25 January 2024
EMA/66027/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prevenar 20

Invented name: Prevenar 20 (*)

(*previously known as Apexxnar)

International non-proprietary name: pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)

Procedure No. EMEA/H/C/005451/II/0012

Note

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

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Table of contents

List of abbreviations

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine (Prevenar, Prevenar7)
13vPnC	13-valent pneumococcal conjugate vaccine (Prevenar13)
20vPnC	20vPnC 20-valent pneumococcal conjugate vaccine (Prevenar 20)
ADR	adverse drug reaction
AE	adverse event
AOM	acute otitis media
CAP	community-acquired pneumonia
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
(e)CRF	(electronic) case report form
CRM197	cross-reactive material 197 (nontoxic variant of diphtheria toxin)
CRP	c-reactive protein
CSR	clinical study report
DTPa	diphtheria, tetanus, and pertussis (acellular) vaccine
ECDC	European Centre for Disease Prevention and Control
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FHA	filamentous hemagglutinin
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titre
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hib	Haemophilus influenzae type b

HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella vaccine
NDCMC	newly diagnosed chronic medical condition
NI	non-inferiority
OPA	opsonophagocytic activity
PIP	Paediatric Investigational Plan
PPSV23	23-valent pneumococcal polysaccharide vaccine
PRN	Pertactin
PT	pertussis toxin
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 15 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include infants, children and adolescents from 6 weeks to less than 18 years of age for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae*, based on final results from studies B7471003, B7471011, B7471012, B7471013 and B7471014. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0159/2020 (initial PIP), P/0380/2021 (first PIP modification) and P/0239/2022 (second PIP modification) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0239/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

Similarity

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

Derogation(s) of market exclusivity

Not applicable.

Scientific advice

The MAH did seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Philadelphy Co-Rapporteur: Jean-Michel Race

Timetable	Actual dates
Submission date	15 November 2022
Start of procedure:	31 December 2022
Rapporteur's preliminary assessment report circulated on:	27 February 2023
PRAC Rapporteur Assessment Report circulated on:	03 March 2023
Co-Rapporteur critique circulated on :	09 March 2023
Updated PRAC Rapporteur Assessment Report circulated on:	09 March 2023 and 28 March 2023
Updated Joint assessment report circulated on:	23 March 2023
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 03 2023
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 June 2023
PRAC preliminary assessment report on the MAH's responses circulated on:	23 June 2023
Updated Rapporteur's assessment report on the MAH's responses circulated on:	14 July 2023
Clarification meeting took place on:	12 July 2023
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	20 July 2023
Rapporteur Joint assessment report circulated on:	20 September 2023
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	12 October 2023
SAG experts meeting to address questions raised by the CHMP (Annex 6)	12 October 2023
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30 November 2023
Updated Rapporteur's assessment report on the MAH's responses circulated on:	07 December 2023
4th Request for supplementary information and extension of timetable adopted by the CHMP on:	14 December 2023

Timetable	Actual dates
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 January 2024
Rapporteur's updated assessment report on the MAH's responses circulated on:	18 January 2024 and 25 January 2024
An Oral explanation took place on:	22 January 2024
CHMP opinion:	25 January 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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

State the claimed therapeutic indication

The MAH applied for an extension of indication for Prevenar 20 (20vPnC). The indication applied for is "active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age."

Epidemiology

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

Invasive Pneumococcal Disease

A global meta-analysis of surveillance data from 42 sites with mature 13vPnC paediatric programs estimated that the 7 additional 20vPnC serotypes account for ~36% of IPD cases in children <5 years of age. Eight serotypes accounted for ~52% of IPD in 13vPnC-using sites, including serotypes

15B/C (9.5%), 12F (5.8%), 10A (5.5%), 22F (5.3%), and 33F (4.3%). In Europe, an estimated 35% and 33% of IPD in 2019 are due to the 7 additional 20vPnC serotypes among children <1 and 1 through 4 years of age, respectively, based on IPD surveillance from 26 European countries. The most common 20vPnC serotypes were 8 and 10A among children <1 year of age and 10A and 15B/C among children 1 to 4 years of age in 2019. In 2020 during the COVID-19 pandemic, a substantial decline in the number of IPD cases was observed but IPD rates have rebounded to at or above pre-COVID levels.

Pneumonia

A substantial burden of bacteremic pneumonia including para-pneumonic effusions and empyemas are caused by the 20vPnC serotypes. While the serotype distribution of non-bacteremic pneumonia currently cannot be determined due to the lack of sensitive and specific diagnostic tests, evidence of the substantial proportion of bacteremic pneumonia due to the 20vPnC serotypes and the impact of pneumococcal conjugate vaccines on all-cause pneumonia suggest 20vPnC will likely help protect against childhood pneumonia.

Acute Otitis Media

AOM is a common infection in young children worldwide — one of the most common reasons for clinic visits and antimicrobial prescriptions in developed countries. The majority of AOM is due to bacteria, and among bacterial OM globally, *S pneumoniae* is one of the most common causes, causing 24% and ~26% of cases as reported from studies in the USA and Israel, respectively, during the 13vPnC period. Studies in France, Germany, Israel, and USA during the 13vPnC period found that 12% to 31% of acute or complicated pneumococcal OM cases were caused by the 7 additional 20vPnC serotypes not covered by 13vPnC (Ben-Shimol, Pichichero, JMI, and Kaplan datasets on file).

Overall

A modelling analysis of 9 European countries (Austria, Finland, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom) estimated that 1082 IPD cases, 65,124 pneumonia cases, 780,236 AOM cases per year in children <5 years of age are caused by 20vPnC serotypes, representing an annual direct healthcare cost of approximately €166 million per year.

The 7 additional serotypes were not only selected based on their prevalence in IPD and mucosal disease around the world, but also on characteristics that make them medically important, including antibiotic resistance (10A, 11A, 15B and the closely related 15C, 22F, and 33F), association with outbreaks (8, 12F), and a tendency to greater disease severity such as an association with meningitis or higher case fatality rates (10A, 11A, 12F, 15B/C, 22F, 33F).

Aetiology and pathogenesis

S. pneumoniae are gram-positive encapsulated diplococci and a significant cause of disease associated with mortality and morbidity in children. The capsular polysaccharides of *S. pneumoniae* play important roles in virulence and immune evasion mechanisms and are used to classify pneumococcal serotypes. Currently, more than 100 different serotypes have been identified, which vary both by the chemical structure of their seroreactive capsular polysaccharides and in their ability to cause disease, with the majority of invasive disease caused by a relatively limited number of serotypes.

In a human host, *S pneumoniae* colonizes the nasopharynx and can present with a variety of clinical manifestations. The clinical forms vary in prevalence, severity, and associated sequelae and can be grouped into 2 broad classifications:

- invasive disease, such as meningitis, bacteremic pneumonia, or primary bacteremia, and

- non-invasive (or mucosal) disease, which includes non-bacteremic pneumonia, sinusitis, and AOM.

