	n	GMT[a]		
6A	480	16910.9	311	5653.8	2.99 (2.46, 3.64)	<0.001
15A	485	69527.8	315	5332.2	13.04 (11.13, 15.27)	<0.001
15C	480	34539.1	308	4398.4	7.85 (6.29, 9.81)	<0.001
16F	485	31544.9	313	5449.7	5.79 (5.01, 6.69)	<0.001
23A	474	28591.7	296	4882.0	5.86 (4.88, 7.03)	<0.001
23B	485	5988.2	312	370.5	16.16 (12.03, 21.72)	<0.001
24F	478	11102.2	297	2771.8	4.01 (3.40, 4.72)	<0.001
31	484	46163.7	311	2563.0	18.01 (15.09, 21.50)	<0.001
35B	482	40102.8	311	7812.5	5.13 (4.45, 5.93)	<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: [P013V116: adam-adsl; adimm]

Secondary Immunogenicity Endpoints

Serotype-Specific IgG GMCs for All Serotypes

Between-group comparisons of IgG GMCs for all serotypes at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs (Table 10, Table 11, Figure 4, Figure 5).

Table 10 Analysis of Postvaccination IgG GMCs for Common Serotypes (Per-Protocol Population)

Pneumococcal Serotype	V116 (N = 527)		PPSV23 (N = 347)		GMC Ratio[a] (V116 / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
3	462	1.56	299	1.88	0.83 (0.72, 0.95)
7F	462	7.33	299	7.37	0.99 (0.86, 1.15)
8	462	13.68	299	17.86	0.77 (0.67, 0.87)
9N	462	7.11	299	9.41	0.76 (0.65, 0.88)
10A	462	8.47	299	4.69	1.81 (1.50, 2.17)
11A	462	7.47	299	4.32	1.73 (1.49, 2.01)
12F	462	1.78	299	1.38	1.28 (1.07, 1.54)
17F	462	14.75	298	6.13	2.41 (2.06, 2.81)
19A	462	13.50	299	15.97	0.85 (0.71, 1.00)
20A	462	9.09	299	5.75	1.58 (1.34, 1.87)
22F	462	14.20	299	10.23	1.39 (1.17, 1.64)
33F	462	6.75	299	9.34	0.72 (0.61, 0.85)

[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: [P013V116: adam-adsl; adimm]

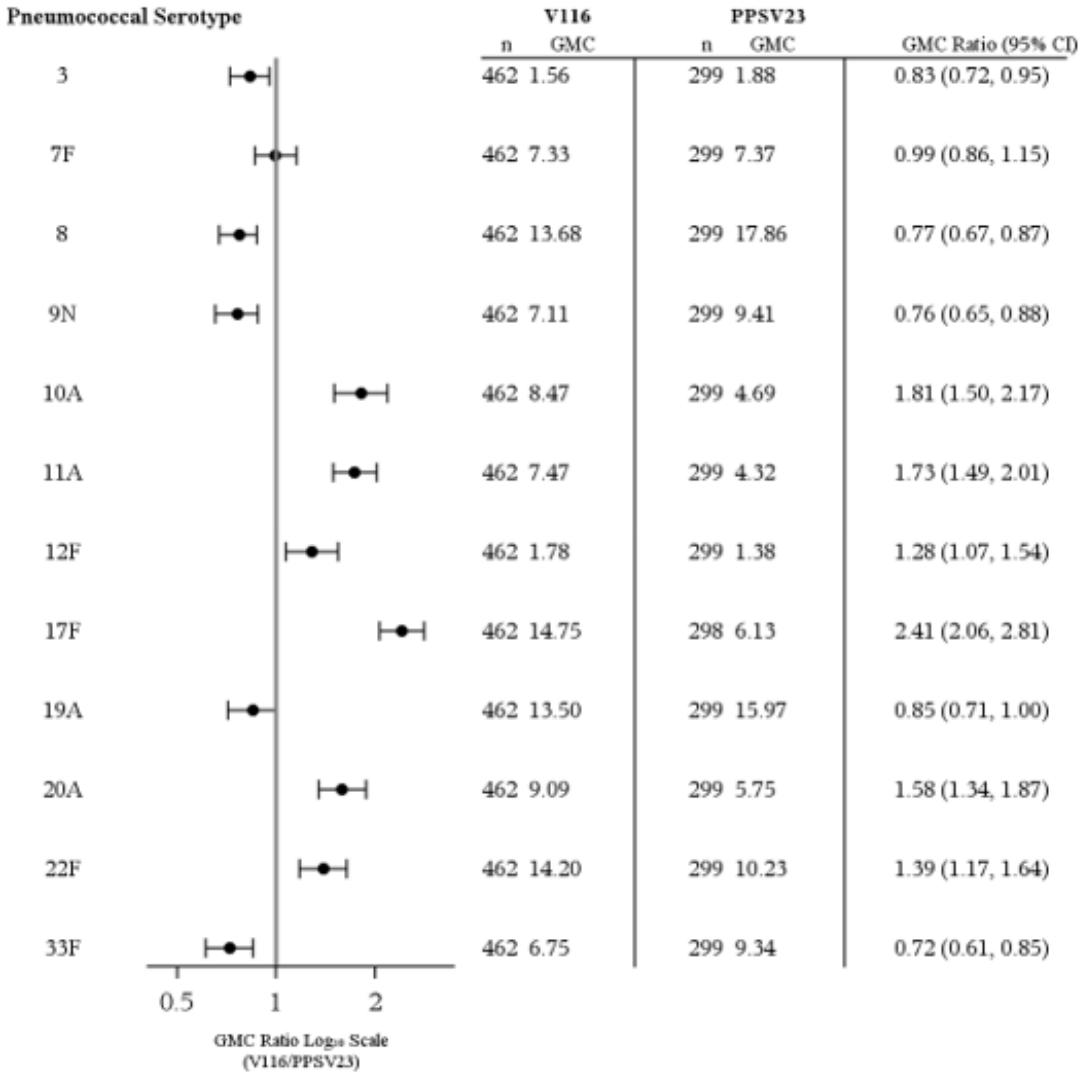
Table 11 Analysis of Postvaccination IgG GMCs for Unique Serotypes (Per-Protocol Population)

Pneumococcal Serotype	V116 (N = 527)		PPSV23 (N = 347)		GMC Ratio[a] (V116 / PPSV23) (95% CI)[a]
	n	GMC[a]	n	GMC[a]	
6A	462	11.98	299	6.25	1.92 (1.59, 2.31)
15A	462	12.00	299	1.24	9.67 (8.07, 11.60)
15C	462	13.54	299	2.55	5.32 (4.35, 6.50)
16F	462	2.35	299	0.18	12.97 (11.04, 15.24)
23A	462	7.17	299	1.05	6.84 (5.56, 8.43)
23B	462	6.47	299	1.29	5.03 (4.18, 6.04)
24F	462	2.39	299	0.22	10.72 (8.83, 13.01)
31	462	4.67	299	0.27	17.38 (14.92, 20.24)
35B	462	8.96	299	0.89	10.10 (8.72, 11.70)

[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: [P013V116: adam-adsl; adimm]

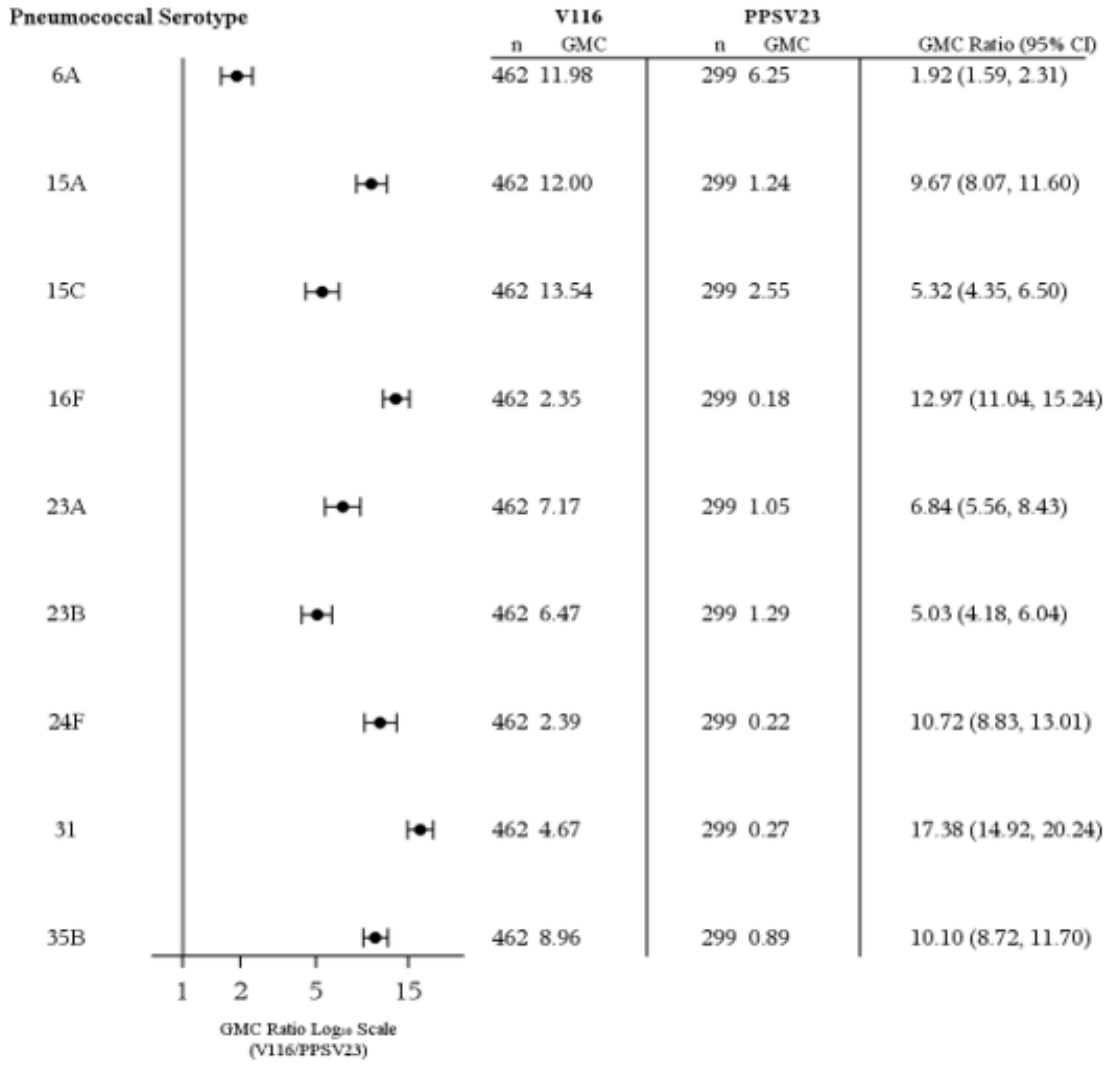
Figure 4 Forest Plot of Postvaccination IgG GMC Ratios for Common Serotypes (Per-Protocol Population)



Source: [P013V116: adam-adsl; adimm]

The number of participants included in the IgG analysis for both day 1 and day 30 time points were lower than expected due to insufficient blood sample volumes. As the sample size still exceeded the sample size determined by the sample size calculation (due to over-recruitment), precision is still expected to be adequate. It should however be noted that although the number of participants is only slightly lower (~5%) than in the OPA analysis, the percentage of participants with data available for both time points is substantially lower in the IgG analysis than in the OPA analysis (66.8% vs. 81.0%). Hence, assumptions regarding missing data are more important in this analysis. Since insufficient blood sample volume is not expected to be related to vaccination or to immunogenicity, bias seems unlikely. As this is a secondary outcome, no sensitivity analyses were requested.

Figure 5 Forest Plot of Postvaccination IgG GMC Ratios for Unique Serotypes (Per-Protocol Population)



Source: [P013V116: adam-adsl; adimm]

The distribution of serotype-specific IgG concentrations at 30 days postvaccination was generally comparable between the intervention groups for the 12 common serotypes and higher in the V116 group for the 9 serotypes unique to V116 compared with the PPSV23 group as shown by RCDCs.

Serotype-Specific GMFRs for All Serotypes

For both OPA (Table 12) and IgG responses, serotype-specific GMFRs from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 common serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116.

Table 12 Summary of OPA Antibody Responses (Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 (N = 527) Observed Response	V116 (N = 527) 95% CI[a]	PPSV23 (N = 347) n	PPSV23 (N = 347) Observed Response	PPSV23 (N = 347) 95% CI[a]
Common Serotypes							
3	GMT (Day 1)	454	55.5	(47.9, 64.2)	297	53.4	(44.6, 64.1)
	GMT (Day 30)	447	527.8	(483.1, 576.7)	291	518.2	(464.9, 577.7)
	GMFR	413	7.9	(6.8, 9.1)	274	7.6	(6.4, 9.0)
	% ≥ 4-fold rise	413	64.6% (267/413)	(59.8, 69.3)	274	66.1% (181/274)	(60.1, 71.6)
7F	GMT (Day 1)	456	1247.0	(1098.3, 1415.9)	299	1359.4	(1164.3, 1587.3)
	GMT (Day 30)	447	20530.6	(18543.7, 22730.4)	287	14378.9	(12628.3, 16372.2)
	GMFR	417	15.8	(13.7, 18.3)	271	10.5	(9.0, 12.4)
	% ≥ 4-fold rise	417	84.2% (351/417)	(80.5, 87.5)	271	79.7% (216/271)	(74.4, 84.3)
8	GMT (Day 1)	432	382.4	(332.3, 440.0)	284	409.3	(342.3, 489.5)
	GMT (Day 30)	444	12284.1	(11333.1, 13314.8)	284	9001.0	(8128.9, 9966.7)
	GMFR	391	30.5	(25.9, 36.0)	255	21.7	(17.8, 26.4)
	% ≥ 4-fold rise	391	92.3% (361/391)	(89.2, 94.8)	255	90.6% (231/255)	(86.3, 93.9)
9N	GMT (Day 1)	457	2510.4	(2280.9, 2762.9)	299	2291.3	(2023.4, 2594.8)
	GMT (Day 30)	440	35901.5	(32555.8, 39591.1)	281	18464.9	(16401.6, 20787.8)

Summary of OPA Antibody Responses
(Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 (N = 527) Observed Response	V116 (N = 527) 95% CI[a]	PPSV23 (N = 347) n	PPSV23 (N = 347) Observed Response	PPSV23 (N = 347) 95% CI[a]
9N	GMFR	412	13.9	(12.1, 15.9)	265	8.0	(6.8, 9.3)
	% ≥ 4-fold rise	412	82.8% (341/412)	(78.8, 86.3)	265	71.7% (190/265)	(65.9, 77.0)
10A	GMT (Day 1)	408	778.6	(623.2, 972.8)	280	780.9	(597.8, 1020.2)
	GMT (Day 30)	450	13736.6	(12621.2, 14950.6)	286	5402.0	(4600.8, 6342.7)
	GMFR	373	15.4	(12.5, 19.0)	255	6.0	(4.7, 7.5)
	% ≥ 4-fold rise	373	73.5% (274/373)	(68.7, 77.9)	255	47.5% (121/255)	(41.2, 53.8)
11A	GMT (Day 1)	426	506.7	(406.8, 631.1)	278	469.8	(358.6, 615.6)
	GMT (Day 30)	447	10407.4	(9444.7, 11468.2)	283	3129.0	(2678.1, 3655.8)
	GMFR	387	18.6	(14.9, 23.4)	249	5.9	(4.5, 7.8)
	% ≥ 4-fold rise	387	76.2% (295/387)	(71.7, 80.4)	249	46.2% (115/249)	(39.9, 52.6)
12F	GMT (Day 1)	462	17.9	(15.3, 20.8)	301	18.5	(15.3, 22.5)
	GMT (Day 30)	444	14756.4	(13478.0, 16156.0)	288	4820.5	(4208.9, 5521.1)
	GMFR	420	452.7	(378.6, 541.4)	275	149.3	(122.1, 182.6)
	% ≥ 4-fold rise	420	96.7% (406/420)	(94.5, 98.2)	275	96.0% (264/275)	(93.0, 98.0)
17F	GMT (Day 1)	442	1104.9	(960.1, 1271.4)	292	1023.2	(854.3, 1225.5)
	GMT (Day 30)	434	40202.9	(36413.0, 44387.2)	278	11217.5	(9821.4, 12812.2)

Summary of OPA Antibody Responses
(Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 (N = 527) Observed Response	V116 (N = 527) 95% CI[a]	PPSV23 (N = 347) n	PPSV23 (N = 347) Observed Response	PPSV23 (N = 347) 95% CI[a]
17F	GMFR	395	33.3	(28.3, 39.2)	258	9.9	(8.2, 11.8)
	% ≥ 4-fold rise	395	92.4% (365/395)	(89.3, 94.8)	258	74.0% (191/258)	(68.2, 79.3)
19A	GMT (Day 1)	452	1315.7	(1140.1, 1518.4)	302	1300.5	(1100.4, 1537.0)
	GMT (Day 30)	442	9072.4	(8203.7, 10033.2)	284	9713.0	(8428.0, 11194.0)
	GMFR	408	6.6	(5.6, 7.7)	272	7.2	(6.1, 8.7)
	% ≥ 4-fold rise	408	57.8% (236/408)	(52.9, 62.7)	272	64.0% (174/272)	(58.0, 69.7)
20A	GMT (Day 1)	443	3566.3	(3190.5, 3986.5)	297	3405.0	(3013.5, 3847.3)
	GMT (Day 30)	398	37646.2	(33955.0, 41738.7)	270	14797.1	(12639.1, 17323.6)
	GMFR	361	10.4	(9.0, 12.0)	256	4.1	(3.5, 4.9)
	% ≥ 4-fold rise	361	77.8% (281/361)	(73.2, 82.0)	256	48.0% (123/256)	(41.8, 54.4)
22F	GMT (Day 1)	444	858.0	(722.6, 1018.7)	287	942.4	(772.6, 1149.6)
	GMT (Day 30)	445	20092.0	(18311.9, 22045.2)	288	7804.8	(6800.4, 8957.7)
	GMFR	402	22.2	(18.3, 26.8)	262	8.4	(6.8, 10.3)
	% ≥ 4-fold rise	402	84.1% (338/402)	(80.1, 87.5)	262	65.3% (171/262)	(59.2, 71.0)
33F	GMT (Day 1)	462	4085.6	(3722.4, 4484.2)	302	3906.7	(3514.1, 4343.2)
	GMT (Day 30)	442	73090.5	(66757.4, 80024.4)	279	40967.4	(35209.4, 47667.1)

Summary of OPA Antibody Responses
(Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 Observed Response	V116 95% CI[a]	PPSV23 (N = 347) n	PPSV23 Observed Response	PPSV23 95% CI[a]
33F	GMFR	416	18.2	(16.1, 20.5)	267	10.0	(8.6, 11.6)
	% ≥ 4-fold rise	416	88.9% (370/416)	(85.5, 91.8)	267	74.2% (198/267)	(68.5, 79.3)
Unique Serotypes							
6A	GMT (Day 1)	423	656.7	(538.4, 801.0)	276	710.1	(556.2, 906.6)
	GMT (Day 30)	437	16937.0	(14955.1, 19181.6)	281	5661.6	(4819.4, 6650.9)
	GMFR	380	22.1	(17.8, 27.4)	246	7.1	(5.6, 9.0)
	% ≥ 4-fold rise	380	76.3% (290/380)	(71.7, 80.5)	246	55.7% (137/246)	(49.2, 62.0)
15A	GMT (Day 1)	451	2628.4	(2396.2, 2883.0)	299	2537.4	(2236.4, 2879.0)
	GMT (Day 30)	434	69348.6	(62719.2, 76678.8)	284	5334.8	(4687.7, 6071.3)
	GMFR	400	26.6	(23.3, 30.4)	268	2.0	(1.8, 2.3)
	% ≥ 4-fold rise	400	91.3% (365/400)	(88.0, 93.8)	268	22.8% (61/268)	(17.9, 28.3)
15C	GMT (Day 1)	408	198.2	(154.9, 253.6)	273	260.9	(192.7, 353.3)
	GMT (Day 30)	437	34000.8	(29952.4, 38596.3)	276	4476.4	(3662.0, 5471.9)
	GMFR	365	124.5	(95.0, 163.3)	241	13.4	(10.2, 17.7)
	% ≥ 4-fold rise	365	90.7% (331/365)	(87.2, 93.5)	241	68.9% (166/241)	(62.6, 74.7)

Summary of OPA Antibody Responses
(Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 Observed Response	V116 95% CI[a]	PPSV23 (N = 347) n	PPSV23 Observed Response	PPSV23 95% CI[a]
16F	GMT (Day 1)	457	4128.9	(3721.2, 4581.4)	294	3931.6	(3482.4, 4438.7)
	GMT (Day 30)	428	31870.7	(29019.8, 35001.7)	278	5338.0	(4713.7, 6044.9)
	GMFR	400	7.6	(6.7, 8.6)	259	1.5	(1.3, 1.6)
	% ≥ 4-fold rise	400	67.5% (270/400)	(62.7, 72.1)	259	13.5% (35/259)	(9.6, 18.3)
23A	GMT (Day 1)	372	1904.1	(1590.9, 2279.0)	249	2037.1	(1646.7, 2520.1)
	GMT (Day 30)	425	28305.3	(25277.9, 31695.3)	266	5017.9	(4304.8, 5849.1)
	GMFR	323	14.2	(11.7, 17.2)	219	2.2	(1.8, 2.7)
	% ≥ 4-fold rise	323	75.2% (243/323)	(70.2, 79.8)	219	27.4% (60/219)	(21.6, 33.8)
23B	GMT (Day 1)	429	40.9	(31.5, 53.1)	285	40.6	(29.4, 56.1)
	GMT (Day 30)	446	6006.9	(5234.2, 6893.6)	268	377.6	(274.2, 519.8)
	GMFR	390	92.9	(70.3, 122.8)	241	6.2	(4.5, 8.4)
	% ≥ 4-fold rise	390	78.2% (305/390)	(73.8, 82.2)	241	42.7% (103/241)	(36.4, 49.2)
24F	GMT (Day 1)	400	2487.3	(2139.9, 2891.1)	262	2542.0	(2100.9, 3075.8)
	GMT (Day 30)	435	11137.5	(10159.4, 12209.9)	249	2821.6	(2399.3, 3318.2)
	GMFR	357	4.4	(3.8, 5.1)	214	1.1	(0.9, 1.3)
	% ≥ 4-fold rise	357	47.6% (170/357)	(42.3, 52.9)	214	7.9% (17/214)	(4.7, 12.4)

Summary of OPA Antibody Responses
(Per-Protocol Population)

Pneumococcal Serotype	Endpoint	V116 (N = 527) n	V116 Observed Response	V116 95% CI[a]	PPSV23 (N = 347) n	PPSV23 Observed Response	PPSV23 95% CI[a]
31	GMT (Day 1)	446	1555.4	(1329.5, 1819.8)	286	1557.7	(1287.9, 1884.1)
	GMT (Day 30)	424	46506.1	(42222.3, 51224.6)	275	2611.0	(2198.8, 3100.5)
	GMFR	386	28.8	(24.1, 34.4)	250	1.6	(1.3, 1.8)
	% ≥ 4-fold rise	386	89.9% (347/386)	(86.4, 92.7)	250	13.6% (34/250)	(9.6, 18.5)
35B	GMT (Day 1)	451	6900.5	(6279.4, 7583.1)	297	5915.2	(5252.2, 6662.0)
	GMT (Day 30)	418	41029.9	(37391.9, 45021.7)	270	7484.0	(6513.8, 8598.6)
	GMFR	387	6.0	(5.3, 6.8)	256	1.3	(1.2, 1.4)
	% ≥ 4-fold rise	387	60.7% (235/387)	(55.7, 65.6)	256	7.8% (20/256)	(4.8, 11.8)

[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 titers (1/dil); OPA=opsonophagocytic activity; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adimm]

Proportion of Participants with ≥4-Fold Rise in Immune Responses for All Serotypes

For both OPA (Table 12) and IgG responses, the proportions of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 common serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116.

Exploratory Immunogenicity Endpoints

Immune Responses for Serotypes Within a Serogroup

V116 elicited immune responses to serotype 6C (cross-reactive to serotype 6A) and serotype 15B (cross-reactive to serotype 15C), as assessed by OPA titres and IgG concentrations for serotypes within a serogroup in V116 at 30 days postvaccination.

The distribution of serotype-specific OPA titres and IgG concentrations at 30 days postvaccination with V116 was generally consistent between serotype 15B and serotype 15C, as shown by RCDCs. The distribution of serotype-specific OPA titres and IgG concentrations at 30 days postvaccination with V116 was higher for serotype 6A compared with serotype 6C.

Serotype 15B was analysed post hoc, using the same methodology conducted for the primary immunogenicity analyses. The results indicated that the estimated GMT ratio (V116/PPSV23) for serotype 15B was 3.78 with a lower bound of the 95% CI of 3.03. In a post hoc analysis, V116 elicited an immune response to the cross-reactive serotype 15B that met the noninferiority criterion, which was pre-specified for the set of common serotypes between V116 and PPSV23.

Immunogenicity Results Summary Primary Immunogenicity Endpoints

- 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.
- 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.

Secondary Immunogenicity Endpoints

- Between-group comparisons of IgG GMCs for common and unique serotypes at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs.
- For both OPA and IgG responses, serotype-specific GMFRs and the proportions of participants with a ≥4-fold rise in serotype-specific responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the

12 common serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116.

V116 met the predefined criterion for noninferiority compared to PPSV23 for each of the 12 shared serotypes at 30 days postvaccination. Generally, V116 outperformed PPSV23 for almost all shared serotypes (3 and 19A being the exceptions. This was to be expected, as glycoconjugate vaccines are generally known to elicit a stronger immune response as compared to purely polysaccharide vaccines. V116 also met the predefined criterion for superiority compared to PPSV23 for each of the 9 serotypes unique to V116 at 30 days postvaccination. The GMT ratio (V116/PPSV23) for most of the unique serotypes were considerable, for some in the ranges of 15-20-fold.

The IgG GMCs for all serotypes at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs, although the differences were smaller between the vaccines as compared to the OPA analysis. This suggests that PPSV23 elicits a larger ratio of non-functional binding antibodies as compared to V116.

For both OPA and IgG responses, serotype-specific GMFRs from baseline to 30 days postvaccination were generally higher in the V116 group compared with the PPSV23 group for almost all serotypes (3 and 19A being the exceptions again).

For both OPA and IgG responses, the proportions of participants with a ≥4-fold rise in antibody responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 shared serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116.

All immunogenicity analyses in the pivotal study were conducted 30 days post-vaccination and the persistence of the immune response beyond that is currently unknown.

In summary, V116 met the predefined criteria for non-inferiority and superiority, but also clearly outperformed PPSV23 immunogenicity-wise for most of the shared serotypes.

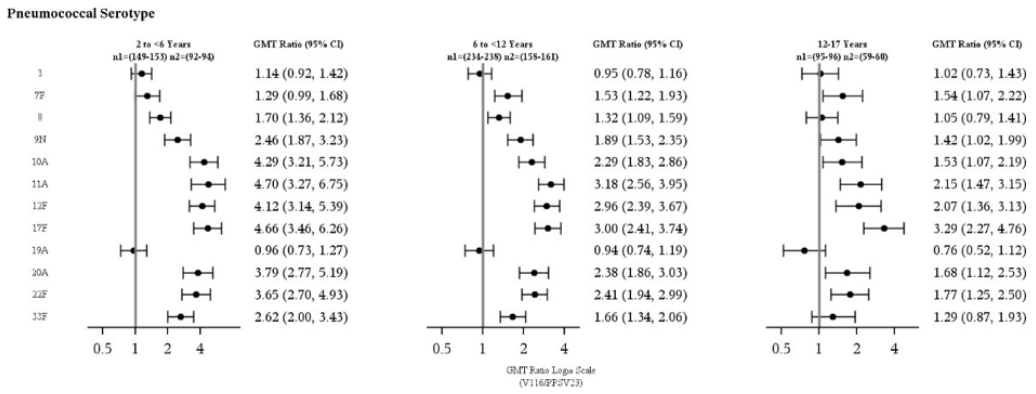
All immunogenicity analyses in the pivotal study were conducted 30 days post-vaccination and the persistence of the immune response beyond that is currently unknown. Potentially, the at risk-children could need additional boosters. The CHMP asked if the MAH had plans to investigate the duration of the immunity further and if there was any data regarding that forthcoming. The MAH indicated that long-term immunogenicity is only planned to be investigated in the adult cohorts and these data have been submitted as a PAM for the MAA of Capvaxive. As no other data is forthcoming, the issue was considered resolved.

Ancillary analyses

Subgroup Analyses

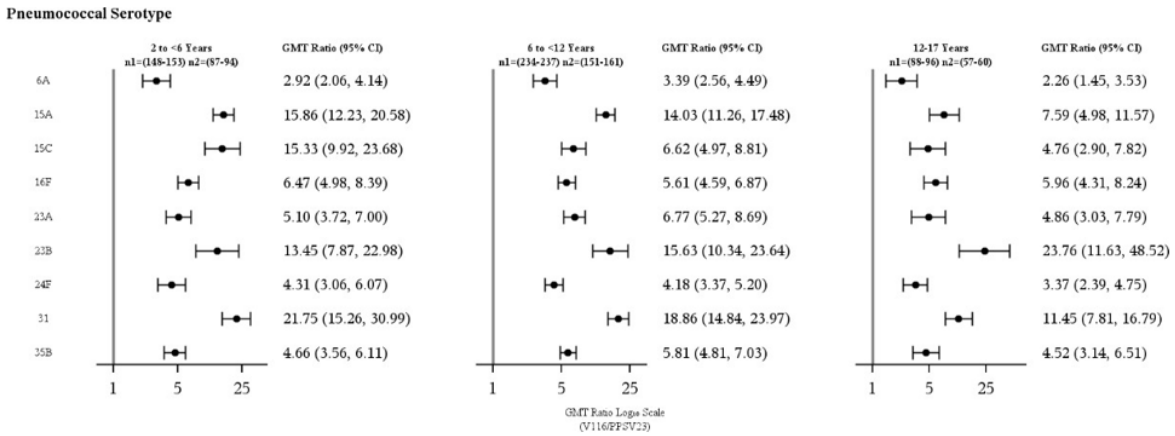
Serotype-specific OPA GMTs and their corresponding between-group 95% CIs at 30 days postvaccination were calculated within each intervention group for each subgroup if there were ≥5% of the total vaccinated participants in each intervention group within that subgroup. There were no major differences within each of the subgroup categories analysed as assessed by OPA GMTs at 30 days postvaccination for all 21 serotypes contained in the vaccine such as age, sex, race, ethnicity, increased-risk conditions, number of increased-risk conditions, type of increased-risk conditions, prior pneumococcal vaccination status and primary PCV regimen. As expected, larger statistical variation could be seen in smaller cohorts. Some of the key findings are shown below:

Figure 6 Forest Plot of Postvaccination OPA GMT Ratios for Common Serotypes by Age Group (Per-Protocol Population)



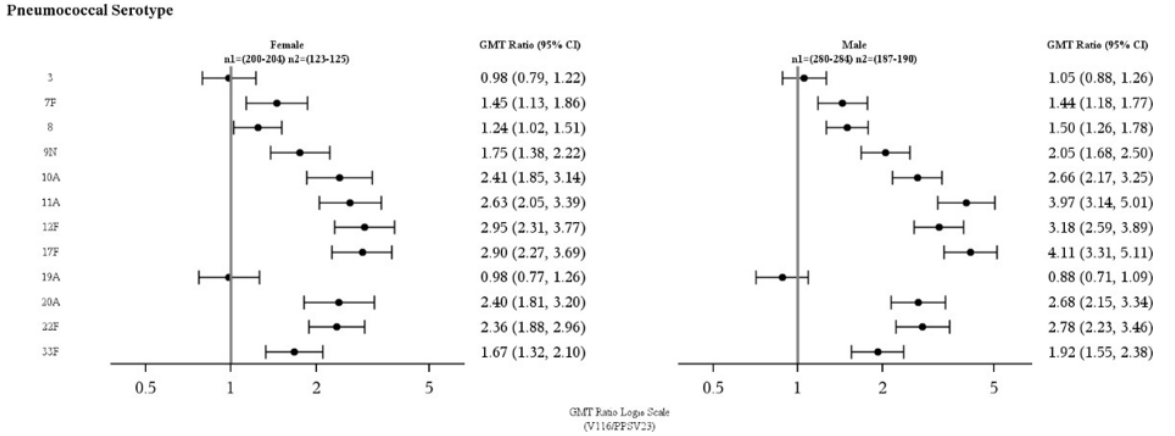
n1 = Number of participants contributing to the analysis from the V116 group across all common serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all common serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 7 Forest Plot of Postvaccination OPA GMT Ratios for Unique Serotypes by Age Group (Per-Protocol Population)



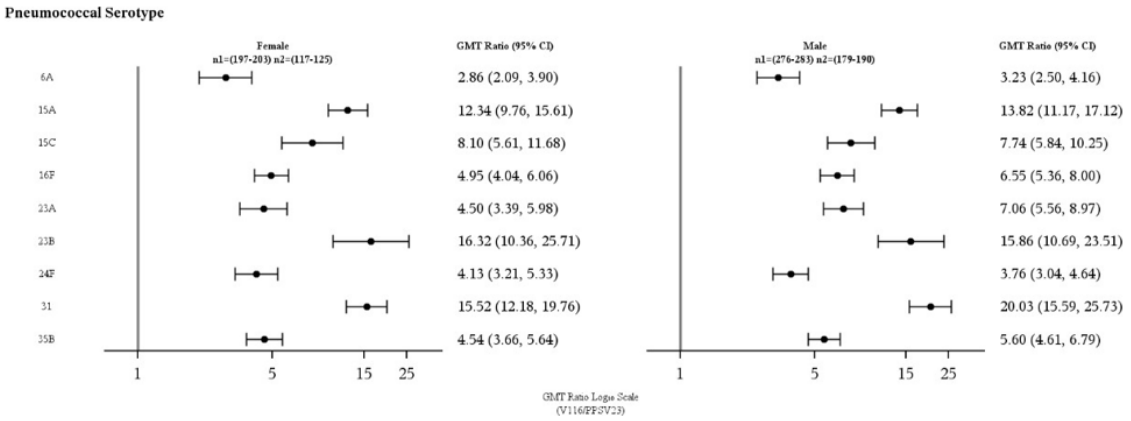
n1 = Number of participants contributing to the analysis from the V116 group across all unique serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all unique serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 8 Forest Plot of Postvaccination OPA GMT Ratios for Common Serotypes by Sex (Per-Protocol Population)