Clinical presentation, diagnosis

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

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

Management

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data. Most cases with clinical symptoms consistent with IPD require initiation of empiric treatment before bacterial culture results are known. Initial treatment generally includes broad-spectrum antibiotics that have efficacy against *S. pneumoniae* as well as other likely pathogens. The increase in pneumococcal resistance to penicillin and other commonly used antimicrobial agents complicates treatment decisions and may lead to treatment failures with subsequent increased morbidity and healthcare costs.

Prevention of PD in children includes universal routine childhood vaccination with PCVs as well as prophylactic use of antibiotics and pneumococcal polysaccharide vaccine (PPV) in special populations (e.g., children with functional or anatomic asplenia). Pneumococcal vaccines have shown efficacy and effectiveness against invasive and non-invasive pneumococcal disease caused by the serotypes contained in those vaccines in both children and adults.

Despite reductions in disease due to 7vPnC and 13vPnC, a significant burden of paediatric pneumococcal disease remains, with a substantial proportion caused by the 20vPnC serotypes – mainly the 7 additional 20vPnC serotypes. By 2015, although paediatric pneumococcal deaths had declined by an estimated 51% since 2000, *S pneumoniae* still accounted for 3.7 million cases of severe pneumococcal disease and 294,000 deaths in children <5 years of age globally.

2.1.2. About the product

20vPnC is a pneumococcal conjugate vaccine modelled after 7vPnC and 13vPnC and contains 20 serotype-specific capsular polysaccharides of *S pneumoniae*, each covalently linked (ie, conjugated) to CRM197. Pneumococcal conjugate vaccines are known to generate robust, functional, and memory immune responses to the vaccine serotypes, which are not possible with plain polysaccharide vaccines. Due to engagement of T-cells by the capsular polysaccharide conjugate, anti-capsular responses are elicited, with generation of memory B cells, allowing for an anamnestic (booster) response on re-exposure. This results in a durable immunity.

Additionally, pneumococcal conjugate vaccines protect against mucosal disease such as non-bacteremic pneumonia, otitis media, and to prevent carriage acquisition and reduce carriage density leading to indirect protection.

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

Paediatric Clinical Development Program

This application includes data obtained from 5 clinical trials (one Phase 2 and four Phase 3 trials) performed in 5156 infants and 831 children ≥15 months to <18 years of age. The pivotal immunogenicity data are from B7471012, conducted in infants vaccinated on a 3-dose (2 infant doses and a toddler dose) schedule in Europe. This trial incorporated vaccination windows that span schedules of vaccine administration at 2, 4, and 11 months and at 3, 5, and 12 months.

Data from infants vaccinated on a 4-dose (3 infant doses and a toddler dose) schedule are also provided from safety and immunogenicity Phase 2 trial B7471003, Phase 3 trial B7471011(pivotal study for 4-dose schedule), and Phase 3 safety trial B7471013. B7471013 includes safety data in a subgroup of preterm infants born at ≥34 to <37 weeks gestational age. B7471014 provides safety and immunogenicity data in children ≥15 months to <5 years of age with at least 3 prior doses of 13vPnC and children ≥5 to <18 years of age, who all received a single dose of 20vPnC.

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

EMA/CHMP/SAWP/81062/2020 (Feb 2020)

The Scientific Advice pertained to the following non-clinical and clinical aspects:

- The overall clinical development plan for 20vPnC, and agreement that nonclinical and clinical data generated to date support initiation of the Phase 3 clinical development program in infants, children, and adolescents up to 17 years of age
- The proposed Phase 3 clinical development program to support the proposed indication, age range, and label wording, including proposed licensure criteria, study designs, endpoints, and safety database
- The validated Luminex-based assay platform to measure serotype-specific IgG antibodies in serum and the proposed IgG antibody threshold values

Follow-up SA EMA/CHMP/SAWP/583803/2020 (Nov 2020)

The Scientific Advice pertained to the following clinical aspects:

- the proposed endpoints for study B7471012 (2+1 vaccination schedule) and handling of failure to meet non-inferiority criteria for certain serotypes;
- the proposed design of B7471014 and potential Product Information implications if the study is successful.

The MAH generally followed the CHMP's advice regarding the design of pivotal trials. Specifically, the MAH agreed to use both response rate and IgG GMC as primary endpoints. In addition, the post-Dose-2 primary objectives were included per CHMP scientific advice. Nevertheless, the MAH considers that responses after the toddler dose (Dose 3) are most relevant for clinical protection and carriage reduction. Other aspects that were not followed, including design of the study B7471014 are discussed in the respective parts of the assessment report.

PIP

An additional trial which was agreed in the PIP was ongoing at the time of variation submission: Study B7471027 - Randomised, active-controlled trial to evaluate safety and immunogenicity of 20-valent

pneumococcal polysaccharide conjugate vaccine (20vPnC) compared to 13-valent pneumococcal polysaccharide conjugate vaccine (13vPnC) in healthy infants from 12 months to less than 24 months of age. This trial is supposed to assess whether 1 or 2 doses of 20vPnC to toddlers ≥12 to <24 months of age with 2 prior infant doses of 13vPnC can elicit acceptable responses. The last participant visit in this toddler trial was in June 2023.

2.1.4. General comments on compliance with GCP

The MAH stated that all studies were conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

An overview of the clinical studies included in the present submission is provided in Table 1. No efficacy studies were conducted with 20vPnC.

This application is based on the inference of 20vPnC efficacy for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of non-inferior immune responses to 13vPnC.

The paediatric clinical development program for 20vPnC includes 4 immunogenicity trials– three Phase 3 trials (B7471012, B7471011, and B7471014) and one Phase 2 trial (B7471003):

- B7471012 is a phase 3, randomized, active-controlled trial conducted in infants and toddlers, using a 3-dose schedule (2 infant doses and a toddler dose)
- B7471011 is a phase 3, randomized active-controlled trial conducted in infants and toddlers, using an alternative immunization series consisting of 4 doses (3 infant doses and a toddler dose).
- B7471014 is a phase 3, single-arm, single-dose study conducted in children ⩾15 months to <18 years of age.
- B7471003 is a phase 2, randomized, active-controlled, double-blind trial in infants, using a 4-dose schedule

The program also included a randomized active-controlled Phase 3 safety trial B7471013 conducted in infants in whom vaccine was administered as a 4-dose series.

An additional trial (B7471027) in Europe with a 13vPnC control group to describe immune responses after 1 or 2 doses of 20vPnC in toddlers ⩾12 to <24 months of age with 2 prior infant doses of 13vPnC was completed in June 2023.