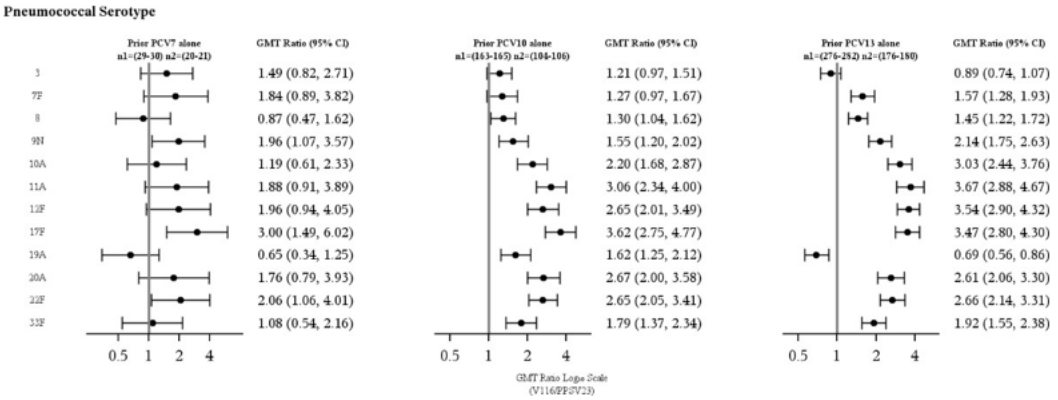
n1 = Number of participants contributing to the analysis from the V116 group across all common serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all common serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 9 Forest Plot of Postvaccination OPA GMT Ratios for Unique Serotypes by Sex (Per-Protocol Population)



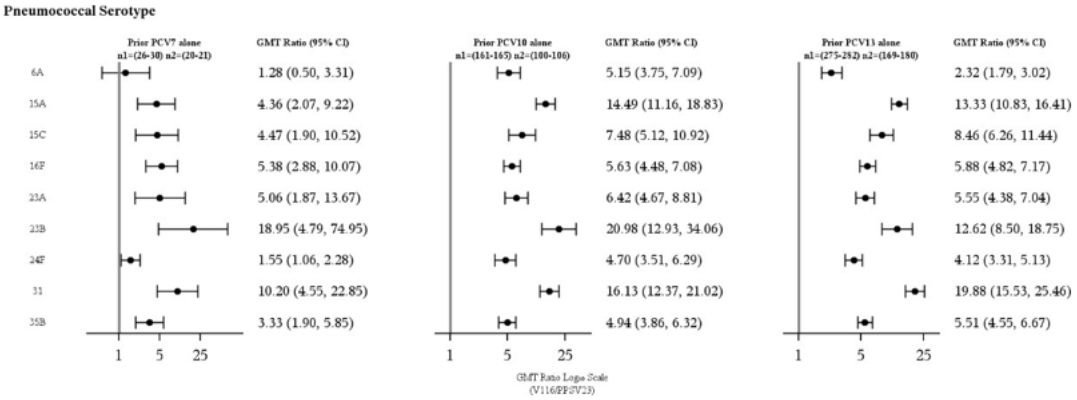
n1 = Number of participants contributing to the analysis from the V116 group across all unique serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all unique serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 10 Forest Plot of Postvaccination OPA GMT Ratios for Common Serotypes by Prior Pneumococcal Vaccination (Per-Protocol Population)



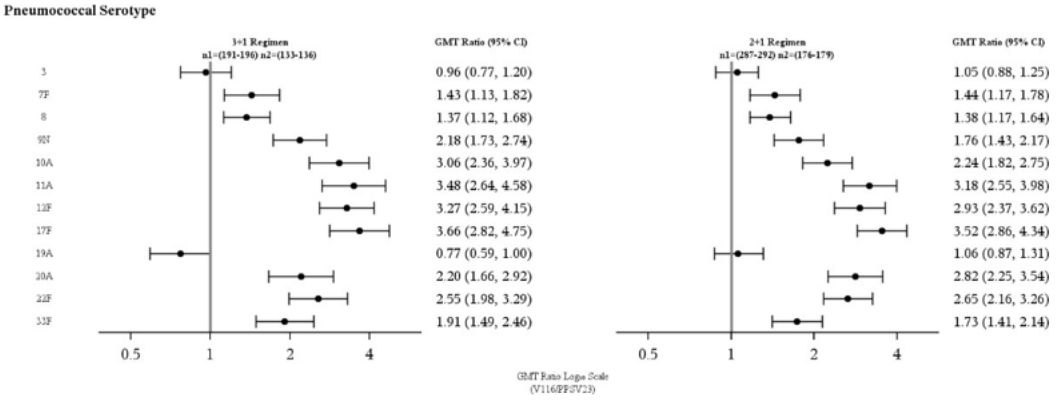
n1 = Number of participants contributing to the analysis from the V116 group across all common serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all common serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 11 Forest Plot of Postvaccination OPA GMT Ratios for Unique Serotypes by Prior Pneumococcal Vaccination (Per-Protocol Population)



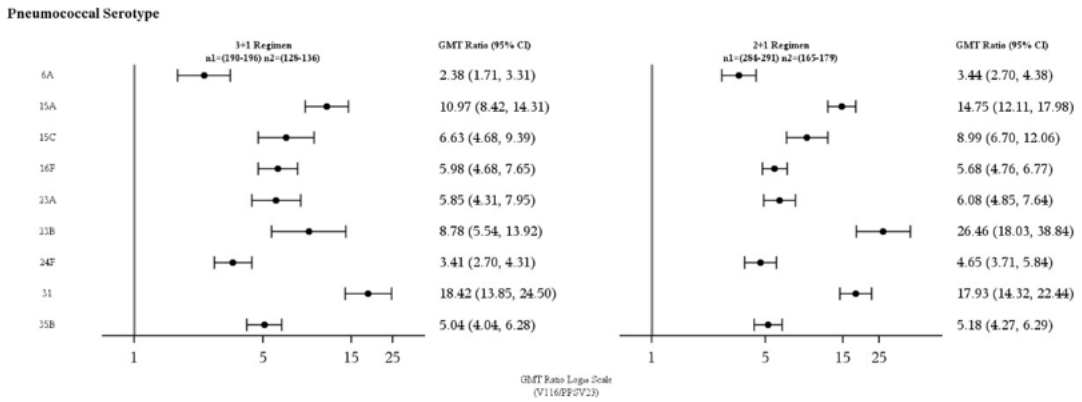
n1 = Number of participants contributing to the analysis from the V116 group across all unique serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all unique serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 12 Forest Plot of Postvaccination OPA GMT Ratios for Common Serotypes by Prior PCV Primary Regimen (Per-Protocol Population)



n1 = Number of participants contributing to the analysis from the V116 group across all common serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all common serotypes.
Source: [P013V116: adam-adsl; adimm]

Figure 13 Forest Plot of Postvaccination OPA GMT Ratios for Unique Serotypes by Prior PCV Primary Regimen (Per-Protocol Population)



n1 = Number of participants contributing to the analysis from the V116 group across all unique serotypes;
n2 = Number of participants contributing to the analysis from the PPSV23 group across all unique serotypes.
Source: [P013V116: adam-adsl; adimm]

Considering the highly heterogenous background of the study participants with regard to age, prior pneumococcal vaccination and PCV regimen, it is important to as far as possible exclude that a possible inferior immunogenicity in a subgroup is being masked by the response of the total group. Therefore, some key data has been included in this report from the subgroup analyses. As can be seen in the Figure 6 and Figure 9 , the responses were similar with regards to age and sex. With regard to OPA GMT-ratios, some differences could be seen between cohorts having received PCV7, PCV10 and PCV13 alone prior, with the PCV7-group noticeably showing the smallest ratios (Figure 10 and Figure 11). It is however noted that the group is small (n = 20-30, depending on the serotype). When looking at the data, it is also seen that smaller ratios are partially caused by PPSV23 having a better effect for some serotypes for those having previously received PCV7 as compared to PCV13. This could speculatively be due to the children having received PCV7 being generally of older age (since PCV7 is an older vaccine), and thus having been exposed to more pneumococcal infections, causing a heightened natural immunity that is boosted by the larger quantities of antigen included in PPSV23. Importantly, V116 is not performing generally inferior to PPSV23 in this subgroup. Taken together, these findings do not raise any alarm.

Finally, it was seen that prior PCV regimen (2+1 vs 3+1) was not a factor causing considerably changes in the performance of V116 as compared to PPSV23.

Summary of main study

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

Table 13 Summary of Efficacy for trial V116-013 (also referred to as P013V116)

Title: V116-013 A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Children and Adolescents With Increased Risk of Pneumococcal Disease.

Study identifier	IND: 19316, UTN: U1111-1293-4944, NCT: NCT06177912, jRCT: jRCT2031230559, EU CT: 2023-506236-32, CSR Identification: P013V116		
Design	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator phase 3		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		19-JAN-2024 to 26-FEB-2025 not applicable not applicable
Hypothesis	Non-inferiority and superiority		
Treatments groups	V116, pneumococcal 21-valent conjugate vaccine (test product)		Single dose, 0.5 ml intramuscular injection, 4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B)
	PPSV23, pneumococcal 23-valent polysaccharide vaccine (comparator)		Single dose, 0.5 ml intramuscular injection, 25 µg of each PnPs antigen (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)
Endpoints and definitions	Primary endpoint	Serotype-specific OPA responses	To compare the serotype-specific opsonophagocytic (OPA) geometric mean titres (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.)
	Secondary endpoint	Serotype-specific IgG responses	To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V116 compared with PPSV23.

	Secondary endpoint	Serotype-specific OPA and IgG responses	To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses and IgG responses from baseline to 30 days postvaccination within each vaccination group.
Database lock	18-MAR-2025		
Results and Analysis			
Analysis description	**Primary Endpoint: Serotype-specific OPA GMT for Common Serotypes**		
Analysis population and time point description	Immunogenicity analyses were based on the PP population, which was defined as all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Most randomised participants were included in the PP population for the OPA analyses for at least 1 timepoint (91.0%), and for both Day 1 and Day 30 timepoints (81.0%). Most randomised participants were included in the PP population for the IgG analyses for at least 1 timepoint (86.3%). A total of 66.8% of participants were included in the IgG analyses for both Day 1 and Day 30 timepoints. The reasons for exclusion from the PP population were generally comparable between intervention groups. Supportive immunogenicity analyses were conducted for the primary immunogenicity endpoints using the FAS population. The FAS population was defined as all randomised participants who received study vaccination and had at least 1 serology result.		
Descriptive statistics and estimate variability	Treatment group	V116	PPSV23
	Number of subjects	See Table 8 Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population).	
	Serotype-specific OPA GMT		
	Primary endpoint	Comparison groups	V116 vs PPSV23

Effect estimate per comparison		Serotype-specific OPA GMT ratio (V116/PPSV23)	Refer to Table 8- Analysis of Postvaccination OPA GMTs for Common Serotypes (Per-Protocol Population) 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	>0.50 for all common serotypes
		P-value	$p<0.001$ for all common serotypes
Analysis description	**Primary Endpoint: Serotype-specific OPA GMT for Unique Serotypes**		
Descriptive statistics and estimate variability	Treatment group	V116	PPSV23
	Number of subjects	See Table 9 OPA GMTs for Unique Serotypes (Per-Protocol Population)	
Effect estimate per comparison	Primary endpoint	Comparison groups	V116 vs PPSV23
		Serotype-specific OPA GMT ratio (V116/PPSV23)	Refer to Table 9- Analysis of Postvaccination OPA GMTs for Unique Serotypes (Per-Protocol Population). 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	>2.0 for all unique serotypes
		P-value	$p<0.001$ for all unique serotypes
Analysis description	**Secondary Endpoint: Serotype-specific IgG GMCs**		
Descriptive statistics and estimate variability	Treatment group	V116	PPSV23

	Number of subjects	See Table 10 & Table 11	
Effect estimate per comparison	Secondary endpoint	Comparison groups	V116 vs PPSV23
		Serotype-specific IgG GMC	Refer to Table 10 & Table 11.
		95% CI	Between-group comparisons of IgG GMCs at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs. No statistical hypothesis testing was conducted.
Analysis description	**Secondary Endpoint: Serotype-specific GMFR and proportions of participants with a ≥4-fold rise in OPA GMT and IgG GMC**		
Descriptive statistics and estimate variability	Treatment group	V116	PPSV23
	Number of subjects	Variable between the different serotypes and analyses. The analysed PPSV23-vaccinee-samples ranged between *n* = 214-275, and the V116-vaccinee-samples *n* = 323-420 for OPA antibody responses and n = 230 and n = 358-359 for IgG antibody responses.	
Effect estimate per comparison	Secondary endpoint	Comparison groups	V116 vs PPSV23
		Serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in OPA GMT and IgG GMC	For both OPA and IgG responses, serotype-specific GMFRs from baseline to 30 days postvaccination were generally comparable in both intervention groups

		95% CI	for the 12 common serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116. Likewise, the proportions of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 common serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116. No statistical hypothesis testing was conducted.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

V116 (Capvaxive) is a polyvalent, glycoconjugate pneumococcal vaccine currently indicated in adults ≥18 years of age for the prevention of invasive disease and pneumonia caused by the *S. pneumoniae* serotypes covered by the vaccine. In this application for extension of indication, the MAH submitted data from the study V116-0013, a randomised, double-blind, active comparator-controlled, parallel-group, multisite phase 3 study, that aimed to investigate the safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years, which have completed a primary pneumococcal vaccination regimen and are at increased risk for pneumococcal disease. These children, on top of their primary vaccination with glycoconjugate pneumococcal vaccines, receive in most EU countries a dose of PPSV23 between the ages of 2-18 years to enhance their protection against pneumococcal disease. This treatment broadens the immunity against serotypes exclusive to the PPSV23, as well as boosts immunity against serotypes included in PPSV23 and PCVs. The aim of the MAH is to provide a glycoconjugate alternative to the PPSV23 "booster" administered to these at risk-children and adolescents (that is, V116 is in this study not investigated for primary vaccination against pneumococcal disease).

This application does not contain any clinical efficacy data. Methodologically, the MAH aimed to establish efficacy via functional immunogenicity and immunobridging to the comparator. This approach is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1). The primary endpoints were to demonstrate non-inferiority of V116 to PPSV23 for the 12 shared

serotypes, and to demonstrate superiority for the 9 unique serotypes only included in V116. The statistical criterion for noninferiority required the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PPSV23] to be >0.5 for the shared serotypes at 30 days postvaccination. The predefined criterion for superiority to PPSV23 was the 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.

The secondary endpoints were to evaluate the serotype-specific IgG GMCs at 30 days post-vaccination with V116 compared to the comparator. Also included in the secondary objectives were serotype-specific GMFR and proportion of participants ≥4-fold rise in serotype-specific OPA-responses from baseline to 30 days post-vaccination.

The clinical investigator study sites for V116-013 were located in 13 countries: Canada, Chile, Colombia, Finland, France, Israel, Japan, Poland, Spain, Sweden, Thailand, Türkiye, and the US. Enrolled participants were randomised in a 3:2 ratio to receive a single dose of V116 or PPSV23 on Day 1. Randomization was stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions), by prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and 1 prior PPSV23 dose, prior PCV10 alone, prior PCV10 and 1 prior PPSV23 dose, prior PCV13 alone, or prior PCV13 and 1 prior PPSV23 dose), and age (≥2 to <6 years or ≥6 to <18 years).

Randomisation was stratified by number of increased risk conditions (1 vs. ≥2) and by a combined factor for age (≥2 to <6 years vs ³6 to <18 years), primary vaccination series (PCV7, PCV10, PCV13), and prior receipt of PPSV23 vaccine. These are considered relevant factors, but as very few participants had ≥2 risk conditions or prior receipt of PPSV23 vaccine, some strata levels are expected to be very sparse. While this may decrease statistical efficiency and increase the risk of failure to achieve balance, the results do not raise concerns in this regard.

The overall study design, endpoints and objectives to achieve these aims are according to established precedent and regarded as acceptable by the CHMP.

While V116 was only investigated as booster in children and adolescents who have completed a primary pneumococcal vaccination regimen, with proposed wording of the therapeutic indication there was a potential for V116 to be perceived as indicated for use also as a primary vaccination regimen in paediatrics. The suitability of a single dose in children who have not previously received a full priming series has not been established. Whilst it may be clear from the information in section 4.2 that V116 is intended for children and adolescents who have previously completed a primary paediatric pneumococcal regimen, ideally this should also be reflected in the indication. The Applicant was asked to either update the indication to reflect this or should justify the suitability of a single dose of V116 in children and adolescents who have not previously received a primary pneumococcal vaccination regimen. They agreed to include the criteria of primary vaccination in the indication, and the issue was thus resolved.

Furthermore, the CHMP recommended removing the "at increased risk" from the indication. The study population does not fully represent the entire at risk-population (for instance children with (functional) asplenia, immunocompromising conditions, or following hematopoietic stem cell transplantation) but the results can be used to show immunogenicity of this vaccine in the extended age group and therefore supports the extension of indication. In the indication wording there is a general statement that the vaccine should be given in accordance with official recommendations – allowing use to be limited to only those who are in need of it as stated in official recommendations. It is acknowledged that the clinical benefit of a "booster" pneumococcal vaccination for healthy children already having received pneumococcal vaccination is less clear compared to children with factors putting them at high

risk of severe pneumococcal disease, but this wording allows NITAGs to determine if and how to recommend use in a broader group. The MAH agreed to this change.

There were only few dropouts, with 98.3% of participants completing the study in both intervention groups. Most discontinuations were due to withdrawal by parents or guardians, indicating good acceptability of the interventions. Important protocol deviations were observed in 13.8% of the participants, mainly related to participants being pneumococcal vaccine naïve or receiving a prohibited prior pneumococcal vaccine regimen. As these deviations were balanced between groups and concerning participants were excluded from the per-protocol population, their impact on the robustness of the study data is considered minimal.

The primary analysis was performed in the per-protocol population, with sensitivity analysis in the full analysis set, which is appropriate. A constrained longitudinal data analysis model was used so that participants with a missing baseline or follow-up serology result could be included in the analysis. In this model, missingness is assumed to be at random, which may not be a plausible assumption for all missing data. However, missingness was relatively limited and is not expected to have a major impact on conclusions.