The clinical development of 20vPnC for paediatric immunization was modelled upon the experience and clinical data of 13vPnC. The immunogenicity, safety, and post-licensure data on effectiveness with 13vPnC are relevant to 20vPnC since the vaccines are manufactured and formulated similarly and contain

the same 13 polysaccharide conjugates.

13vPnC was registered on the basis of immunological NI compared with 7vPnC for the 4-dose regimen (and descriptive summary for the 3-dose regimen) and used the percentage of participants with predefined (⩾0.35 µg/mL) serotype-specific IgG concentrations and IgG geometric mean concentrations (GMCs) as endpoints. Real-world effectiveness studies and data from surveillance systems around the world following the introduction of 13vPnC have confirmed significant reductions above and beyond those observed from 7vPnC in serotype specific IPD, pneumonia and AOM caused by all of the 7 common serotypes.

GCP

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

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

- Tabular overview of clinical studies

Table 1. Tabular overview of clinical studies in paediatric population

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Participants (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment
Phase 2 trial					
B7471003 (USA)	Phase 2, randomized, active-controlled, double-blind trial in infants Primary (Safety) Objective: To describe safety profile of 20vPnC in healthy infants Secondary (Immunogenicity) describe the immunogenicity of 20vPnC in healthy infants Exploratory Objectives: To further the immunogenicity of 20vPnC in healthy infants To describe the immune responses to concomitantly administered diphtheria and pertussis vaccine antigens	20vPnC Or 13vPnC (control)	20vPnC Randomized: 232 Vaccinated: 231 Completed 1-month visit Dose 4: 193 Completed 6-month follow-telephone contact: 206 13vPnC Randomized: 228 Vaccinated: 227 Completed 1-month visit Dose 4: 188 Completed 6-month follow-telephone contact: 189	20vPnC Sex: 120 M / 112 F Age[a] [mean / median (min, max)]: 64.5/64.0 (44, 95) days Race (W/B/A/O): 161/35/9/27 13vPnC Sex: 113 M / 115 F Age[a] [mean / median (min, max)]: 64.5/64.0 (45, 89) days Race (W/B/A/O): 171/29/5/23	4 doses of 20vPnC or 13vPnC administered at 2, 4, 6, and 12 months of age (Doses 1–4, respectively); with 6 months of safety follow-up after Dose 4 3 doses of Pediarix co-administered with Doses 1-3 of 20vPnC or 13vPnC

Protocol No. (Country)	Study Design and Objectives	Treatment Groups	No. of Participants (by Treatment	Demographics (by Treatment Group)	Duration of Treatment
Phase 3 trials					
B7471012 (Australia, Belgium, Czech Republic, Denmark, Estonia, Finland, Italy, Netherland, Norway, Poland, Slovakia)	Phase 3, randomized, double-blind, active-controlled infants, using a schedule of 2 infant doses and a Primary Objectives: Safety: To describe the safety profile of 20vPnC Pneumococcal Immunogenicity: To demonstrate that the serotype-specific IgG GMCs for 13 serotypes in the 20vPnC group are non-inferior to GMCs for the corresponding serotypes in the 13vPnC at 1 month after Dose 3 To demonstrate that the serotype-specific IgG GMCs for 7 additional serotypes in the 20vPnC group are non- the lowest among the 13 serotypes in the 13vPnC month after Dose 3 To demonstrate that the serotype-specific IgG GMCs for 13 serotypes in the 20vPnC group are non-inferior to the corresponding serotypes in the 13vPnC group at 1 after Dose 2 To demonstrate that the serotype-specific IgG GMCs for 7 additional serotypes in the 20vPnC group are non- the lowest among the 13 serotypes in the 13vPnC month after Dose 2 To demonstrate that the percentages of participants predefined serotype-specific IgG concentrations for the serotypes in the 20vPnC group are non-inferior to those corresponding serotypes in the 13vPnC group at 1 after Dose 2 To demonstrate that the percentages of participants predefined serotype-specific IgG concentrations for the additional serotypes in the 20vPnC group are non- the lowest among the 13 serotypes in the 13vPnC	20vPnC or 13vPnC (control)	20vPnC Randomized: 603 Vaccinated: 601 Completed 1-month visit Dose 3: 583 13vPnC Randomized: 604 Vaccinated: 603 Completed 1-month visit Dose 3: 590	20vPnC Sex: 299 M / 302 Age [mean / median (min, 69.2 / 68.0 (43, days Race (W/B/A/O): 585/0/8/8 13vPnC Sex: 311 M / 292 Age [mean / median (min, 69.7 / 68.0 (43, days Race (W/B/A/O): 592/1/5/5	3 doses of 20vPnC or 13vPnC administered at 2-3, 4-5, and 11-12 months of age (Doses 1-3, respectively); with 1 month safety follow-up after Dose 3 3 doses of Infanrix hexa co-administered with Doses 1-3 of 20vPnC or 13vPnC 1 dose of M-M-R-VAXPRO and Varilrix co-administered with Dose 3 of 20vPnC or 13vPnC

Protocol No. (Country)	Study Design and Objectives	Treatment Groups	No. of Participants (by Treatment	Demographics (by Treatment Group)	Duration of Treatment
	month after Dose 2				
B7471012, continued	Concomitant Immunogenicity: To demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are non-inferior to immune responses induced by concomitant vaccine antigens given with 13vPnC at 1 month after Dose 3 Secondary (Immunogenicity) Objectives: To further describe the immune responses induced by 20vPnC To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC Exploratory (Immunogenicity) Objectives: To further describe the immunogenicity of 20vPnC To further describe the immune responses induced by concomitant vaccine antigens given with 20vPnC or				
B7471011 (USA/PR)	Phase 3, randomized, double-blind, active-controlled infants, using a schedule of 3 infant doses and a Primary Objectives: Safety: To describe the safety profile of 20vPnC Pneumococcal Immunogenicity: To demonstrate percentages of participants with predefined serotype-IgG concentrations for the 13 serotypes in the 20vPnC are non-inferior to the percentages for the serotypes in the 13vPnC group at 1 month after Dose 3 To demonstrate that the percentages of participants predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are non-the lowest percentage among the 13 serotypes in the group at 1 month after Dose 3	20vPnC or 13vPnC (control)	20vPnC Randomized: Vaccinated: 1001 Completed 1-month visit after Dose 4: 851 Completed 6-follow-up contact: 885 13vPnC Randomized: 993 Vaccinated: 990	20vPnC Sex: 518 M / 483 F Age [mean / median (min, max)]: 65.9/64.0 (42, 97) days Race (W/B/A/O): 754/110/16/121 13vPnC Sex: 505 M / 482 F Age [mean /	4 doses of 20vPnC or 13vPnC administered at 2, 4, 6, and 12–15 months of age (Doses 1–4, respectively); with 6 months of safety follow-up after Dose 4 3 doses of Pediarix and Hiberix co-

					median (min, max)]:	administered
	To demonstrate that the serotype-specific IgG GMCs for 13 serotypes in the 20vPnC group are non-inferior to GMCs for the corresponding serotypes in the 13vPnC at 1 month after Dose 4 To demonstrate that the serotype-specific IgG GMCs for 7 additional serotypes in the 20vPnC group are non- the lowest IgG GMC among the 13 serotypes in the group at 1 month after Dose 4 Concomitant Immunogenicity: To demonstrate that percentages of participants with prespecified antibody to specific concomitant vaccine antigens when given 20vPnC are non-inferior to the corresponding when the antigens are given with 13vPnC at 1 month		Completed 1-visit after Dose 4: 839 Completed 6-follow-up contact: 842	65.6/64.0 (43, 96) days Race (W/B/A/O): 742/108/16/121	with Doses 1-3 of 20vPnC or 13vPnC 1 dose of M-M-RII and Varivax co-administered with Dose 4 of 20vPnC or 13vPnC

	Dose 3 Key Secondary (Pneumococcal Immunogenicity) Objectives: To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are non-inferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3 To demonstrate that the serotype-specific IgG GMC for the 7 additional serotypes in the 20vPnC group are non-inferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 3 Secondary (Immunogenicity) Objectives: To further describe the immunogenicity of 20vPnC To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC To demonstrate that GMCs to specific concomitant vaccine antigens when given with 20vPnC are non-inferior to the corresponding GMCs when the antigens are given with 13vPnC at 1 month after Dose 4 Exploratory (Immunogenicity) Objectives: To further describe the immunogenicity of 20vPnC To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC				
B7471013 (Argentina, Canada, Chile, Czech Republic, Finland, Germany, Greece, Hungary,	Phase 3, randomized, double-blind trial in infants, using schedule of 3 infant doses and a toddler dose Primary Objective: To describe the safety profile of Exploratory Objective: To describe the safety profile	20vPnC or 13vPnC (control)	20vPnC Randomized: Vaccinated: 1000 Completed 1-visit after Dose 4: 917 Completed 6-	20vPnC Sex: 517 M / 483 F Age [mean/median (min, max)]: 64.6/ 64.0 (43, 98) days Race (W/B/A/O): 868/55/21/56	4 doses administered at 2, 4, 6, and 12–15 months of age (Doses 1–4, respectively); with 6 months of safety follow-up

Spain, and USA/PR)			follow-up contact: 940 <u>13vPnC</u> Randomized: 505 Vaccinated: 504 Completed 1-visit after Dose 4: 460 Completed 6-follow-up contact: 468	<u>13vPnC</u> Sex: 244 M / 259 F Age [mean/median (min, max)]: 65.0/ 64.0 (43, 97) days Race (W/B/A/O): 445/15/10/33	after Dose 4
B7471014 (USA)	Phase 3 single-arm trial of a single dose in children ≥15 months to 17 years of age with a 4-cohort design based Age Primary Objectives: Safety: To describe the safety profile of 20vPnC Immunogenicity: Cohort 1 and Cohort 2: To the serotype-specific IgG concentrations for the 7 serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC Cohort 3 and Cohort 4: To demonstrate that the specific OPA titres for the 7 additional serotypes 1 after 20vPnC are superior to the corresponding OPA before 20vPnC	20vPnC	<u>Cohort 1 **(≥15 <24 months)**</u> Enrolled: 210 Vaccinated: 209 Completed 1-follow-up after vaccination: 207 Completed 6-follow-up contact: 207 <u>Cohort 2 **(≥2** to years)</u> Enrolled: 219	<u>Cohort 1</u> Sex: 117 M / 92 F Age [mean/median (min, max)]: 18.3/18.1 (15, 24) months Race (W/B/A/O): 168/26/3/12 <u>Cohort 2</u> Sex: 106 M / 110 F Age [mean/median	Single dose with 6 months of safety follow-up after Dose 4

	Secondary (Immunogenicity) Objective: To further describe the immune responses to 20vPnC in Cohorts 1, 2, 3, and 4 Exploratory (Immunogenicity) Objective: To further describe the immune responses to 20vPnC in Cohorts 1, 2, 3, and 4		Vaccinated: 216 Completed 1-follow-up after vaccination: 210 Completed 6-follow-up contact: 210	(min, max)]: 3.0/3.0 (2, 4) years Race (W/B/A/O): 173/26/0/17	
B7471014 continue			<u>Cohort 3 **(≥5** to years)</u> Enrolled: 203 Vaccinated: 201 Completed 1-follow-up after vaccination: 200 Completed 6-follow-up contact: 199 <u>Cohort 4 **(≥10** <18 years)</u> Enrolled: 207 Vaccinated: 205	<u>Cohort 3</u> Sex: 108 M / 93 F Age [mean/median (min, max)]: (5, 9) years Race (W/B/A/O): 174/22/0/5 <u>Cohort 4</u> Sex: 115 M / 90 F Age [mean/median (min, max)]: 13.6/14.0 (10,	

			Completed 1-follow-up after vaccination: 204 Completed 6-follow-up contact: 203	17) years Race (W/B/A/O): 178/17/0/10	

Abbreviations: 13vPnC=13-valent pneumococcal conjugate vaccine; 20vPnC=20-valent pneumococcal conjugate vaccine; A=Asian; B=Black/African American; CSR=clinical study report; F=female; FPFV=first participant first visit; LPLV: last participant last visit; M=male; max=maximum; min=minimum; No.=number; O=other (includes American Indian or Alaskan native, native Hawaiian or other Pacific Islander, multiracial, and not reported); PR=Puerto Rico; USA=United States of America; W=White.

a. Age (in days) at first dose. For participants randomized but not vaccinated, age is calculated using enrollment date instead of the date of first dose.

2.3.2. Pharmacokinetics

No pharmacokinetic studies were conducted in support of this application. This is acceptable, as pharmacokinetic studies are not routinely conducted as part of the evaluation of vaccines, as described in the CHMP “Guideline on clinical evaluation of vaccines” (EMEA/CHMP/VWP/164653/05 Rev. 1).

2.3.3. Pharmacodynamics

The pharmacodynamic profile of 20vPnC is defined by the immunogenicity profile.

Given the similarity of 20vPnC to 13vPnC, the clinical development of 20vPnC for paediatric use builds on the record of the safety, immunogenicity, efficacy, and effectiveness established for 13vPnC. The formulation, dose of each polysaccharide conjugate, and dosing schedules of 20vPnC have been modelled after those of 13vPnC. The overall strategy of the development of 20vPnC was agreed by the CHMP via scientific advice. Specific points which were not followed to are mentioned in the respective sections of the assessment report. Immunogenicity results are described in the Clinical Efficacy sections.

Mechanism of action

20vPnC elicits a T-cell dependent immune response to induce antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. In addition, it leads to generation of memory B cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria.