Efficacy data and additional analyses

The participant flow was satisfactory. 882 participants were randomised, of which 876 received study intervention. The percentage of participants who discontinued the study was comparable between the study arms. Both study arms were well-balanced in terms of sex, age, race, ethnicity, country, prior pneumococcal vaccination (primary as well as PPSV23 "boosting") and number of increased risk-conditions for pneumococcal disease. The overall percentage of randomised subjects included in the per protocol population for the OPA analyses for at least 1 timepoint was 91.0% (803/882), and for both Day 1 and Day 30 timepoints 81.0% (714/882). The overall percentage of randomised subjects included in the per protocol population for the IgG GMC analyses for at least 1 timepoint was 86.3% (761/882). A total of 66.8% of subjects (589/882) were included in the IgG GMC analyses for both Day 1 and Day 30 timepoints. The reasons for exclusion from the analyses was generally comparable between the two study arms.

V116 met the predefined criterion for noninferiority compared to PPSV23 for each of the 12 shared serotypes at 30 days postvaccination. Generally, V116 outperformed PPSV23 for almost all shared serotypes. This was to be expected, as glycoconjugate vaccines are generally known to elicit a stronger immune response as compared to purely polysaccharide vaccines. V116 also met the predefined criterion for superiority compared to PPSV23 for each of the 9 serotypes unique to V116 at 30 days postvaccination. The GMT ratio (V116/PPSV23) for most of the unique serotypes were considerable, for some in the ranges of 15-20-fold.

The IgG GMCs for all serotypes at 30 days postvaccination were consistent with the results of the primary analysis of OPA GMTs, although the differences were smaller between the investigational vaccine and the comparator as compared to the OPA analysis. This suggests that PPSV23 elicits a larger ratio of non-functional binding antibodies as compared to V116.

For both OPA and IgG responses, serotype-specific GMFRs from baseline to 30 days postvaccination were generally higher in the V116 group compared with the PPSV23 group for almost all serotypes (3 and 19A being the exceptions again.

For both OPA and IgG responses, the proportions of participants with a ≥4-fold rise in antibody responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 shared serotypes and higher in the V116 group compared with the PPSV23 group for the 9 serotypes unique to V116.

All immunogenicity analyses in the pivotal study were conducted 30 days post-vaccination and the persistence of the immune response beyond that is currently unknown. Potentially, the at risk-children could need additional boosters. The CHMP asked if the MAH plans to investigate the duration of the immunity further and if there is any data regarding that forthcoming. The MAH responded that long-term immunogenicity is only planned to be investigated in the adult cohorts and these data have been submitted as a PAM for the MAA of Capvaxive. As no other data is forthcoming, the issue was considered resolved.

Considering the highly heterogenous background of the study participants with regard to age, prior pneumococcal vaccination and PCV regimen, it is important to as far as possible exclude that a possible inferior immunogenicity in a subgroup is being masked by the response of the total group. Therefore, some key data has been included in this report from the subgroup analyses. As can be seen in the Figure 6 and Figure 9, the responses were similar with regards to age and sex. With regard to OPA GMT-ratios, some differences could be seen between cohorts having received PCV7, PCV10 and PCV13 alone prior, with the PCV7-group noticeably showing the smallest ratios (Figure 10 and Figure 11). It is however noted that the group is small (n = 20-30, depending on the serotype). When looking at the data, it is also seen that smaller ratios are partially caused by PPSV23 having a better effect for some serotypes for those having previously received PCV7 as compared to PCV13. This could, speculative, be due to the children having received PCV7 being generally of older age (since PCV7 is an older vaccine), and thus having been exposed to more pneumococcal infections, causing a heightened natural immunity that is boosted by PPSV23. Importantly, V116 immune responses were comparable to those of PPSV23 in this subgroup. Taken together, these findings do not raise any alarm. Finally, it was seen that prior PCV regimen (2+1 vs 3+1) was not a factor causing considerably changes in the performance of V116 as compared to PPSV23.

The secondary endpoints supported the primary endpoints findings.

It is noted that there are no vaccine efficacy data for V116 in the supplied dossier. The use of immunogenicity data instead of vaccine efficacy entails several uncertainties. The primary evidence for the efficacy of PPSV23 comes from studies conducted in the 1970's in healthy, young adult gold miners in South Africa, a population that is much different from the investigated cohort in V116-013. Therefore, demonstrating non-inferiority by immunobridging V116 to PPSV23 for the 12 shared serotypes only shows the relative performance of the investigational vaccine to PPSV23 with regard to eliciting an immune response, but does not prove any particular clinical efficacy. Moreover, the efficacy against the unique serotypes in V116 is based on statistical superiority against the (presumed) "lack of response" by PPSV23.

The PPSV23 SmPC is not approved as centralised procedure, but in the US Pneumovax package insert it is stated that "In a study using a pneumococcal vaccine containing eight (types 1, 3, 6, 7, 14, 18, 19, and 23) capsular polysaccharides, vaccinated children and young adults aged 2 to 25 years who had sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated". Further: "A retrospective cohort analysis study based on the U.S. Centers for Disease Control and Prevention (CDC) pneumococcal surveillance system, showed 57% (95%CI: 45% to 66%) overall protective effectiveness against invasive infections caused by serotypes included in PNEUMOVAX 23 in persons >6 years of age, 65 to 84% effectiveness among specific patient groups (e.g., persons with diabetes

mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% (95%CI: 57% to 85%) effectiveness in immunocompetent persons aged >65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients".

In the academic literature, effectiveness trials in at risk-children generally support a moderately strong protection by PPSV23 against pneumococcal disease (data not shown). It is also noted that PPSV23 is recommended by many EU national health authorities for at risk-children >2 years of age, that is, the clinical use of the comparator for the intended indication is established, prevalent and have been ongoing for many years. It can be noted by the secondary endpoints in V116-013 that all serotypes contained in V116 were immunogenic, and that V116 was shown in the MAA to be NI to PPSV23 and PCV20 for shared serotypes in adults. Children 2-17 years of age typically have a stronger immune response, especially compared to the elderly. Taken together, it can be reasonably likely be assumed that V116 has a clinical relevance in the protection against invasive pneumococcal diseases and pneumococcal pneumonia in the investigated group, but the exact clinical efficacy remains unknown.

Hypo responsiveness is a well-recognised phenomenon associated with conjugate vaccines administered following prior vaccination with polysaccharide vaccines, such as PPSV23, and has been documented in previous studies (e.g. for PCV20 [EMA/12384/2022, p111]). Although this effect could not be investigated in the current study, as very few participants received prior polysaccharide vaccination (>5 years ago) and recent polysaccharide vaccination was an exclusion criterion, the potential for reduced immune responses upon sequential administration should be acknowledged in clinical practice for V116. In line with existing product information for PCV20, a statement regarding prior polysaccharide vaccination in Section 4.2 of the SmPC of V116 was included.

In summary, it can be concluded that V116 generally elicits a stronger immune response to the serotypes it contains compared to PPSV23. Most likely, V116 would be valuable alternative to PPSV23 for "boosting" the paediatric increased-risk population who has received primary pneumococcal vaccination.

2.4.3. Conclusions on the clinical efficacy

V116 met the predefined primary endpoint criteria for non-inferiority and superiority for shared and unique serotypes compared to PPSV23, respectively. It can be concluded that V116 generally elicits a stronger immune response to the serotypes it contains compared to PPSV23 and could therefore be valuable alternative to PPSV23 for "boosting" the paediatric increased-risk population who has received primary pneumococcal vaccination. However, it is important to note that immunogenicity and clinical efficacy are not identical. Especially regarding the unique serotypes in V116, even if statistical superiority has been established vis-à-vis the comparator, it is not possible to infer the exact clinical outcome from the observed immune response.

2.5. Clinical safety

Introduction

For the existing indication the safety for Capvaxive was assessed in 6 Phase 3 studies clinical, conducted across the Americas, Europe, Asia Pacific and Africa which included 4 914 individuals ≥ 18 years of age, with or without stable underlying medical conditions. Participants enrolled in the Phase 3 studies included adults across different age groups; approximately 32% were 18 to 49 years of age,

32% were 50 to 64 years of age, 29% were 65 to 74 years of age, and 8% were 75 years of age and older. Of those vaccinated, 14% had received other prior pneumococcal vaccines, 33% had risk factors for pneumococcal disease and approximately 4% were adults living with HIV, which is associated with high risk of pneumococcal disease.

The most frequently reported adverse reactions following vaccination with Capvaxive in individuals 18 years of age and older were solicited. Overall, the most frequently reported adverse reactions were injection-site pain (52.9%), fatigue (25.3%), headache (17.1%), and myalgia (10.4%). The majority of local and systemic adverse reactions for individuals who received Capvaxive were mild or moderate (based on intensity or size) and of short duration; severe reactions occurred in ≤ 1.0% of adults.

The safety profile in this study of V116 is based on the results of V116-013, a Phase 3 study in children and adolescents aged ≥2 to <18 year who are at an increased risk for pneumococcal disease due to chronic conditions and who have completed a primary pneumococcal vaccination regimen. Randomization was stratified by the number of increased-risk conditions for pneumococcal disease, by prior pneumococcal vaccination, and age (≥2 to <6 years or ≥6 to <18 years).

Safety evaluation

The methods used for safety evaluation in this study (P013V116) were consistent with those used in the Phase 3 clinical program in adults that served as the basis for V116 licensure in this age group. Participants or the participants' legally authorised representative used an to report safety information. Postvaccination safety evaluations included:

• Solicited injection-site events: redness (erythema), swelling, and pain/tenderness (pain); reported Day 1 to Day 5 postvaccination.

• Solicited systemic events: headache, muscle aches all over body (myalgia), tiredness (fatigue), hives or welts (urticaria), irritability, joint pain (arthralgia), drowsiness (somnolence), feeling sick (malaise); reported Day 1 to Day 5 postvaccination.

• Solicited body temperature: reported Day 1 to Day 5 postvaccination Note: A temperature of ≥100.4 ° F (38.0° C) was reported as a solicited systemic event of pyrexia from Day 1 to Day 5 postvaccination.

• Unsolicited events: reported Day 1 to Day 30 postvaccination.

All SAEs were collected from Day 1 through the duration of participation in the study.

Solicited injection-site and systemic AEs were collected 5 days after vaccination. Unsolicited AEs were collected through 30 days postvaccination, and SAEs were collected throughout the entire study duration. It is agreed with the MAH that the methods used for safety evaluation in this study (P013V116) were consistent with those used in the Phase 3 clinical program in adults that served as the basis for V116 licensure in adults.

It is noted that there are some differences in type and number of solicited AEs in the clinical program in adults compared to clinical program in study P013V116. It is agreed that this approach ensures that the studies are tailored to the specific needs and vulnerabilities of the population being investigated.

Safety Analyses

Safety analyses were based on the APaT population, defined as all randomised participants who received 1 dose of study intervention. Participants were included in the intervention group according to the study intervention they actually received.

Patient exposure and disposition

Disposition of all randomised participants are shown in Table 14 below.

Table 14: 2 Disposition of Participants (All Randomised Participants)

	V116		PPSV23		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	531		351		882	
Vaccinated at Visit 1						
V116	528	(99.4)	0	(0.0)	528	(59.9)
PPSV23	0	(0.0)	348	(99.1)	348	(39.5)
Trial Disposition						
Completed	522	(98.3)	345	(98.3)	867	(98.3)
Discontinued	9	(1.7)	6	(1.7)	15	(1.7)
Death	0	(0.0)	2	(0.6)	2	(0.2)
Lost To Follow-Up	2	(0.4)	0	(0.0)	2	(0.2)
Randomized By Mistake Without Study Treatment	1	(0.2)	1	(0.3)	2	(0.2)
Withdrawal By Parent/Guardian	5	(0.9)	3	(0.9)	8	(0.9)
Other	1	(0.2)	0	(0.0)	1	(0.1)

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

Source: [P013V116: adam-adsl; adex]

Safety analyses were based on the APaT population, in total 874 participants, which included 527 participants vaccinated with V116 and 347 participants vaccinated with PPSV23, at visit 1. Participants were included in the intervention group according to the study vaccine actually received.

Most of the participants (867) completed the study. The percentage of participants who discontinued the study was comparable between intervention groups. The most frequent reason for study discontinuation in both groups was withdrawal by parent/guardian by parent/guardian (n=8), randomised by mistake without study treatment (n=2) and lost to follow-up (n=2). For two participants in the PPSV23 group, study participation was discontinued due to death.

Adverse events

The proportions of participants with AEs, including injection-site AEs and systemic AEs, for each study arm (V116 and PPSV23 group) are illustrated in Table 15, below.

Table 15: 3 Analysis of Adverse Event Summary (All Participants as Treated Population)

	V116		PPSV23		Difference in % vs PPSV23
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	527		347		
with one or more adverse events	426	(80.8)	264	(76.1)	4.8 (-0.8, 10.5)
injection-site	382	(72.5)	202	(58.2)	
systemic	313	(59.4)	204	(58.8)	
with no adverse event	101	(19.2)	83	(23.9)	
with vaccine-related[b] adverse events	404	(76.7)	234	(67.4)	9.2 (3.2, 15.4)
injection-site	382	(72.5)	202	(58.2)	
systemic	231	(43.8)	141	(40.6)	
with serious adverse events	29	(5.5)	25	(7.2)	-1.7 (-5.3, 1.5)
with serious vaccine-related adverse events	1	(0.2)	2	(0.6)	-0.4 (-1.9, 0.6)
who died	0	(0.0)	2	(0.6)	-0.6 (-2.1, 0.2)

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine. All injection site adverse events are considered to be vaccine-related.
Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.
CI=confidence interval; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

AEs were reported for the majority of participants in each intervention group (80.8% vs. 76.1%). The proportions of participants with various types of AEs, including systemic AEs, vaccine-related systemic AEs, and SAEs, were generally similar between the two intervention groups. However, the proportions of participants with vaccine-related injection-site AEs were found to be higher in the V116 group, at 72.5%, compared to the PPSV23 group, which had a rate of 58.2% (Table 15) (for more information about injection-site AEs, please see chapter 2.5.1).

SAEs were reported for less than 7.2% in each intervention group. One SAE of syncope in the V116 group and 2 SAEs of anaphylactic reaction in the PPSV23 group were considered vaccine related by the investigator (Table 15) (for more information about the case reported with syncope, please see chapter 2.5.1). There were no deaths in the V116 group and 2 (0.6%) deaths in the PPSV23 group; neither death was considered to be vaccine related. During the procedure the MAH was requested to revise the SmPC to remove syncope from section 4.8 but since Syncope is described as SAE in text in SmPC 4.8 above table, it was agreed to keep Syncope as an AR in table 1, according to the MAH's first proposal.

Most Frequently Reported Adverse Event

The proportions of participants with AEs, by descending frequency in the V116 group (incidence $\geq$ 5% in one or more vaccination groups) are illustrated in Table 16 and in Figure 14, below.

Table 16 Participants With Adverse Events by Descending Frequency in the V116 Group (Incidence ≥ 5% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more adverse events	426	(80.8)	264	(76.1)
with no adverse events	101	(19.2)	83	(23.9)
Injection site pain[a]	357	(67.7)	189	(54.5)
Injection site erythema[a]	130	(24.7)	57	(16.4)
Fatigue[a]	107	(20.3)	73	(21.0)
Injection site swelling[a]	99	(18.8)	63	(18.2)
Headache[a]	94	(17.8)	53	(15.3)
Malaise[a]	70	(13.3)	33	(9.5)
Irritability[a]	61	(11.6)	38	(11.0)
Somnolence[a]	50	(9.5)	32	(9.2)
Myalgia[a]	34	(6.5)	18	(5.2)
Pyrexia[a]	33	(6.3)	25	(7.2)
Nasopharyngitis	27	(5.1)	12	(3.5)
Arthralgia[a]	24	(4.6)	20	(5.8)

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

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.

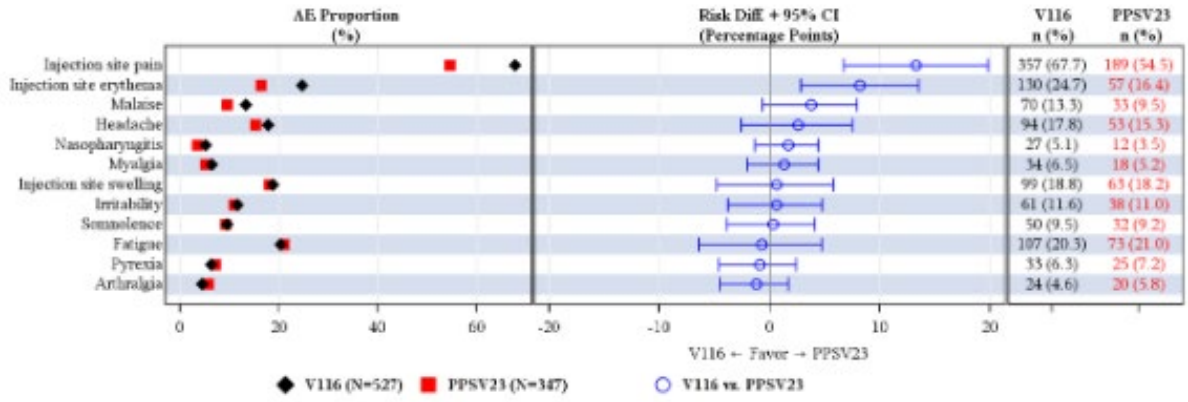
[a] Injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria were solicited from Day 1 through Day 5 postvaccination but may have been reported spontaneously after Day 5. Pyrexia was defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination but may have been reported spontaneously after Day 5 without reported temperature.

MedDRA version 27.1 was used in the reporting of this study.

PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Figure 14 Rainfall Plot of Adverse Events (Incidence ≥ 5% in One or More Vaccination Groups) (All Participants as Treated Population)



Source: [P013V116: adam-adsl; adaece]

The most frequently reported AEs (≥5%) in both intervention groups were the solicited AEs.