Primary and secondary pharmacology

Human serological responses against *Streptococcus pneumoniae* were evaluated in support of the paediatric clinical evaluation of 20-valent pneumococcal conjugate vaccine (20vPnC) using direct-binding Luminex immunoassays (dLIAs) and opsonophagocytic activity (OPA) assays specific for the 20vPnC serotypes and the cross-reactive serotypes 6C and 15C. Additionally, immune responses in infants/ toddlers to specific concomitant vaccine antigens were evaluated using immunoassays.

Direct Luminex Anti-Pneumococcal Immunoassays

The high-throughput multiplex dLIAs used in development of 20vPnC quantitatively measure the amount of serotype-specific immunoglobulin G (IgG) antibody present in the sample. Three multiplex dLIAs were used: the 13-plex dLIA that measures IgG concentrations to the 13vPnC serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), the 7-plex dLIA that measures IgG concentrations to the 7 additional serotypes of 20vPnC (8, 10A, 11A, 12F, 15B, 22F, and 33F), and the 2-plex dLIA that measures IgG concentrations to cross-reactive serotypes 6C and 15C. Pfizer's 13-plex dLIA was validated and then bridged to the World Health Organization (WHO) standardised enzyme-linked immunosorbent assay (ELISA) using incurred samples from historical 13vPnC Phase 3 paediatric studies. A second dLIA was validated for the 7 additional serotypes (the 7-plex dLIA) and a third dLIA was validated for the cross-reactive serotypes 6C and 15C (2-plex dLIA), to support Pfizer's 20vPnC paediatric Phase 3 trials.

In these assays, each serotype-specific pneumococcal capsular polysaccharide is individually conjugated to poly-L-lysine (PLL), and the polysaccharide-PLL conjugates are chemically coupled to spectrally distinct Luminex microspheres. The microspheres are pooled and incubated with diluted serum samples to allow serotype-specific primary antibodies to bind to the immobilised polysaccharide antigens. The microspheres are washed to separate non-bound antibodies, and an R-Phycoerythrin-conjugated goat anti-human IgG secondary antibody is used to detect bound primary antibodies on the microspheres. Fluorescence values, expressed as median fluorescent intensities, are measured using a Luminex plate reader and correlated with the concentration in µg/mL of bound capsular polysaccharide specific IgG antibodies according to the reference standard curve. Assay results are reported in µg/mL of IgG antibodies.

Table 2. List of 20vPnC dLIA Bioanalytical Method Validation Studies

Title	Document ID	Validated Assay Parameters		
		Serotype	LLOQ (µg/mL)	Assay range (µg/mL)
13 Matched Serotypes (13vPnC Serotypes)				
Validation Report for a 13-plex Direct Luminex Immunoassay for Detection of Antibodies to S. pneumoniae in Human Serum Assessment of Standard Curve Bias for the Pneumococcal 13-plex Direct Luminex Immunoassay using Historical Data	VR-MVR-10025 VR-VTR-10424[a]	1	0.002	0.000018–0.027175
		3	0.004	0.000019–0.011600
		4	0.005	0.000044–0.026640
		5	0.005[a]	0.000098–0.023994
		6A	0.005	0.000052–0.031440
		6B	0.015	0.000019–0.028914
		7F	0.003	0.000017–0.026518
		9V	0.013	0.000034–0.020575
		14	0.005	0.000080–0.048643
		18C	0.002	0.000015–0.023323
		19A	0.038	0.000029–0.044313
		19F	0.012	0.000077–0.046677
		23F	0.009	0.000031–0.047600

Abbreviations: ID = identification number; LLOQ = lower limit of quantitation.

Note: The LLOQ is the lowest non-diluted sample concentration that can be determined with acceptable linearity, precision, and standard curve bias. The assay range is the range of diluted sample concentrations that can be measured in the assay with acceptable dilutional linearity, precision, and standard curve bias

[a]. Standard curve bias analysis report VR-VTR-10424 supports a change in the serotype 5 LLOQ (from 0.002 to 0.005) and the assay range limits compared with what is reported in VR-MVR-10025.

Although there is no established correlate of protection for pneumococcal conjugate vaccines that directly predicts protection for an individual, an IgG concentration of 0.35 µg/mL, developed from a meta-analysis of results from efficacy studies of 7vPnC and 9vPnC against IPD, is accepted by the WHO and has also been accepted by the EMA as a reference level for comparing new pneumococcal conjugate vaccines to existing ones for the purposes of bridging back to the efficacy demonstrated in these trials. The percentage of participants with an IgG concentration of ≥0.35 µg/mL after a series of 3 infant doses, measured by ELISA, correlated with the percent of vaccine efficacy of the studies combined (93%). Since this concentration (≥0.35 µg/mL) was developed from the 7vPnC data, the applicability of this level to other serotypes is less clear.

Using a Deming regression analysis of the linear relationship between ELISA and dLIA platforms, the MAH bridged IgG titres obtained with the company 13-plex dLIA to the titres obtained with the WHO ELISA in order to determine dLIA thresholds representing serotype-specific IgG concentrations ≥0.35 µg/mL in the established ELISA format. The 7-plex dLIA was not bridged to WHO standards.

To support the primary pneumococcal immunogenicity endpoints, IgG concentrations were classified based on serotype-specific IgG reference concentrations as defined below:

Serotypes	Reference Concentration (µg/mL)
1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F, 23F	≥0.35
5	≥0.23
6B	≥0.10
19A	≥0.12
8, 10A, 11A, 12F, 15B, 22F, 33F	≥0.35
6C, 15C (cross-reactive seroytpes)	≥0.35

Pneumococcal Opsonophagocytic Activity Assays

The OPA assays used in the development of 20vPnC quantitatively assess functional anti-S *pneumoniae* antibodies by measuring bacterial killing in reactions containing serially diluted test sera, baby rabbit complement, and differentiated effector cells (HL-60). The OPA titre is the reciprocal of the highest test serum dilution resulting in 50% reduction in the number of bacterial colony-forming units (CFUs) when compared with the control without test serum (defined as the background CFU). Titres from multiple determinations per sample are reported as geometric mean titres (GMTs).

Pfizer's OPA assays for the 13vPnC serotypes were validated previously and have been used routinely in support of 13vPnC clinical trials and registration. Similar OPA assay procedures were developed for the 7 additional 20vPnC serotypes. The OPA assays for the 7 additional serotypes and for serotype 15C were validated to support the Phase 3 trials of 20vPnC.

ASSAYS FOR CONCOMITANT VACCINE ANTIGENS

Diphtheria, Tetanus, Pertussis Hexaplex Luminex Assay (DTP-6 IgG)

The DTP-6 IgG is a direct binding immunoassay that measures IgG antibodies to pertussis toxin (PTx), filamentous hemagglutinin (FHA), pertactin (PRN), and Fimbriae 2/3 (FIM 2/3) of Bordetella pertussis; diphtheria toxoid (DTd) of Corynebacterium diphtheriae; and tetanus toxoid (TTd) of Clostridium tetani

simultaneously from a single serum sample. It is based on the method published by Van Gageldonk et al. The assay has been validated by PPD Vaccine and Biologics (Wayne, PA, USA) through assessment of assay specificity, robustness, precision, and linearity.