The most frequently reported AEs in the V116 group were injection-site pain (67.7%), injection-site erythema (24.7%), fatigue (20.3%), injection-site swelling (18.8%), headache (17.8%), malaise (13.3%), irritability (11.6%), somnolence (9.5%), myalgia (6.5%) and pyrexia (6.3%). Arthralgia was reported in 4.6% in the V116 group (Table 16, Figure 14).

Nasopharyngitis was reported for 5.1% of participants in the V116 group and for 3.5% in of participants in the PPSV23 group (Table 16, Figure 14).

Solicited Adverse Events

The proportions of participants with solicited AEs, for each study arm (V116 and PPSV23 group) are illustrated in Table 17 below.

Table 17: 4 Analysis of Participants With Solicited Adverse Events (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23		Difference in % vs PPSV23
	n	(%)	n	(%)	Estimate (95 % CI)[a]
Participants in population	527		347		
with one or more solicited adverse events	405	(76.9)	233	(67.1)	
with no solicited adverse events	122	(23.1)	114	(32.9)	
Solicited injection site adverse event	**381**	**(72.3)**	**202**	**(58.2)**	
Injection site erythema	128	(24.3)	57	(16.4)	7.9 (2.4, 13.1)
Injection site pain	357	(67.7)	189	(54.5)	13.3 (6.7, 19.8)
Injection site swelling	99	(18.8)	63	(18.2)	0.6 (-4.8, 5.8)
Solicited systemic adverse event	**241**	**(45.7)**	**140**	**(40.3)**	
Arthralgia	23	(4.4)	19	(5.5)	-1.1 (-4.4, 1.8)
Fatigue	106	(20.1)	73	(21.0)	-0.9 (-6.5, 4.5)
Headache	90	(17.1)	53	(15.3)	1.8 (-3.3, 6.7)
Irritability	61	(11.6)	38	(11.0)	0.6 (-3.8, 4.8)
Malaise	70	(13.3)	32	(9.2)	4.1 (-0.3, 8.2)
Myalgia	33	(6.3)	18	(5.2)	1.1 (-2.3, 4.2)
Pyrexia	24	(4.6)	20	(5.8)	-1.2 (-4.5, 1.7)
Somnolence	50	(9.5)	32	(9.2)	0.3 (-3.9, 4.1)
Urticaria	14	(2.7)	6	(1.7)	0.9 (-1.3, 2.9)

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

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

Injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria 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.

MedDRA version 27.1 was used in the reporting of this study.

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

Source: [P013V116: adam-adsl; adaece]

In this study solicited AEs were reported by the majority of participants in each intervention group (76.9% and 67.1%, respectively). The proportion of participants with solicited injection-site AEs was higher in the V116 group compared with the PPSV23 group. This difference is mainly caused by a higher proportion of participants in the V116 group reported with injection-site pain (67.7% vs. 54.5%) and injection-site erythema (24.3% vs. 16.4%). Most participants in both intervention groups had injection-site pain and injection-site erythema with a maximum intensity of mild (Grade 1) or moderate (Grade 2); severe reactions (Grade 3, defined as an event that prevents normal daily activity or size > 10 cm) occurred in ≤ 1.7% and in ≤ 2% of the participants, respectively. No new safety concerns have been identified. Based on data from this study the MAH proposed to include injection-site pain and injection-site erythema to be listed in the SmPC section 4.8., for the age group 2 to less than 18 years of age, categorizing it as a very common, and this is agreed. No new safety concerns have been identified.

The proportions of participants with solicited AE of fatigue were comparable between intervention groups (20.1% vs. 21.0%). The proportions of participants with solicited AE of injection-site swelling were comparable between intervention groups (18.8% vs. 18.2%). The proportions of participants with solicited AE of headache were comparable between intervention groups (17.1% vs. 15.3%). The proportions of participants with malaise were comparable between intervention groups (13.3% vs. 9.2%). The proportions of participants with solicited AE of irritability were comparable between intervention groups (11.6% vs. 11.0%). Most participants in both intervention groups had these solicited AEs with a maximum intensity of mild (Grade 1) or moderate (Grade 2) and of short duration (≤3 days); severe reactions (Grade 3, defined as an event that prevents normal daily activity or size >

10 cm) occurred in ≤ 1.7% and in ≤ 0.6% of the participants, respectively and none experienced a maximum intensity grade of potentially life-threatening (Grade 4). Based on data from this study the MAH proposed to include fatigue, injection-site swelling, headache, malaise and irritability to be listed in the SmPC section 4.8., for the age group 2 to less than 18 years of age, categorizing it as a very common adverse reaction, and this is agreed. No new safety concerns have been identified.

The proportions of participants with solicited AE of arthralgia were comparable between intervention groups (4.4% vs. 5.5%). The proportions of participants with solicited AE of somnolence were comparable between intervention groups (9.5% vs. 9.2%). The proportions of participants with solicited AE of myalgia were comparable between intervention groups (6.3% vs. 5.2%). Most participants had these solicited AEs with a maximum intensity of mild (Grade 1) or moderate (Grade 2) and of short duration (≤3 days). Fewer than 3% of the participants had these AEs with severe intensity (Grade 3), and none experienced a maximum intensity grade of potentially life-threatening (Grade 4). Based on data from this study, the MAH proposed to include arthralgia, somnolence and myalgia to be listed in the SmPC section 4.8., for the age group 2 to less than 18 years of age, categorising it as a common adverse reaction, and this is agreed. No new safety concerns have been identified.

The incidence of pyrexia was similar in both the V116 and PPSV23 groups, with 4.6% and 5.8% of participants experiencing this solicited AE, respectively. Most participants in the V116 group experienced mild (Grade 1) or moderate (Grade 2) pyrexia. Severe (Grade 3) pyrexia, defined as a fever exceeding 40°C, was rare, affecting 0.4% of the participants in the V116 group. Based on the study's findings, the MAH proposed to include pyrexia in the SmPC section 4.8 for the age group 2 to less than 18 years, categorizing it as a common adverse reaction, and this is agreed. No new safety concerns have been identified.

The V116 group had a slightly higher proportion of participants with solicited AE of urticaria (2.7%) compared to the PPSV23 group (1.7%). Most cases (13 out of 14) in the V116 group were considered vaccine-related by the investigator. The MAH proposed to list urticaria as a common adverse reaction in the SmPC section 4.8 for individuals aged 2 to less than 18 years. In line with the request of the CHMP the MAH has conducted a review of unsolicited urticaria reported as unsolicited and solicited. It is agreed with the MAH that urticaria is accurately characterised in the SmPC based on the current available data the in the paediatric population.

Unsolicited Adverse Events

Analysis of participants with solicited AEs, for each study arm are illustrated in Table 18, below.

Table 18 Analysis of Participants With Unsolicited Adverse Events (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23		Difference in % vs PPSV23
	n	(%)	n	(%)	Estimate (95 % CI)[a]
Participants in population	527		347		
with one or more unsolicited adverse events	162	(30.7)	97	(28.0)	2.8 (-3.4, 8.9)
with no unsolicited adverse events	365	(69.3)	250	(72.0)	

[a] Estimated differences and CIs are calculated based on the Miettinen & Nurminen method.
Every participant is counted a single time for each applicable row and column.
Reported unsolicited events include nonserious and serious adverse events within 30 days of vaccination, excluding adverse event terms injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria solicited Day 1 through Day 5 postvaccination and pyrexia defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination.
MedDRA version 27.1 was used in the reporting of this study.
CI=confidence interval; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Analysis of participants with solicited AEs related to study vaccine, for each study arm are illustrated in Table 19, below.

Table 19 Participants With Unsolicited Adverse Events Related to Study Vaccine (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more unsolicited adverse events related to study vaccine	30	(5.7)	18	(5.2)
with no unsolicited adverse events related to study vaccine	497	(94.3)	329	(94.8)
Gastrointestinal disorders	**9**	**(1.7)**	**4**	**(1.2)**
Abdominal discomfort	0	(0.0)	1	(0.3)
Abdominal pain	1	(0.2)	0	(0.0)
Abdominal pain upper	1	(0.2)	1	(0.3)
Diarrhoea	5	(0.9)	1	(0.3)
Nausea	1	(0.2)	1	(0.3)
Vomiting	1	(0.2)	2	(0.6)
General disorders and administration site conditions	**13**	**(2.5)**	**5**	**(1.4)**
Axillary pain	0	(0.0)	1	(0.3)
Chills	1	(0.2)	1	(0.3)
Feeling hot	4	(0.8)	0	(0.0)
Injection site erythema	2	(0.4)	1	(0.3)
Injection site induration	0	(0.0)	1	(0.3)
Injection site oedema	1	(0.2)	0	(0.0)
Injection site papule	1	(0.2)	0	(0.0)
Injection site pruritus	3	(0.6)	1	(0.3)
Injection site swelling	0	(0.0)	1	(0.3)
Malaise	0	(0.0)	1	(0.3)
Pyrexia	1	(0.2)	0	(0.0)
Swelling	1	(0.2)	0	(0.0)
Immune system disorders	**0**	**(0.0)**	**2**	**(0.6)**
Anaphylactic reaction	0	(0.0)	2	(0.6)
Infections and infestations	**2**	**(0.4)**	**1**	**(0.3)**
Nasopharyngitis	0	(0.0)	1	(0.3)
Pharyngitis	1	(0.2)	0	(0.0)
Rhinitis	1	(0.2)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(0.4)**	**2**	**(0.6)**
Decreased appetite	1	(0.2)	0	(0.0)
Hyperglycaemia	1	(0.2)	1	(0.3)
Increased insulin requirement	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**

	V116		PPSV23	
	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**
Synovitis	0	(0.0)	1	(0.3)
Nervous system disorders	**2**	**(0.4)**	**1**	**(0.3)**
Dizziness	1	(0.2)	1	(0.3)
Syncope	1	(0.2)	0	(0.0)
Psychiatric disorders	**1**	**(0.2)**	**0**	**(0.0)**
Depressed mood	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.2)**	**2**	**(0.6)**
Nasal congestion	0	(0.0)	1	(0.3)
Nasal pruritus	1	(0.2)	0	(0.0)
Oropharyngeal pain	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**2**	**(0.4)**	**1**	**(0.3)**
Blister	1	(0.2)	0	(0.0)
Eczema	1	(0.2)	0	(0.0)
Papule	1	(0.2)	0	(0.0)
Urticaria	1	(0.2)	1	(0.3)
Vascular disorders	**1**	**(0.2)**	**0**	**(0.0)**
Neurogenic shock	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Reported unsolicited adverse events include nonserious and serious adverse events within 30 days of vaccination, excluding adverse event terms injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria solicited Day 1 through Day 5 postvaccination and pyrexia defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

The proportions of participants with unsolicited AEs reported from Day 1 through Day 30 postvaccination (excluding solicited AEs reported Day 1 through Day 5) were comparable between intervention groups. Unsolicited AEs were reported for 30.7% of participants in the V116 group and for 28% in of participants in the PPSV23 group.

The unsolicited AE of nasopharyngitis was reported for 5.1% of participants in the V116 group and for 3.5% in of participants in the PPSV23 group. No case of nasopharyngitis in the V116 group was assessed by the investigator as vaccine related (Table 20). Most participants in the V116 group experienced mild (Grade 1) or moderate (Grade 2) nasopharyngitis. Severe nasopharyngitis, was rare, affecting 0.8% of the participants in the V116 group. No new safety concern detected.

Unsolicited AEs (injection-site and systemic) were considered to be vaccine-related for <6% of participants in each intervention group.

Adverse Events Considered Related to Study Intervention

Participants with systemic AEs related to study vaccine are presented in Table 20, below.

Table 20 Participants With Systemic Adverse Events Related to Study Vaccine (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more systemic adverse events related to study vaccine	231	(43.8)	141	(40.6)
with no systemic adverse events related to study vaccine	296	(56.2)	206	(59.4)
Gastrointestinal disorders	**9**	**(1.7)**	**4**	**(1.2)**
Abdominal discomfort	0	(0.0)	1	(0.3)
Abdominal pain	1	(0.2)	0	(0.0)
Abdominal pain upper	1	(0.2)	1	(0.3)
Diarrhoea	5	(0.9)	1	(0.3)
Nausea	1	(0.2)	1	(0.3)
Vomiting	1	(0.2)	2	(0.6)
General disorders and administration site conditions	**148**	**(28.1)**	**93**	**(26.8)**
Axillary pain	0	(0.0)	1	(0.3)
Chills	1	(0.2)	1	(0.3)
Fatigue[a]	98	(18.6)	65	(18.7)
Feeling hot	4	(0.8)	0	(0.0)
Malaise[a]	65	(12.3)	32	(9.2)
Pyrexia[a]	25	(4.7)	20	(5.8)
Swelling	1	(0.2)	0	(0.0)
Immune system disorders	**0**	**(0.0)**	**2**	**(0.6)**
Anaphylactic reaction	0	(0.0)	2	(0.6)
Infections and infestations	**2**	**(0.4)**	**1**	**(0.3)**
Nasopharyngitis	0	(0.0)	1	(0.3)
Pharyngitis	1	(0.2)	0	(0.0)
Rhinitis	1	(0.2)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(0.4)**	**2**	**(0.6)**
Decreased appetite	1	(0.2)	0	(0.0)
Hyperglycaemia	1	(0.2)	1	(0.3)
Increased insulin requirement	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**51**	**(9.7)**	**30**	**(8.6)**
Arthralgia[a]	22	(4.2)	16	(4.6)
Myalgia[a]	33	(6.3)	17	(4.9)
Synovitis	0	(0.0)	1	(0.3)
Nervous system disorders	**112**	**(21.3)**	**71**	**(20.5)**

	V116		PPSV23	
	n	(%)	n	(%)
Nervous system disorders	**112**	**(21.3)**	**71**	**(20.5)**
Dizziness	1	(0.2)	1	(0.3)
Headache[a]	80	(15.2)	50	(14.4)
Somnolence[a]	48	(9.1)	29	(8.4)
Syncope	1	(0.2)	0	(0.0)
Psychiatric disorders	**58**	**(11.0)**	**37**	**(10.7)**
Depressed mood	1	(0.2)	0	(0.0)
Irritability[a]	57	(10.8)	37	(10.7)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.2)**	**2**	**(0.6)**
Nasal congestion	0	(0.0)	1	(0.3)
Nasal pruritus	1	(0.2)	0	(0.0)
Oropharyngeal pain	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**13**	**(2.5)**	**7**	**(2.0)**
Blister	1	(0.2)	0	(0.0)
Eczema	1	(0.2)	0	(0.0)
Papule	1	(0.2)	0	(0.0)
Urticaria[a]	13	(2.5)	7	(2.0)
Vascular disorders	**1**	**(0.2)**	**0**	**(0.0)**
Neurogenic shock	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.
[a] Arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria were solicited from Day 1 through Day 5 postvaccination but may have been reported spontaneously after Day 5. Pyrexia was defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination but may have been reported spontaneously after Day 5 without reported temperature.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

More than 40% of the participants in both intervention groups had one or more systemic AE related to study vaccine (43.8% vs. 40.6%). Overall, the proportion of participants with vaccine-related systemic AEs was comparable between participants in the V116 group compared to participants in the PPSV23 group.

The most frequently reported (≥5%) vaccine-related systemic AEs in both intervention groups were the solicited systemic AEs of fatigue (18.6% vs. 18.7%), headache (15.2% vs. 14.4%), malaise (12.3% vs. 9.2%), irritability (10.8% vs. 10.7%), somnolence (9.1% vs. 8.4%) and myalgia (6.3% vs. 4.9%). Overall, the proportion of participants with vaccine-related AEs was comparable between participants in the V116 group compared to participants in the PPSV23 group. The intensity of these AEs was primarily mild (Grade 1) or moderate (Grade 2) and with short duration (< 3 days). Overall, fewer participants than 3% experienced solicited AEs with a severe intensity (Grade 3). Based on data from this study the MAH proposed to include fatigue, headache, malaise, irritability, somnolence, and myalgia to be listed in the SmPC section 4.8., for the age group 2 to less than 18 years of age, and this is agreed. No new safety concerns have been identified.

Participants with unsolicited AEs related to study vaccine are presented in table below.

Table 21 Participants With Unsolicited Adverse Events Related to Study Vaccine (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more unsolicited adverse events related to study vaccine	30	(5.7)	18	(5.2)
with no unsolicited adverse events related to study vaccine	497	(94.3)	329	(94.8)
Gastrointestinal disorders	**9**	**(1.7)**	**4**	**(1.2)**
Abdominal discomfort	0	(0.0)	1	(0.3)
Abdominal pain	1	(0.2)	0	(0.0)
Abdominal pain upper	1	(0.2)	1	(0.3)
Diarrhoea	5	(0.9)	1	(0.3)
Nausea	1	(0.2)	1	(0.3)
Vomiting	1	(0.2)	2	(0.6)
General disorders and administration site conditions	**13**	**(2.5)**	**5**	**(1.4)**
Axillary pain	0	(0.0)	1	(0.3)
Chills	1	(0.2)	1	(0.3)
Feeling hot	4	(0.8)	0	(0.0)
Injection site erythema	2	(0.4)	1	(0.3)
Injection site induration	0	(0.0)	1	(0.3)
Injection site oedema	1	(0.2)	0	(0.0)
Injection site papule	1	(0.2)	0	(0.0)
Injection site pruritus	3	(0.6)	1	(0.3)
Injection site swelling	0	(0.0)	1	(0.3)
Malaise	0	(0.0)	1	(0.3)
Pyrexia	1	(0.2)	0	(0.0)
Swelling	1	(0.2)	0	(0.0)
Immune system disorders	**0**	**(0.0)**	**2**	**(0.6)**
Anaphylactic reaction	0	(0.0)	2	(0.6)
Infections and infestations	**2**	**(0.4)**	**1**	**(0.3)**
Nasopharyngitis	0	(0.0)	1	(0.3)
Pharyngitis	1	(0.2)	0	(0.0)
Rhinitis	1	(0.2)	0	(0.0)
Metabolism and nutrition disorders	**2**	**(0.4)**	**2**	**(0.6)**
Decreased appetite	1	(0.2)	0	(0.0)
Hyperglycaemia	1	(0.2)	1	(0.3)
Increased insulin requirement	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**

Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**
Synovitis	0	(0.0)	1	(0.3)
Nervous system disorders	**2**	**(0.4)**	**1**	**(0.3)**
Dizziness	1	(0.2)	1	(0.3)
Syncope	1	(0.2)	0	(0.0)
Psychiatric disorders	**1**	**(0.2)**	**0**	**(0.0)**
Depressed mood	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.2)**	**2**	**(0.6)**
Nasal congestion	0	(0.0)	1	(0.3)
Nasal pruritus	1	(0.2)	0	(0.0)
Oropharyngeal pain	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**2**	**(0.4)**	**1**	**(0.3)**
Blister	1	(0.2)	0	(0.0)
Eczema	1	(0.2)	0	(0.0)
Papule	1	(0.2)	0	(0.0)
Urticaria	1	(0.2)	1	(0.3)
Vascular disorders	**1**	**(0.2)**	**0**	**(0.0)**
Neurogenic shock	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Reported unsolicited adverse events include nonserious and serious adverse events within 30 days of vaccination, excluding adverse event terms injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria solicited Day 1 through Day 5 postvaccination and pyrexia defined as maximum temperature ≥ 100.4 °F (38.0 °C) solicited from Day 1 through Day 5 postvaccination.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Few participants were reported with unsolicited vaccine-related systemic AEs in both intervention groups and was comparable between participants in the V116 group compared to participants in the PPSV23 group (5.7% vs. 5.2%). All events by PT were reported in <1% of the participants in both intervention groups.

There was one case with neurogenic shock reported in the V116 group as systemic unsolicited vaccine-related AE. Notably, this case was not listed as a SAE, and no cases of neurogenic shock were reported in the PPSV23 group. The MAH proposed not to list neurogenic shock as an adverse reaction in the SmPC section 4.8 for individuals aged 2 to less than 18 years. In line with the request of the CHMP the MAH conducted a review on the case reported with neurogenic shock. Based on the case narrative there is insufficient information to determine the exact definition or term of this event. Regardless of this it is agreed with the MAH that it does not motivate the classification as an SAE or listing in the SmPC and sufficient to monitor its occurrence through regular follow-up in upcoming PSURs. No new safety concerns were identified.

One case of urticaria in the V116 group was listed in Table 19 as unsolicited vaccine-related AE and 13 cases were reported as vaccine-related systemic AEs.

No case of vaccine-related Anaphylactic reaction was reported in the V116 group. The MAH conducted a review of unsolicited AEs of Dizziness, Nausea, Diarrhoea, Vomiting, Injection-site pruritus and Chills. The CHMP assessment regarding all these unsolicited AEs indicates that there are few cases identified for these terms for the majority of these cases, other underlying factors could explain the respective reaction. Therefore, causality cannot be firmly confirmed. Thus, no new safety concerns are detected

here, and it is sufficient to monitor the occurrence of these reactions through regular follow-up in upcoming PSURs.

Reactogenicity

Most participants in either group had solicited AEs with a maximum intensity of mild (Grade 1) or moderate (Grade 2) and none experienced a maximum intensity grade of potentially life-threatening (Grade 4). In line with the request of the CHMP the MAH provided clarification of solicited SAEs which is acknowledged and agreed upon. Furthermore, the MAH revised the SmPC to present a summary of the grade, intensity, and duration of the majority of local and systemic adverse reactions in participants who received V116 in this study.

Most participants, in both intervention groups, had solicited AEs of short duration (≤3 days) in both intervention groups.

The proportion of participants with injection-site pain and injection-site erythema was higher in the V116 group compared to the PPSV23 group. In both groups most participants had injection-site pain or injection-site erythema with a maximum intensity of mild (Grade 1) or moderate (Grade 2). Severe (Grade 3) injection-site pain or injection site-erythema, was rare, affecting 0.9% and 1.7% of the participants respectively, in the V116 group and none had a maximum intensity grade of potentially life-threatening (Grade 4). One participant in each intervention group had an event (injection-site erythema in the V116 group and injection-site pain in the PPSV23 group) with duration > 10 days. Most participants in both groups had a maximum size of injection-site erythema or injection-site swelling of > 0 to $\leq$ 5 cm, categorised as mild.

Pyrexia was reported at a lower frequency in participants receiving the V116 intervention compared to those in the PPSV23 group. In both intervention groups most participants had pyrexia for a duration of $\leq$ 3 days and with a maximum intensity of mild (Grade 1) or moderate (Grade 2). Severe (Grade 3) pyrexia, defined as a fever exceeding 40°C, was rare, affecting 0.4% of the participants in the V116 group and 0.3% in the PPSV23 group, and none had a maximum intensity grade of potentially life-threatening (Grade 4).

In total in the V116 group 14 cases (2.7%) with urticaria was reported as solicited AEs. All cases in both intervention groups were reported as mild (Grade 1) or moderate (Grade 2) intensity grade.

Subgroup Analysis

Subgroup analysis by age

The safety profile of the vaccine has been evaluated across different age subgroups, including those who received V116 and PPSV23 and is presented in Table 22 and Table 23, below.

Table 22 Adverse Event Summary by Age Group (All Participants as Treated Population)

	2 to <6 Years				6 to <12 Years				12 to 17 Years			
	V116		PPSV23		V116		PPSV23		V116		PPSV23	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	165		107		250		170		111		70	
with one or more adverse events	125	(75.8)	79	(73.8)	219	(87.6)	130	(76.5)	81	(73.0)	55	(78.6)
injection-site	97	(58.8)	53	(49.5)	208	(83.2)	108	(63.5)	77	(69.4)	41	(58.6)
systemic	99	(60.0)	62	(57.9)	149	(59.6)	100	(58.8)	64	(57.7)	42	(60.0)
with no adverse event	40	(24.2)	28	(26.2)	31	(12.4)	40	(23.5)	30	(27.0)	15	(21.4)
with vaccine-related[a] adverse events	108	(65.5)	61	(57.0)	214	(85.6)	121	(71.2)	81	(73.0)	52	(74.3)
injection-site	97	(58.8)	53	(49.5)	208	(83.2)	108	(63.5)	77	(69.4)	41	(58.6)
systemic	65	(39.4)	34	(31.8)	113	(45.2)	72	(42.4)	52	(46.8)	35	(50.0)
with serious adverse events	16	(9.7)	10	(9.3)	8	(3.2)	12	(7.1)	5	(4.5)	3	(4.3)
with serious vaccine-related adverse events	1	(0.6)	0	(0.0)	0	(0.0)	2	(1.2)	0	(0.0)	0	(0.0)
who died	0	(0.0)	2	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the vaccine. All injection site adverse events are considered to be vaccine-related.
Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Table 23 Participants With Solicited Adverse Events by Age Group (Incidence >0% in Any Column) (All Participants as Treated Population)

	2 to <6 Years				6 to <12 Years				12 to 17 Years			
	V116		PPSV23		V116		PPSV23		V116		PPSV23	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	165		107		250		170		111		70	
with one or more solicited adverse events	108	(65.5)	61	(57.0)	216	(86.4)	121	(71.2)	80	(72.1)	51	(72.9)
with no solicited adverse events	57	(34.5)	46	(43.0)	34	(13.6)	49	(28.8)	31	(27.9)	19	(27.1)
Solicited injection site adverse event	**97**	**(58.8)**	**53**	**(49.5)**	**208**	**(83.2)**	**108**	**(63.5)**	**76**	**(68.5)**	**41**	**(58.6)**
Injection site erythema	43	(26.1)	18	(16.8)	63	(25.2)	32	(18.8)	22	(19.8)	7	(10.0)
Injection site pain	88	(53.3)	48	(44.9)	197	(78.8)	103	(60.6)	72	(64.9)	38	(54.3)
Injection site swelling	28	(17.0)	17	(15.9)	57	(22.8)	37	(21.8)	14	(12.6)	9	(12.9)
Solicited systemic adverse event	**65**	**(39.4)**	**34**	**(31.8)**	**123**	**(49.2)**	**70**	**(41.2)**	**52**	**(46.8)**	**36**	**(51.4)**
Arthralgia	3	(1.8)	2	(1.9)	11	(4.4)	10	(5.9)	9	(8.1)	7	(10.0)
Fatigue	20	(12.1)	16	(15.0)	58	(23.2)	38	(22.4)	27	(24.3)	19	(27.1)
Headache	7	(4.2)	4	(3.7)	58	(23.2)	32	(18.8)	24	(21.6)	17	(24.3)
Irritability	32	(19.4)	20	(18.7)	21	(8.4)	14	(8.2)	8	(7.2)	4	(5.7)
Malaise	21	(12.7)	6	(5.6)	39	(15.6)	17	(10.0)	10	(9.0)	9	(12.9)
Myalgia	6	(3.6)	4	(3.7)	19	(7.6)	9	(5.3)	7	(6.3)	5	(7.1)
Pyrexia	12	(7.3)	7	(6.5)	10	(4.0)	9	(5.3)	2	(1.8)	4	(5.7)
Somnolence	15	(9.1)	6	(5.6)	24	(9.6)	14	(8.2)	11	(9.9)	12	(17.1)

	2 to <6 Years				6 to <12 Years				12 to 17 Years			
	V116		PPSV23		V116		PPSV23		V116		PPSV23	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Solicited systemic adverse event	**65**	**(39.4)**	**34**	**(31.8)**	**123**	**(49.2)**	**70**	**(41.2)**	**52**	**(46.8)**	**36**	**(51.4)**
Urticaria	3	(1.8)	0	(0.0)	8	(3.2)	6	(3.5)	3	(2.7)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Injection site erythema, injection site pain, injection site swelling, arthralgia, fatigue, headache, irritability, malaise, myalgia, somnolence, and urticaria 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.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23 = pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

The safety profile of the vaccine was generally consistent across different age subgroups, and this consistency is observed in both the V116 and PPSV23 groups, as detailed in Table 22 and Table 23, with the exception of injection-site pain. All age subgroups that received PPSV23 had lower rates of injection-site pain compared to their counterparts in the V116 group, as presented in Table 23. The proportion of participants experiencing injection-site pain as a solicited AE varied across age subgroups in the V116 group: participants aged 6 to less than 12 years reported the highest rate of injection-site pain at 78.8%. Participants aged 2 to less than 6 years and 12 to 17 years experienced lower rates, at 53.3% and 64.9%, respectively. The overall rate of AE, injection-site pain in children and adolescents (2 to less than 18 years of age) who received V116 was 67.7%. Based on this rate, the MAH suggested classifying injection-site pain as a very common adverse event. This classification is agreed upon to ensure the safety profile of V116 accurately reflects the potential risks associated with injection-site pain in all age-groups. No further specification of injection-site pain is required, as the current classification accurately reflects the potential risks associated with this adverse event across all age groups.

Subgroup analysis by sex, race and ethnicity

Overall, the safety profile within each sex subgroup was generally consistent with the overall study population.

It is noted that the proportion of participants in both intervention groups with 1 or more AEs and vaccine-related AEs was lower in the Black or African American subgroup compared with other race subgroups. In the V116 group, injection-site AEs and solicited injection-site AEs were reported for lower proportions of participants in the American Indian or Alaska Native and Black or African American subgroups compared with participants in the Asian, Multiple, or White subgroups. The observed variations in AE rates across subgroups analysed by sex, race, and ethnicity, did not detect any new safety concerns.

Subgroup Analysis by Number and Type of Increased-risk Conditions

The safety profile of the vaccine was evaluated in participants with specific concurrent increased-risk conditions for pneumococcal disease.

The safety profile in participants with a specific concurrent increased-risk condition for pneumococcal disease (chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only, and/or diabetes mellitus only) was generally consistent with the overall study population.

It is noted that participants with chronic kidney disease had a lower proportion of injection-site AEs and solicited injection-site AEs, compared to participants with chronic heart disease only, chronic liver disease only, chronic lung disease only, and/or diabetes mellitus only in the V116 group.

Overall, no safety concerns were detected in this analysis, indicating that the vaccine's safety profile remains consistent across participants with various concurrent increased-risk conditions for pneumococcal disease and who have completed a primary pneumococcal vaccination regimen.

Subgroup analysis by prior pneumococcal vaccination

A trend was observed towards a lower proportion of participants with one or more solicited AEs, solicited injection-site AEs, solicited systemic AEs and with vaccine related AEs in the V116 group with prior PCV7 vaccination compared to those with prior PCV10 or PCV13 vaccination. However, the group with prior PCV7 vaccination was relatively small, comprising approximately 6% of participants who received prior PCV7 alone. All participants in the prior PCV7 alone group belonged to the older age group (≥6 to <18 years). The time period between the last PCV7 vaccination and V116 vaccination was thereby longer, which could be a contributing factor to the observed difference. While the trend towards lower AE rates in the prior PCV7 group is noteworthy, the small sample size and differences in age and vaccination timing may have contributed to this observation, and therefore, it should be interpreted with caution, and no new safety concern is detected.

Overall, the safety profile for participants by prior pneumococcal vaccination status (prior PCV7 alone, prior PCV10 alone, and prior PCV13 alone) was generally consistent with the overall study population.

The safety profile for participants by prior PCV primary regimen (3+1 regimen, 2+1 regimen, and others) was generally consistent with the overall study population.

2.5.1. Serious adverse event/deaths/other significant events

2.5.1.1. Serious Adverse Events

Participants with Serious Adverse Event (SAE) in V116 and in PPSV23 group are presented in Table 24, below.

Table 24 Participants With Serious Adverse Events (Incidence >0% in One or More Vaccination groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more serious adverse events	29	(5.5)	25	(7.2)
with no serious adverse events	498	(94.5)	322	(92.8)
Cardiac disorders	**2**	**(0.4)**	**1**	**(0.3)**
Cardiac failure	1	(0.2)	0	(0.0)
Cardiogenic shock	2	(0.4)	0	(0.0)
Cardiopulmonary failure	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**1**	**(0.2)**	**2**	**(0.6)**
Constipation	0	(0.0)	1	(0.3)
Cyclic vomiting syndrome	1	(0.2)	0	(0.0)
Inflammatory bowel disease	0	(0.0)	1	(0.3)
Immune system disorders	**0**	**(0.0)**	**2**	**(0.6)**
Anaphylactic reaction	0	(0.0)	2	(0.6)
Infections and infestations	**16**	**(3.0)**	**14**	**(4.0)**
Achromobacter infection	0	(0.0)	1	(0.3)
Bronchitis	1	(0.2)	0	(0.0)
COVID-19	1	(0.2)	0	(0.0)
Cellulitis	1	(0.2)	0	(0.0)
Cystitis viral	0	(0.0)	1	(0.3)
Dengue fever	2	(0.4)	1	(0.3)
Gastroenteritis	0	(0.0)	1	(0.3)
Gastroenteritis rotavirus	1	(0.2)	0	(0.0)
Lower respiratory tract infection	1	(0.2)	0	(0.0)
Medical device site infection	0	(0.0)	1	(0.3)
Metapneumovirus infection	0	(0.0)	1	(0.3)
Otitis media	0	(0.0)	1	(0.3)
Peritonitis	0	(0.0)	1	(0.3)
Pertussis	0	(0.0)	1	(0.3)
Pneumonia	3	(0.6)	1	(0.3)
Pneumonia bacterial	1	(0.2)	0	(0.0)
Pneumonia respiratory syncytial viral	1	(0.2)	0	(0.0)
Pneumonia viral	2	(0.4)	0	(0.0)
Respiratory tract infection bacterial	1	(0.2)	0	(0.0)
Respiratory tract infection viral	1	(0.2)	2	(0.6)
Septic shock	0	(0.0)	1	(0.3)
Tonsillitis	0	(0.0)	1	(0.3)
Urinary tract infection	4	(0.8)	0	(0.0)
Varicella	0	(0.0)	1	(0.3)

	V116		PPSV23	
	n	(%)	n	(%)
Infections and infestations	**16**	**(3.0)**	**14**	**(4.0)**
Viral infection	1	(0.2)	1	(0.3)
Viral pharyngitis	0	(0.0)	1	(0.3)
Injury, poisoning and procedural complications	**2**	**(0.4)**	**1**	**(0.3)**
Abdominal wound dehiscence	1	(0.2)	0	(0.0)
Forearm fracture	1	(0.2)	0	(0.0)
Limb injury	0	(0.0)	1	(0.3)
Metabolism and nutrition disorders	**3**	**(0.6)**	**2**	**(0.6)**
Diabetic ketoacidosis	3	(0.6)	1	(0.3)
Diabetic metabolic decompensation	0	(0.0)	1	(0.3)
Nervous system disorders	**1**	**(0.2)**	**2**	**(0.6)**
Febrile convulsion	0	(0.0)	1	(0.3)
Seizure	0	(0.0)	1	(0.3)
Syncope	1	(0.2)	0	(0.0)
Psychiatric disorders	**1**	**(0.2)**	**0**	**(0.0)**
Suicide attempt	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(1.1)**	**2**	**(0.6)**
Asthma	4	(0.8)	2	(0.6)
Asthmatic crisis	1	(0.2)	0	(0.0)
Haemoptysis	1	(0.2)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**1**	**(0.3)**
Air embolism	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Reported serious adverse events occurred from Day 1 through the duration of participation in the study.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Participants with vaccine-related SAEs in V116 and in PPSV23 group are presented in Table 25 below.

Table 25 Participants With Serious Vaccine-related Adverse Events (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more serious vaccine-related adverse events	1	(0.2)	2	(0.6)
with no serious vaccine-related adverse events	526	(99.8)	345	(99.4)
Immune system disorders	**0**	**(0.0)**	**2**	**(0.6)**
Anaphylactic reaction	0	(0.0)	2	(0.6)
Nervous system disorders	**1**	**(0.2)**	**0**	**(0.0)**
Syncope	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Reported serious vaccine-related adverse events occurred from Day 1 through the duration of participation in the study.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

Participants in the V116 group with Serious Adverse Event (SAE) are listed in table below.