The purified 6 antigens conjugated to a set of 6 spectrally unique Luminex microspheres (1 antigen per microsphere) and serum containing DTP-6 antibody are added into a 96-well plate to form an antibody-antigen complex. The bound antibody-antigen complexes are detected using phycoerythrin (PE)-labelled monoclonal secondary to human IgG. The resulting fluorescent signal from the addition of the secondary antibody is measured using a Bio-Plex fluorescence analyser (or equivalent). Antibody titres are determined in this direct binding format, where the fluorescent signal from the PE-labelled monoclonal secondary detection anti-human IgG1-4 antibody (HP6043) is directly proportional to the amount of anti-DTP serum IgG antibodies bound to the antigen-microspheres.

For each DTP antigen, binding of the anti-IgG-PE is compared with a reference standard serum using a 4-parameter logistic regression function. The reference standard comprises a pool of sera from adults 18–40 years of age (n=25) vaccinated with a commercially available vaccine, Adacel™ (Sanofi Pasteur, Swiftwater, PA) that contains all 6 antigens. The reference serum was calibrated to WHO National Institute of Biologics Standards and Controls (NIBSC) 06/140 for 3 antigens (PTx, FHA, and PRN), FDA Lot 3 for FIM 2/3, NIBSC TE-3 for TTd, and NIBSC 00/496 for DTd. In routine testing, each assay plate contains a reference standard (diluted at 1:25 [1:50 final in plate] followed by an 11-point, 3 fold serial dilution), 4 quality control samples (tested as a single dilution in duplicate at 1:1000), and up to 32 clinical test samples (tested as a single dilution in duplicate at 1:1000, with a retest at 1:10,000 as needed).

Anti-Haemophilus influenzae Type b (Hib) Enzyme-Linked Immunosorbent Assay (ELISA)

The commercially available VaccZyme™ Human anti-Hib ELISA kit, which measures serum IgG antibodies specific to Hib, was validated by ACM Global (Fulford, York, UK).

Microwells supplied with the kit are precoated with the Hib capsular polysaccharide antigen conjugated to human serum albumin. The calibrators, controls and diluted test sera are added to the wells and antibodies recognising the Hib antigen bind during the first incubation. After washing the wells to remove all unbound proteins, purified peroxidase-labelled rabbit anti-human IgG (γ chain specific) conjugate is added. The conjugate binds to the captured human antibody, and the excess unbound conjugate is removed by a further wash step. The bound conjugate is visualised with 3,3',5,5' tetramethylbenzidine substrate which gives a blue reaction product, the intensity of which is proportional to the concentration of antibody in the sample. Phosphoric acid is added to each well to stop the reaction. This produces a yellow end point colour, which is read at 450 nm.

Assay for the Detection of Antibodies to Hepatitis B Surface Antigen

Siemens Healthcare's anti-HBs2 assay – a double antigen sandwich immunoassay using direct, chemiluminometric technology to measure serum IgG antibodies to hepatitis B surface antigen (HBsAg) – was validated by ACM Global (Fulford, York, UK).

HBsAg (ad and ay) are covalently coupled to magnetic latex particles in the Solid Phase. In the Lite Reagent, the HBsAg (ad and ay) is labelled with acridinium ester. Nonmagnetic latex particles are added from the ancillary well. The sample is incubated simultaneously with Lite Reagent, Solid Phase, and Ancillary Reagent. Antibody-antigen complexes will form if anti-HBsAg is present in the sample. A direct relationship exists between the amount of anti-HBsAg activity in the patient sample and the amount of relative light units (RLUs) detected by the system.

Poliovirus Neutralization Assay for Serotypes 1, 2, and 3

The poliovirus neutralization assay for serotypes 1, 2 and 3 – based on the neutralization assay described in the WHO Manual for the Virological Investigation of Polio – was altered to make it fit for purpose as a high through-put assay and validated by Viroclinics Biosciences (Schaijk, The Netherlands).

In this microneutralization assay, a constant amount of virus is mixed with serial dilutions of serum samples. If neutralizing antibodies specific for poliovirus are present, the virus is neutralized and its cytopathic effect on indicator cells is prevented. Indicator cells in this assay are human epithelial type 2 (Hep-2) Cincinnati cells. After the incubation period, the presence or absence of viable cells is measured by adding cell viability marker WST-8 and measuring the optical density at 450 nm using a microplate reader. The presence or absence of cells can also be assessed by crystal violet staining. The neutralization GMTs are estimated from the proportion of virus-positive and virus-negative wells in the serum dilution series by the Spearman-Karber method.

Measles, Mumps, Rubella (MMR) and Varicella Zoster Virus (VZV) Quantitative IgG Assays

The LIAISON® MMR and VZV quantitative IgG immunoassays, developed and manufactured by DiaSorin (Saluggia, Italy), measure specific IgG to MMR and VZV through indirect chemiluminescence. All 4 assays were validated independently by Pfizer by performing a descriptive assessment of precision and dilutional linearity.

Each of the 4 assays are performed independently on the LIAISON® XL analyser. The critical components of each test are magnetic particles (solid phase) coated with recombinant antigen, or purified viral particles, and a mouse monoclonal anti-human IgG antibody linked to an isoluminol derivative (isoluminol-antibody conjugate). During the first incubation step of the assay, IgG specific to the respective virus present in calibrators, test samples, or controls, binds to the solid phase. Next, during the second incubation, the isoluminol-antibody conjugate reacts with virus-specific IgG bound to the solid phase. After each incubation, unbound material is removed with a wash cycle. Subsequently, starter reagents are added and a chemiluminescence reaction is induced. The chemiluminescence signal is proportional to the amount of bound isoluminol-antibody conjugate and is measured by a photomultiplier. A signal is measured as RLUs. RLU results are read off a calibrated standard curve and expressed in Arbitrary Unit/mL (AU/mL) for measles and mumps, International Unit/mL (IU/mL) for rubella, and milli International Unit/mL (mIU/mL) for varicella assays. The positivity cut-off, or minimum result that is considered indicative of exposure to virus or previous vaccination and considered adequate laboratory evidence of immunity, as published by DiaSorin are as follows for each antigen:

- Measles –16.5 AU/mL
- Mumps – 11.0 AU/mL

- Rubella – 10 IU/mL
- Varicella – 150 mIU/mL

To support the primary concomitant immunogenicity estimands, the antibody concentrations were classified based on prespecified antibody thresholds for the concomitant vaccine antigens:

Antigen	Prespecified Level
Diphtheria toxoid	≥0.1 IU/mL
Tetanus toxoid	≥0.1 IU/mL
Pertussis antigens (PT, FHA, PRN)	≥ the observed antipertussis antibody concentration achieved by 95% of 13vPnC recipients
HBsAg	≥10 mIU/mL
Poliovirus strains (types 1, 2, and 3)	≥1:8
Hib	≥0.15 µg/mL anti-PRP Alternative: ≥1.0 µg/mL anti-PRP[a]

Abbreviations: 13vPnC = 13-valent pneumococcal conjugate vaccine; anti-PRP = anti–polyribosylribitol phosphate; FHA = filamentous hemagglutinin; HBsAg = hepatitis B surface antigen; Hib = Haemophilus influenzae type b; PRN = pertactin; PT = pertussis toxin.

a. Secondary concomitant immunogenicity endpoint 1 month after Dose 3.

Bridging

The MAH used high-throughput multiplex dLIAs to measure the amount of serotype-specific immunoglobulin G (IgG) antibodies in study participants.

The MAH provided a formal bridging study report (VR-VTR-10106) for the 13 serotypes shared with 13vPnC as requested in the first round of assessment. Residual sera obtained from various 13vPnC clinical studies, including pivotal licensure studies were tested with dLIA and results were bridged to the original ELISA results using Deming regression. Different reference standards were used in the dLIA and the historical ELISA data. This approach raises some concerns since the quality of sera might be different after years of storage (evaporation, freeze/thaw, etc.). For instance, evaporation over years could lead to higher antibody concentrations in the sera which might also explain the greater dynamic range of dLIA observed by the MAH: “The 13-plex dLIA platform is better in differentiating pre- and post- immunization samples for all serotypes because the dLIA provides a more specific measurement of IgG antibody concentrations especially at the lower end of the assay ranges.” Therefore, an investigation of 13-plex dLIA/ELISA concordance should ideally not only be performed on the same sera but should also be performed in a temporally related manner using the same standards. Aside from such concerns however, multiplex dLIAs can be considered in general as valuable tools to investigate serum IgG responses to pneumococcal conjugate vaccines and the number of enclosed samples and the linearity shown is considered sufficient for bridging purposes.

In the present bridging report, the serum selection focused on time points one month after the infant immunization series and one month after the toddler dose. Panels D1/D2 and D3/D4 represent pairs of

infant pre-/post immunization samples. Two panels (E1 and E2) from the “before toddler dose” time point were included to add serum samples with lower serum IgG concentrations. Overall, 1,528 samples with sufficient remaining volume were analyzed in the dLIA platform. The selection of sera is considered appropriate.

However, despite comprehensive analyses the validity and clinical relevance of the proposed dLIA thresholds for endpoint evaluation remain unclear:

First, regarding the 13 shared serotypes the MAH states within the Response: “(…) Equivalent IgG threshold values by dLIA for serotypes 5, 6B and 19A were shown to be 0.23, 0.10 and 0.12 µg/mL, respectively. Although 8 of the remaining 10 serotypes bridged to dLIA values below 0.35 µg/mL, MAH chose to take a conservative approach and use 0.35 µg/mL for the dLIA for the remaining serotypes (…)”. This latter notion is inconsistent with data provided in Table 3 of the bridging report (see below) showing 6 of the 9 of the remaining serotypes to be >0.35 µg/mL. The assessment will focus on data as presented in the formal bridging report.

Table 3. **Relationships between WHO ELISA and dLIA Serum IgG Concentrations and Estimated dLIA Cutoff for Serotypes 1, 4, 6A, 7F, 9V, 14, 18C, 19F, 23F Based on All Post Immunization Data**

Serotype	Size	Deming Regression	95% CI Slope	dLIA Cutoff[a]
1	783	$\log_{10}$(dLIA)=1.04* $\log_{10}$(ELISA)-0.07	(1.018, 1.061)	0.29
4	1337	$\log_{10}$(dLIA)=1.16* $\log_{10}$(ELISA)+0.09	(1.133, 1.193)	0.37
6A	783	$\log_{10}$(dLIA)=1.32* $\log_{10}$(ELISA)+0.11	(1.280, 1.356)	0.32
7F	783	$\log_{10}$(dLIA)=1.12* $\log_{10}$(ELISA)+0.08	(1.079, 1.162)	0.37
9V	1337	$\log_{10}$(dLIA)=1.28* $\log_{10}$(ELISA)+0.16	(1.235, 1.330)	0.38
14	1337	$\log_{10}$(dLIA)=1.10* $\log_{10}$(ELISA)-0.03	(1.077, 1.127)	0.29
18C	1337	$\log_{10}$(dLIA)=1.14* $\log_{10}$(ELISA)+0.21	(1.106, 1.166)	0.49
19F	1337	$\log_{10}$(dLIA)=1.06* $\log_{10}$(ELISA)+0.07	(1.041, 1.077)	0.39
23F	1334	$\log_{10}$(dLIA)=1.27* $\log_{10}$(ELISA)+0.18	(1.239, 1.294)	0.40

This summary table is based on Attachment Bridging 2.1.

a. dLIA cutoff values were calculated as described in Section 5.1.

According to the MAH: “Maintaining the original ELISA-based protective threshold cutoff value of 0.35 µg/mL in the dLIA platform for serotypes 1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F and 23F does not affect the vaccine responder rate. For serotypes 5, 6B, and 19A, lower cutoff values are needed for the dLIA platform to match the proportions of vaccine responders to those determined by ELISA. Cutoff values of 0.23, 0.10, and 0.12 µg/mL for serotypes 5, 6B, and 19A, respectively, are recommended for the dLIA platform to best match the vaccine responder rates established by the ELISA platform”. Although responder rates might not be substantially overestimated using the 0.35 µg/mL thresholds for serotypes 1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F and 23F according to the MAH´s analyses, best consistency of vaccine responder proportions between both assay platforms, can be generally expected from exploiting the linearity of the bridging experiment and apply resulting serotype-specific thresholds directly.

Third, the MAH also provided novel evaluations based on residual study sera to investigate the concordance between dLIA and ELISA results for the 7 additional serotypes. Such experiments could provide valuable insights into the connection between dLIA and ELISA data for the 7 additional serotypes. However, as for the 13 shared serotypes, dLIA and ELISA assay were not run in parallel. Sera of the 20vPnC study B7471003 were retested using ELISA and data were compared to data originally obtained with dLIA. Values corresponding to 35 µg/mL by ELISA were estimated as follows: 8, 0.41 µg/mL; 10A,

0.21 µg/mL; 11A, 0.40 µg/mL; 12F, 0.69 µg/mL; 15B, 0.57 µg/mL; 22F, 0.27 µg/mL; 33F, 0.28 µg/mL. Since there is no link to clinical efficacy regarding antibody titers in any assay platform, the clinical relevance of threshold titers for the 7 additional serotypes will be unclear in any case, irrespective of whether thresholds would be obtained through quantitative bridging or would be arbitrarily selected (35 µg/mL).