Table 26 Listing of Participants With Serious Adverse Events (All Participants as Treated Population)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	48	48	Haemoptysis	6 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	118	118	Gastroenteritis rotavirus	6 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	37	37	Suicide attempt	0.08 Hours		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	64	64	Dengue fever	1.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	115	115	Cardiogenic shock	23 Hours		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	122	122	Urinary tract infection	2.71 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	129	129	Abdominal wound dehiscence	1.45 Months		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	150	150	Viral infection	6 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	77	77	Pneumonia viral	1.86 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	98	98	Bronchitis	1.43 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	40	40	Urinary tract infection	1.57 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	39	39	Asthmatic crisis	3.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	2	2	Diabetic ketoacidosis	2.57 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	2	2	Pneumonia	2.57 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	5	5	Lower respiratory tract infection	2.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	23	23	Dengue fever	1.71 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	126	126	Pneumonia	2.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	164	164	Respiratory tract infection viral	2.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	12	12	Pneumonia	3.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	23	23	Urinary tract infection	1.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	116	116	Asthma	3.71 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	55	55	Cardiac failure	Continuing		Potentially Life-threatening (Grade 4)	Y	N	NOT RECOVERED/ NOT RESOLVED	1(V116)
TREATMENT	161	161	Cardiogenic shock	2 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	173	173	COVID-19	1.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	170	170	Cellulitis	5 Days		Moderate (Grade 2)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	105	105	Asthma	2.43 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	85	85	Forearm fracture	1.48 Months		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	113	113	Respiratory tract infection bacterial	3.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	95	95	Diabetic ketoacidosis	5 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	1	1	Syncope	4 Days		Moderate (Grade 2)	Y	Y	RECOVERED/ RESOLVED	1(V116)
TREATMENT	152	152	Asthma	5 Days		Severe (Grade 3)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	100	100	Asthma	3 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	45	45	Diabetic ketoacidosis	2.14 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	139	139	Diabetic ketoacidosis	4 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	53	53	Pneumonia respiratory syncytial viral	2.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	125	125	Pneumonia bacterial	1.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	2	2	Cyclic vomiting syndrome	6 Days		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	107	107	Cyclic vomiting syndrome	1.57 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	17	17	Urinary tract infection	1.86 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)
TREATMENT	31	31	Pneumonia viral	1.29 Weeks		Potentially Life-threatening (Grade 4)	Y	N	RECOVERED/ RESOLVED	1(V116)

Particpant with vaccine related Serious Adverse Event is listed below:

Table 27 Listing of Participants With Serious Vaccine-related Adverse Events (All Participants as Treated Population)

Onset Epoch	Rel Day from Start of Trial	Rel Day of Onset Postdose	Adverse Event	Duration	Size	Intensity Grade	Serious	Related	Outcome	Dose Number (Vaccine Given)
TREATMENT	1	1	Syncope	4 Days		Moderate (Grade 2)	Y	Y	RECOVERED/ RESOLVED	1(V116)

Serious Adverse Events of Special Interest

No AEs of special interest were predefined in the protocol for this study.

Deaths

No deaths were reported in the V116 group, and 2 deaths were reported in the PPSV23 group (septic shock and cardiopulmonary failure) as shown in Table 28; none were considered vaccine related.

Table 28 Participants With Adverse Events Resulting in Death (Incidence >0% in One or More Vaccination Groups) (All Participants as Treated Population)

	V116		PPSV23	
	n	(%)	n	(%)
Participants in population	527		347	
with one or more adverse events resulting in death	0	(0.0)	2	(0.6)
with no adverse events resulting in death	527	(100.0)	345	(99.4)
Cardiac disorders	**0**	**(0.0)**	**1**	**(0.3)**
Cardiopulmonary failure	0	(0.0)	1	(0.3)
Infections and infestations	**0**	**(0.0)**	**1**	**(0.3)**
Septic shock	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Reported deaths occurred from Day 1 through the duration of participation in the study.
MedDRA version 27.1 was used in the reporting of this study.
PPSV23=pneumococcal vaccine, polyvalent (23-valent).

Source: [P013V116: adam-adsl; adaece]

No AEs of special interest were predefined in the protocol for this study. No deaths were reported in the V116 group, and 2 deaths were reported in the PPSV23 group (septic shock and cardiopulmonary failure) (Table 28); none were considered vaccine related.

It is agreed that the proportions of participants experiencing SAEs between the two groups, with 5.5% in the V116 group and 7.2% in the PPSV23 group, were comparable as detailed in Table 24.

SAEs for 3 participants were considered to be vaccine-related by the investigator: 1 participant with an SAE of syncope in the V116 group, and 2 participants with an SAE of anaphylactic reaction in the PPSV23 group (Table 25). It is agreed with the MAH that the case of SAE syncope, that has been thoroughly assessed, was related to study vaccination. Based on this case, the MAH suggested that syncope should be listed as an uncommon adverse reaction in section 4.8. In line with the request in of the CHMP the MAH agreed to revise the SmPC to remove syncope from section 4.8 table. However, since Syncope is described as related SAE in text above Tabel 1 in SmPC 4.8, CHMP considered to keep Syncope as an AR in Table 1, according to the MAH's first proposal. Besides this it can be agreed that no other SAEs were related to V116. No new safety concerns were detected.

Based on the narrative information provided by the applicant, the investigator determined that the case with syncope was related to the study.

Discontinuation due to adverse events

This was a single dose study; discontinuation from study intervention due to an AE could not occur.

2.5.2. Discussion on clinical safety

In study V116-013 the safety analysis was based on 874 participants aged 2 to less than 18 years, of whom 527 received a single dose of V116 and all were at an increased risk for pneumococcal disease, with 99.8% having a history of previous vaccination with pneumococcal conjugate vaccine. Most of the participants completed the study. Solicited injection-site and systemic AEs were collected 5 days after

vaccination. Unsolicited AEs were collected through 30 days postvaccination, and SAEs were collected throughout the entire study duration. Most of the participants completed the study, the most common causes of discontinuation were withdrawal by parent/guardian (n=8), randomised by mistake without study treatment n=2) and lost to follow-up (n=2).

The methods used for safety evaluation were consistent with those used in the Phase 3 clinical program that served as the basis for V116 licensure in adults.

Adverse Events

Overall, the proportion of participants with any AEs were comparable between participants in the V116 group (80.8%) compared to participants in the PPSV23 group (76.1%). The proportions of participants with AEs, including systemic AEs, vaccine-related systemic AEs, and SAEs were generally comparable between intervention groups. The proportion of participants with solicited injection-site AEs was higher in the V116 group compared with the PPSV23 group (76.9% and 67.1%, respectively). Which overall does not raise any new safety concern, as also discussed further below.

Most Frequently reported AEs

The most frequently reported solicited AEs following vaccination with V116 were injection-site pain (67.7%), injection-site erythema (24.7%), fatigue (20.1%), injection-site swelling (18.8%), headache (17.1%), malaise (13.3%), irritability (11.6%), somnolence (9.5%), myalgia (6.3%) and pyrexia (4.6%).

Arthralgia was reported in 4.6% in the V116 group and in 5.8% in the PPSV23 group and is, thus, roughly comparable between groups.

Nasopharyngitis was reported an AE for 5.1% of participants in the V116 group and for 3.5% in of participants in the PPSV23 group.

Solicited Adverse Events

The most frequently reported AEs (≥5%) in both intervention groups were the solicited AEs and were reported by the majority of participants in in both the V116 and PPSV23 groups (76.9% and 67.1%, respectively). The majority of local and systemic AEs for individuals who received V116 were mild or moderate (based on intensity or size) and of short duration (≤ 3 days).

The proportion of participants with solicited injection-site AEs was higher in the V116 group compared with the PPSV23 group (72.3% and 58.2%, respectively). This difference is mainly caused by a higher proportion of participants in the V116 group reported with injection-site pain (67.7% vs. 54.5%) and injection-site erythema (24.3% vs. 16.4%). However, in both groups most participants had injection-site pain or injection-site erythema with a maximum intensity of mild or moderate; severe reactions occurred in $\leq$ 1.7% and $\leq$ 2.0% of the participants, respectively. Most participants in both groups had a maximum size of injection-site erythema or injection-site swelling of > 0 to $\leq$ 5 cm, categorised as mild. No new safety concerns have been identified. Based on data from this study the MAH proposed to include injection-site pain and injection-site erythema to be listed in the SmPC section 4.8, as adverse reactions for the age group 2 to less than 18 years of age, categorizing it as a very common, and this is agreed. More participants in the V116 group reported pain at the injection site compared to the participants in the PPSV23 group (67.7% versus 54.5%). This was also observed in the pivotal trials of V116 where more solicited injection site AEs were reported in the V116 group compared to the combined control group (PCV15, PCV20 or PPSV23), but the difference was assessed to be of no clinical importance, which can also be concluded in study V116-013.

The proportions of participants with solicited AEs of fatigue (20.1% vs. 21.0%), injection-site swelling (18.8% vs. 18.2%), headache (17.1% vs. 15.3%), malaise (13.3% vs. 9.2%) and irritability (11.6% vs. 11.0%) were comparable between intervention groups. The proportions of participants with solicited AEs of arthralgia (4.4% vs. 5.5%), somnolence (9.5% vs. 9.2%) and myalgia (6.3% vs. 5.2%) were comparable between intervention groups. Most participants in both intervention groups had these solicited AEs with a maximum intensity of mild (Grade 1) or moderate (Grade 2) and of short duration (≤3 days); severe reactions (Grade 3, defined as an event that prevents normal daily activity or size > 10 cm) occurred in $\leq$ 1.7% and in $\leq$ 0.6% of the participants, respectively and none experienced a maximum intensity grade of potentially life-threatening (Grade 4). No new safety concerns have been identified. Based on data from this study the MAH proposed to include fatigue, injection-site swelling, headache and irritability to be listed and categorised as very common adverse reaction and arthralgia, somnolence and myalgia to be listed and categorised as common adverse reaction in the SmPC section 4.8, for the age group 2 to less than 18 years of age, and this is agreed.

The incidence of pyrexia was similar in both the V116 and PPSV23 groups, with 4.6% and 5.8% of participants experiencing this solicited AE, respectively. Most participants in the V116 group experienced mild or moderate pyrexia. Severe pyrexia, defined as a fever exceeding 40°C, was rare, affecting 0.4% of the participants in the V116 group. No new safety concerns have been identified. Based on the study's findings, the MAH proposed to include pyrexia in the SmPC section 4.8 for the age group 2 to less than 18 years, categorizing it as a common adverse reaction, and this is agreed.

The V116 group had a slightly higher proportion of participants with solicited AE urticaria (2.7%) compared to the PPSV23 group (1.7%). Most cases (13 out of 14) in the V116 group were considered vaccine-related by the investigator. The MAH proposed to list urticaria as a common adverse reaction in the SmPC section 4.8. In line with the request of the CHMP the MAH conducted a review of unsolicited urticaria reported as unsolicited and solicited. It is agreed with the MAH that urticaria is accurately characterised in the SmPC based on the current available data the in the paediatric population.

Unsolicited Adverse Events

Overall, the proportion of participants with unsolicited AEs were comparable between participants in the V116 group (30.7%) compared to participants in the PPSV23 group (28%). Unsolicited AEs (injection-site and systemic) were considered to be vaccine-related for <6% of participants in each intervention group.

Nasopharyngitis was reported as unsolicited events for 5.1% of participants in the V116 group and for 3.5% in of participants in the PPSV23 group. No case of nasopharyngitis in the V116 group was assessed by the investigator as vaccine related. Most participants in the V116 group experienced mild or moderate nasopharyngitis. Severe nasopharyngitis, was rare, affecting 0.8% of the participants in the V116 group.

No case of anaphylactic reaction was reported in the V116 group.

Related Adverse Events

Overall, the proportion of participants with vaccine-related systemic AEs was comparable between participants in the V116 group (43.8%) compared to participants in the PPSV23 group (40.6%). Most

frequently reported (≥5%) vaccine-related systemic AEs in the V116 group were the solicited systemic AEs of fatigue, headache, malaise, irritability, somnolence and myalgia.

Few participants were reported with unsolicited vaccine-related systemic AEs in both intervention groups and was comparable between participants in the V116 group compared to participants in the PPSV23 group (5.7% vs. 5.2%). All these events, reported by PT were reported in < 1% of the participants in both intervention groups. In line with the request of the CHMP, the MAH conducted a review on the case reported with neurogenic shock. Based on the case narrative there is insufficient information to determine the exact definition or term of this event. Regardless of this it is agreed with the MAH that it does not motivate the classification as an SAE or listing in the SmPC and sufficient to monitor its occurrence through regular follow-up in upcoming PSURs. No new safety concerns were identified.

During the procedure, MAH conducted a review of unsolicited AEs of Dizziness, Nausea, Diarrhoea, Vomiting, Injection-site pruritus and Chills. The CHMP assessment regarding all these unsolicited AEs indicates that there are few cases identified for these terms and for the majority of these cases, other underlying factors could explain the respective reaction. Therefore, causality cannot be firmly confirmed. Thus, no new safety concerns are detected here, and it is sufficient to monitor the occurrence of these reactions through regular follow-up in upcoming PSURs.

Otherwise, the data indicates that no new safety concerns were detected based on the unsolicited AEs, including nasopharyngitis, reported in this study.

SAEs for 3 participants were considered to be vaccine-related by the investigator: 1 participant with an SAE of syncope in the V116 group, and 2 participants with an SAE of anaphylactic reaction in the PPSV23 group (see further discussion on syncope, below).

Serious Adverse Events, AEs of special interest and Deaths

No AEs of special interest were predefined in the protocol for this study. No deaths were reported in the V116 group, and 2 deaths were reported in the PPSV23 group (septic shock and cardiopulmonary failure); none were considered vaccine related.

The proportions of participants experiencing SAEs were found to be comparable between the two groups, with 5.5% in the V116 group and 7.2% in the PPSV23 group.

SAEs for 3 participants were considered to be vaccine-related by the investigator: 1 participant with an SAE of syncope in the V116 group, and 2 participants with an SAE of anaphylactic reaction in the PPSV23 group. It is agreed with the MAH that the case of SAE syncope, that has been thoroughly assessed, was related to study vaccination. Based on this case, the MAH suggested that syncope should be listed as an uncommon adverse reaction in section 4.8. In line with the request of the CHMP the MAH agreed to revise the SmPC to remove syncope from section 4.8 table. However, since Syncope is described as related SAE in text above Table 1 in SmPC section 4.8, CHMP reconsidered to retain Syncope as an AR in Table 1, according to the MAH's first proposal. Besides this it can be agreed that no other SAEs were related to V116. No new safety concerns were detected.

Subgroup Analysis

The safety profile of the vaccine was generally consistent across different age subgroups and this consistency is observed in both the V116 and PPSV23 groups, with the exception of injection-site pain. The proportion of participants experiencing injection-site pain as a solicited AE varied across age subgroups in the V116 group and participants aged 6 to less than 12 years reported the highest rate of injection-site pain at 78.8%. Participants aged 2 to less than 6 years and 12 to 17 years experienced

lower rates, at 53.3% and 64.9%, respectively. All age subgroups that received PPSV23 had lower rates of injection-site pain compared to their counterparts in the V116 group. The overall rate of injection-site pain in this study in participants who received V116 was 67.7%. Based on this rate, the MAH suggested classifying injection-site pain as a very common adverse event. This classification is agreed upon to ensure the safety profile of V116 accurately reflects the potential risks associated with injection-site pain in all age-groups. No further specification of injection-site pain is required, as the current classification accurately reflects the potential risks associated with this adverse event across all age groups.

Safety results for each analysed subgroup (sex, race, ethnicity, and number and type of increased-risk conditions) were generally consistent with the overall study population.

In summary no major safety concerns are detected.

2.5.3. Conclusions on clinical safety

The safety analysis aimed to assess the tolerability and safety of the V116 vaccine in children and adolescents aged 2 to less than 18 years, with increased risk conditions for pneumococcal disease and with a previous history of vaccination with pneumococcal conjugate vaccine.

The most frequently reported (≥5%) AEs in both intervention groups were the solicited AEs. Overall, the proportions of participants with AEs, including systemic AEs, vaccine-related systemic AEs, and SAEs were generally comparable between intervention groups. However, the proportion of participants with solicited injection-site AEs, was higher in the V116 group compared with the PPSV23. Most solicited AEs were of short duration and mild or moderate intensity. Injection-site adverse reactions in both groups were predominantly mild or moderate, with most being less than 5 cm in size, indicating that these reactions were transient and did not persist for an extended period. Overall, the safety profile of solicited AEs is considered acceptable, with no new or major safety concerns identified. It is agreed with the MAH that urticaria is accurately characterised in the SmPC based on the current available data the in the paediatric population.

The MAH conducted a review of unsolicited AEs of Dizziness, Nausea, Diarrhoea, Vomiting, Injection-site pruritus and Chills. The CHMP assessment regarding all these unsolicited AES indicates that there are few cases identified for these terms for the majority of these cases, other underlying factors could explain the respective reaction. Therefore, causality cannot be firmly confirmed. Thus, no new safety concerns are detected here, and it is sufficient to monitor the occurrence of these reactions through regular follow-up in upcoming PSURs.

Otherwise, the data indicates that no new safety concerns were detected based on the unsolicited AEs, including nasopharyngitis, reported in this study.

There were no deaths in the V116 group and the proportion of individuals with SAEs was comparable between vaccine groups. One SAE (syncope) was assessed to be related to V116. Based on this case, the MAH suggested that syncope should be listed as an uncommon adverse reaction in section 4.8. In line with the request of the CHMP the MAH agreed to revise the SmPC to remove syncope from section 4.8 table. However, since Syncope is described as related SAE in text above table 1 in SmPC 4.8, CHMP reconsidered to retain Syncope as an AR in table 1, according to the MAH's first proposal.

The safety analysis indicates that the V116 vaccine is well-tolerated in the studied population. A booster vaccination with V116 was not associated with a clinically relevant increased risk of ADRs in children and adolescents ≥2 years to <18 years of age with chronic heart disease, chronic lung

disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease compared to vaccination with PPSV23. The safety profile of V116 in children and adolescents is generally consistent with the known safety profile in adults, no new safety concerns were identified and the reactogenicity are in line with what is expected for a vaccine in this category.

Recommendations for updates to the SmPC are endorsed.

2.5.4. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version (2.0) with this application.

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

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

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

Safety concerns

No new safety concerns are proposed for the paediatric indication.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities are required.

Risk minimisation measures

Not applicable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes to the package leaflet are limited to the additions related to the paediatric indication with no new key safety messages or other information that would warrant a user consultation but rather concerns inclusion of information very similar to that already given for the adult population.

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 children currently includes routine childhood vaccination with PCVs and with the addition of pneumococcal polysaccharide vaccine (PPSV) for those at increased risk of pneumococcal disease. 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.

Unmet medical need

V116 is intended to complement the existing paediatric vaccination regimen for children and adolescents with chronic medical conditions who are at increased risk for pneumococcal disease and is not intended to serve as a primary paediatric regimen. V116 has the potential to broaden protection against pneumococcal disease, addressing the unmet medical need in children and adolescents with chronic medical conditions that confer an increased risk of pneumococcal disease. This broad serotype coverage aims to address the residual burden of pneumococcal disease. As a conjugate vaccine, V116 is expected to provide improved immune and memory responses, longer lasting protection, and better immunogenicity in children compared to polysaccharide vaccines that are currently used to confer broader coverage for at risk children and adolescents.

3.1.3. Main clinical studies

V116-013 was a randomised, double-blind, active comparator-controlled, parallel-group, multisite phase 3 study to investigate the safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years who have completed a primary pneumococcal vaccination regimen and who are at increased risk for pneumococcal disease.

Enrolled participants (*n*=882) were randomised in a 3:2 ratio to receive a single dose of V116 or PPSV23 on Day 1.

Randomization was stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions), by prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and 1 prior PPSV23 dose, prior PCV10 alone, prior PCV10 and 1 prior PPSV23 dose, prior PCV13 alone, or prior PCV13 and 1 prior PPSV23 dose), and age (≥2 to <6 years or ≥6 to <18 years).

3.1.4. Favourable effects

Immunogenicity. Functional antibodies as measured by OPA can be regarded a proxy for clinical efficacy. V116 was compared in the pivotal trial with the licensed pneumococcal polysaccharide vaccine PPSV23. OPA GMTs increased post-vaccination for all serotypes in V116 in study participants.

V116 met the predefined criterion for noninferiority compared to PPSV23 for each of the 12 shared serotypes at 30 days postvaccination. Generally, V116 outperformed PPSV23 for almost all shared serotypes (3 and 19A being the exceptions). V116 also met the predefined criterion for superiority compared to PPSV23 for each of the 9 serotypes unique to V116 at 30 days postvaccination.

The primary immunogenicity endpoints were supported by the secondary analyses.

Children at increased risk for pneumococcal disease. Currently, after receiving routine childhood primary vaccination against pneumococcus, most EU countries offer PPSV23 to children at increased risk for pneumococcal disease to 1) boost their immunity 2) confer a broader coverage of serotypes as compared to those included in the PCVs. It is well-established that glycoconjugate vaccines such as V116 outperform polysaccharide vaccines with regard to the robustness and duration of immunity. V116 could therefore, with its different constitution of pneumococcal serotypes compared to PCVs that currently are indicated for primary vaccination in children, provide a viable alternative to PPSV23 to boost at risk-children.

3.2. Uncertainties and limitations about favourable effects

Immunogenicity. There are no vaccine efficacy data reported for V116 in the supplied dossier. 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 use of immunogenicity data instead of vaccine efficacy entails several uncertainties. The primary evidence for the efficacy of PPSV23 comes from studies conducted in the 1970's in healthy, young adult gold miners in South Africa, a population that is much different from the investigated cohort in V116-013. Therefore, demonstrating NI by immunobridging V116 to PPSV23 for the 12 shared

serotypes only shows the relative performance of the investigational vaccine to PPSV23 with regard to eliciting an immune response, but does not prove any particular clinical efficacy. Moreover, the efficacy against the unique serotypes in V116 is based on statistical superiority against the (presumed) "lack of response" by PPSV23.

The PPSV23 is not authorised by centralised procedure, but in the in the US Pneumovax package insert it is stated that "In a study using a pneumococcal vaccine containing eight (types 1, 3, 6, 7, 14, 18, 19, and 23) capsular polysaccharides, vaccinated children and young adults aged 2 to 25 years who had sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated". Further: "A retrospective cohort analysis study based on the U.S. Centers for Disease Control and Prevention (CDC) pneumococcal surveillance system, showed 57% (95%CI: 45% to 66%) overall protective effectiveness against invasive infections caused by serotypes included in PNEUMOVAX 23 in persons >6 years of age, 65 to 84% effectiveness among specific patient groups (e.g., persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% (95%CI: 57% to 85%) effectiveness in immunocompetent persons aged >65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients".

In the academic literature, effectiveness trials in at risk-children generally support a moderately strong protection by PPSV23 against pneumococcal disease (data not shown). It is also noted that PPSV23 is recommended by many EU national health authorities for at risk-children >2 years of age, that is, the clinical use of the comparator for the intended indication is established, prevalent and have been ongoing for many years. It can be noted by the secondary endpoints in V116-013 that all serotypes contained in V116 were immunogenic, and that V116 was shown in the MAA to be NI to PPSV23 and PCV20 for shared serotypes in adults. Children 2-17 years of age typically have a stronger immune response, especially compared to the elderly. Taken together, it can be reasonably likely assumed that V116 has a clinical relevance in the protection against invasive pneumococcal diseases and pneumococcal pneumonia in the investigated group, but the exact clinical efficacy remains unknown.

Persistence of immune response. All immunogenicity analyses in the pivotal study were conducted 30 days post-vaccination and the persistence of the immune response beyond that is currently unknown. Potentially, the at risk-children could need additional boosters. The CHMP was asked if the MAH planned to investigate the duration of the immunity further and if there is any data regarding that forthcoming. The MAH responded that long-term immunogenicity is only planned to be investigated in the elderly cohorts, and these data have been submitted as a PAM for the MAA of Capvaxive. As no other data is forthcoming, the issue was considered resolved.

Therapeutic indication.

While V116 was only investigated as booster in children and adolescents who have completed a primary pneumococcal vaccination regimen, with the current wording of the therapeutic indication there is a potential for V116 to be perceived as indicated for use also as a primary vaccination regimen in paediatrics. The suitability of a single dose in children who have not previously received a full priming series has not been established. Whilst it may be clear from the information in section 4.2 that V116 is intended for children and adolescents who have previously completed a primary paediatric pneumococcal regimen, ideally this should also be reflected in the indication or otherwise justified. The MAH agreed to include the criteria for primary vaccination in the indication.

Secondly, the CHMP recommended removing the "at increased risk" from the indication. The study population does not fully represent the entire at risk-population (for instance children with (functional)

asplenia, immunocompromising conditions, or following hematopoietic stem cell transplantation) but that the results can be used to show immunogenicity of this vaccine in the extended age group and therefore supports the extension of indication. In the indication wording there is a general statement that the vaccine should be given in accordance with official recommendations – allowing use to be limited to only those who are in need of it as stated in official recommendations. It is acknowledged that the clinical benefit of a "booster" pneumococcal vaccination for healthy children already having received pneumococcal vaccination is less clear compared to children with factors putting them at high risk of severe pneumococcal disease, but this wording allows NITAGs to determine if and how to recommend use in a broader group. The MAH agreed to this change.

3.3. Unfavourable effects

Adverse Events. The most frequently reported AEs in children and adolescents 2 to less than 18 years of age following vaccination with V116 were solicited AEs of injection-site pain (67.7%), injection-site erythema (24.3%), fatigue (20.1%), injection-site swelling (18.8%), headache (17.1%), malaise (13.3%), irritability (11.6%). Moreover, pyrexia was reported for 4.6% of participants.

The majority of participants reported adverse events, from which most were vaccine-related injection site reactions.

Except for a slight overrepresentation of injection-site pain and erythema in the V116 group, the proportions of participants with solicited AEs were comparable between intervention groups.

Most local and systemic adverse reactions were mild or moderate and of short duration (≤ 3 days), with severe reactions occurring in ≤ 5% of participants of participants. The safety profile of solicited AEs is considered acceptable, with no new or major safety concerns identified.

The V116 group had a slightly higher proportion of participants with solicited AE urticaria (2.7%) compared to the PPSV23 group (1.7%). Most cases were considered vaccine-related by the investigator.

SAEs and Deaths. There were no deaths in the V116 group, and the proportion of individuals with SAEs was comparable between vaccine groups. One SAE (syncope) was assessed to be related to V116. Syncope is already included in section 4.4 of the SmPC of V116. Based on this case, the MAH suggested that syncope should be listed as an uncommon adverse reaction in section 4.8. In line with the request of the CHMP the MAH agreed to revise the SmPC to remove syncope from section 4.8 table. However, since Syncope is described as related SAE in text above table 1 in SmPC 4.8, we reconsider to remain Syncope as an AR in table 1, according to the MAH's first proposal.

Discontinuations due to AE. Most of the participants (867) completed the study. The percentage of participants who discontinued the study was comparable between intervention groups. The most frequent reason for study discontinuation in both groups was withdrawal by parent/guardian by parent/guardian (n=8), randomised by mistake without study treatment (n=2) and lost to follow-up (n=2). For two participants in the PPSV23 group, study participation was discontinued due to death.

In summary, V116 is well-tolerated in the studied population, children and adolescents aged 2 to less than 18 years, with no major safety concerns detected. The benefit/risk balance of Capvaxive is positive.

The safety profile of V116 in children and adolescents is generally consistent with the known safety profile in adults.

3.4. Uncertainties and limitations about unfavourable effects

Safety database. In study V116-013 the safety analysis was based on 874 participants aged 2 to less than 18 years, of whom 527 received a single dose of V116 and all were at an increased risk for pneumococcal disease, with 99.8% having a history of previous vaccination with pneumococcal conjugate vaccine. Most of the participants completed the study.

The documented safety exposure is considered sufficient for adequate assessment of the safety profile of V116. However, the size of the safety database limits the detection of more rare adverse events (AEs). Information on rare but serious AEs should be systematically collected post-licensure, which was also recommended for the adult population

3.5. Effects Table

Table 29 Effects Table for Capvaxive indicated for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in children and adolescents 2 to less than 18 years of age who are at increased risk for pneumococcal disease (data cut-off: 18-MAR-2025)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	Non-inferiority of 12 shared serotypes	OPA GMT ratios	Single dose 0.5 ml of V116	Single dose 0.5 ml of PPSV23	NI demonstrated according to the prespecified criterion. However, the clinical efficacy of V116 cannot be established in the investigated population via this method.	V116-013
Primary endpoint	Superiority of 9 unique serotypes	OPA GMT ratios	Single dose 0.5 ml of V116	Single dose 0.5 ml of PPSV23	Superiority demonstrated according to the prespecified criterion. However, the clinical efficacy of V116 cannot be established in the investigated population via this method.	V116-013
Unfavourable Effects						
Solicited Injection-site AEs	Pain	%	67.7	54.5	These were the most commonly reported AEs in study V116-013	V116-013
	Erythema	%	24.3	16.4		
	Swelling	%	18.8	18.2		
Solicited Systemic AEs	Fatigue	%	20.1	21.0		
	Headache	%	17.1	15.3		
	Malaise	%	13.3	9.2		
	Irritability	%	11.6	11.0		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Pyrexia	%	4.6	5.8		

Abbreviations: AEs; Adverse Events, OPA GMT; opsonophagocytic assay geometric mean titres.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The application is based on clinical studies comparing the functional antibody responses to V116 with PPSV23, 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). PPSV23 is the vaccine included in the majority of guidelines globally in this paediatric increased-risk population (in addition to primary vaccination) and of the currently authorised pneumococcal vaccines, PPSV23 affords the broadest serotype protection and has the most serotypes in common with V116 (12 serotypes); therefore, it was chosen as the comparator in the clinical study V116-013.

V116 met the predefined criterion for noninferiority compared to PPSV23 for each of the 12 shared serotypes at 30 days postvaccination (the statistical criterion for noninferiority required the lower bound of the 2-sided 95% [CI of the OPA GMT ratio [V116/PPSV23] to be >0.5 for each serotype). Generally, V116 outperformed PPSV23 for almost all shared serotypes (3 and 19A being the exceptions). This was to be expected, as glycoconjugate vaccines are generally known to elicit a stronger immune response as compared to purely polysaccharide vaccines. V116 also met the predefined criterion for superiority compared to PPSV23 for each of the 9 serotypes unique to V116 at 30 days postvaccination (the predefined criterion for superiority to PPSV23 was the lower bound of 95% CI of the OPA GMT ratio [V116/PPSV23] >2.0 for each serotype). The GMT ratio (V116/PPSV23) for most of the unique serotypes were considerable, for some in the ranges of 15-20-fold. The study thus successfully achieved the primary endpoints.

The secondary endpoints supported the primary endpoints findings.

There are no vaccine efficacy data reported for V116 in the supplied dossier. 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 use of immunogenicity data instead of vaccine efficacy entails several uncertainties. The primary evidence for the efficacy of PPSV23 comes from studies conducted in the 1970's in healthy, young adult gold miners in South Africa, a population that is much different from the investigated cohort in V116-013. Therefore, demonstrating NI by immunobridging V116 to PPSV23 for the 12 shared serotypes only shows the relative performance of the investigational vaccine to PPSV23 with regard to eliciting an immune response, but does not prove any particular clinical efficacy. Moreover, the efficacy against the unique serotypes in V116 is based on statistical superiority against the (presumed) "lack of response" by PPSV23.

The PPSV23 is not approved by the centralised procedure, but in the American Pneumovax PI, it is stated that "In a study using a pneumococcal vaccine containing eight (types 1, 3, 6, 7, 14, 18, 19, and 23) capsular polysaccharides, vaccinated children and young adults aged 2 to 25 years who had

sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated". Further: "A retrospective cohort analysis study based on the U.S. Centers for Disease Control and Prevention (CDC) pneumococcal surveillance system, showed 57% (95%CI: 45% to 66%) overall protective effectiveness against invasive infections caused by serotypes included in PNEUMOVAX 23 in persons >6 years of age, 65 to 84% effectiveness among specific patient groups (e.g., persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% (95%CI: 57% to 85%) effectiveness in immunocompetent persons aged >65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients".

In the academic literature, effectiveness trials in at risk-children generally support a moderately strong protection by PPSV23 against pneumococcal disease (data not shown). It is also noted that PPSV23 is recommended by many EU national health authorities for at risk-children >2 years of age, that is, the clinical use of the comparator for the intended indication is established, prevalent and have been ongoing for many years. It can be noted by the secondary endpoints in V116-013 that all serotypes contained in V116 were immunogenic, and that V116 was shown in the MAA to be NI to PPSV23 and PCV20 for shared serotypes in adults. Children 2-17 years of age typically have a stronger immune response, especially compared to the elderly. Taken together, it can be reasonably likely be assumed that V116 has a clinical relevance in the protection against invasive pneumococcal diseases and pneumococcal pneumonia in the investigated group, but the exact clinical efficacy remains unknown. In summary, it can be concluded that V116 generally elicits a stronger immune response to the serotypes it contains compared to PPSV23. Most likely, V116 would be valuable alternative to PPSV23 for "boosting" the paediatric increased-risk population who has received primary pneumococcal vaccination.

The safety analysis indicates that the V116 vaccine is well-tolerated in the studied population. The safety profile of V116 in children and adolescents is generally consistent with the known safety profile in adults. No new safety concerns were identified and the reactogenicity are in line with what is expected for a vaccine in this category.

Information on safety and efficacy of V116 in children "at increased risk" for pneumococcal disease according to (inter)national guidelines (e.g. those with (functional) asplenia, immunocompromising conditions, or following hematopoietic stem cell transplantation) is currently lacking. These children are at risk of developing pneumococcal disease and are therefore likely to be vaccinated. The dossier submitted only included children with chronic conditions that do not directly affect the immune system (chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and chronic kidney disease).

3.6.2. Balance of benefits and risks

V116 elicits a robust immune response against all 21 serotypes contained withing the vaccine as measured by the rise in functional antibodies using OPA. Although it is not possible to assess the clinical effect size, the provided data together with prior knowledge in the field renders it reasonable to conclude that V116 could provide protection against pneumococcal disease in the investigated population. The safety profile is acceptable. Therefore, it is considered a relevant vaccine for the investigated population for the elicitation of an immune response against a broader spectrum of serotypes compared to the vaccines used for routine childhood vaccination and could provide a valuable option to the current PPSV23 treatment.

The MAH was asked to either update the indication to reflect CHMP's concerns or justify the current wording with regard to the lack of inclusion of primary vaccination-criterion and the "at increased risk"-phrasing. The MAH agreed to change the indication as indicated by the CHMP.

In conclusion, the B/R of V116 is considered to be positive.

3.6.3. Additional considerations on the benefit-risk balance

3.7. Conclusions

The overall benefit/risk balance of Capvaxive is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change<s>:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include active immunisation of children and adolescents 2 to less than 18 years of age for CAPVAXIVE, based on final results from study V116-013 (P013V116); this is a phase 3, randomised, double-blind study to evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents with increased risk of pneumococcal disease; As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000221419 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.