Different dLIAs (7-plex; 13-plex) were used to determine antibody responses against the 20 serotypes contained 20vPnC.

However, in line with general considerations regarding the setup and function of Luminex assays, the described influence of small amounts of polysaccharides on assay performance imply that no quantitative comparison is possible between results derived from different dLIA setups (7-plex;13-plex) containing much larger amounts of different antigens.

The MAH provided a comparison of mean IgG results by serotype between single and multiplex IgG dLIAs. Although the additional effort is appreciated, this approach is not addressing the initial concern of the CHMP regarding the influence of specific mixtures (i.e. 7-plex vs 13-plex) of antigens on serotype-specific assay results.

Furthermore, the MAH employed Pneumococcal Opsonophagocytic Activity Assays to determine serotype-specific antibody responses. Such assays can indicate immunogenicity from a more functional perspective than binding assays such as dLIA. However, OPA assays are not standardized and do not yield an established correlate of protection in the paediatric population.

Experimental approaches to determine concomitant vaccine responses were adequate and equally applied to 13vPnC and 20vPnC groups.

2.3.4. Discussion on clinical pharmacology

Following licensure of 13vPnC vaccine, the MAH changed the IgG assessment assay platform from ELISA to a multiplex dLIA platform which allows many tests concurrently on a single assay plate (many serotypes assessed in one reaction volume). Subsequently, a multiplex dLIA for the 7 additional serotypes was developed and both multiplex assays were used to define serotype-specific antibody responses following vaccination with 20vPnC in the current Variation.

Although the multiplex dLIAs are in principle fit for purpose, proposed analyses show several limitations which might also impact important conclusions on primary endpoints.

Issues with assays/data usage (in context of the performed analyses and conclusions)

13 shared serotypes:

A formal bridging report comparing the used dLIA platform to the WHO ELISA platform was provided on request. Overall, the report indicates that the 13-plex dLIA platform is a suitable alternative to the WHO ELISA platform for measuring serotype-specific serum IgG responses to pneumococcal conjugate vaccines.

Despite comprehensive quantitative bridging experiments, the MAH proposes a threshold of 0.35 µg/mL irrespective of the bridging result for 17/20 serotypes contained in 20vPnC. Best consistency of vaccine responder proportions between both assay platforms can be generally expected from exploiting the linearity of the bridging experiment and apply resulting serotype-specific thresholds directly. Therefore, to address the uncertainties regarding the clinical relevance of the applied thresholds respective analyses for

the endpoint response rate after the last infant dose and after the toddler dose were requested. Although the numbers changed slightly the overall conclusions were not affected by different thresholds.

OPA titres are not an established correlate of protection in the paediatric population but can serve as measure of immunogenicity when presented as fold change.

7 additional serotypes:

The 7-plex dLIA is not bridged to the WHO ELISA since no data for these serotypes are available in this format. A dLIA IgG cutoff of ≥0.35 µg/mL is arbitrarily used as (protective) threshold without direct link to clinically relevant data obtained via a standardized assay platform.

The MAH also provided novel evaluations based on residual study sera to investigate the concordance between dLIA and ELISA results for the 7 additional serotypes. Since there is no link to clinical efficacy regarding antibody titres in any assay platform, the clinical relevance of threshold titres for the 7 additional serotypes will be unclear in any case, irrespective of whether thresholds would be obtained through quantitative bridging or would be arbitrarily selected (35 µg/mL).

In addition, two different assays (13-plex dLIA and 7-plex dLIA) were used to obtain antibody titres for the 13 serotypes also contained in 13vPnC and the 7 additional serotypes, respectively. This design does not allow any quantitative comparisons between the two sets of serotypes since the influence of specific serotype combinations on the dLIA measurement of serotype-specific IgG concentrations is unclear. Accordingly, the determination of NI for the 7 additional serotypes against the (lowest) titre elicited by the 13 shared serotypes is not informative. To allow meaningful comparison of antibody responses between the two serotype sets, measurement of antibody concentrations in one assay would have been required. The current approach limits the interpretation of titres for the 7 additional serotypes in comparison to that of the 13 shared serotypes.

The bridging report revealed that regression-derived dLIA thresholds for responder rate evaluation are used only for 3/13 serotypes in the initially submitted study reports. This is not acceptable since best concordance with the protective 0.35 µg/ml ELISA threshold can be generally expected from directly exploiting the quantitative regression analyses. Additionally requested sensitivity analyses with regression-derived thresholds revealed only minor differences and no impact to the overall conclusions regarding responder-rate-based endpoints. The SmPC has been updated accordingly.

2.3.5. Conclusions on clinical pharmacology

The Applicant applied a dLIA platform assay to estimate IgG titres in all presented studies instead of the WHO standard ELISA. Although a bridging report and a rationale for the subsequent changes to the obtained bridged values were submitted, the CHMP did not agree with the chosen values. Although requested sensitivity analyses did not affect the overall conclusions based on the of affected responder rate endpoints in the respective studies, relevant tables and the SmPC have been updated to reflect the responder rates with the most adequate thresholds.

Overall, direct comparisons between the approved 13vPnC and 20vPnC, using serotype-specific antibody concentrations and fold changes, obtained by identical assays, allow an estimation of immunogenicity for the 13 serotypes. Endpoints and non-inferiority evaluations based on such analyses are considered clinically meaningful.

Two different assays were used to obtain antibody titres for the 13 shared serotypes and the 7 additional serotypes. This design does not allow any quantitative comparisons between the two sets of serotypes since the influence of specific serotype combinations on the dLIA measurement of serotype-specific IgG

concentrations is unclear. Together with the lack of a correlate of protection for the 7 additional serotypes or any clinical data in this regard, the determination of NI for the 7 additional serotypes against the (lowest) titre elicited by the 13 shared serotypes is considered rather uninformative.

2.4. Clinical efficacy

No efficacy studies have been performed with 20vPnC; efficacy is inferred based on immunogenicity. Immunogenicity has been investigated in 4 clinical studies in total, specifically in three phase 3 clinical studies (B7471012, B7471011 and B7471014) and one phase 2 clinical study (B7471003). Studies B7471012 (2+1 dose regimen) and B7471011 (3+1 dose regimen) are considered pivotal as they provide the main evidence for immunogenicity and safety in the target population.

B7471014 is a single-arm trial which evaluated immunogenicity of a single dose of 20vPnC administered to participants ≥15 months to <5 years of age previously immunized with 13vPnC and participants ≥5 years to <18 years of age (regardless of previous vaccination with 7vPnC or 13vPnC) with respect to the 7 additional serotypes.

The primary objectives for the immunogenicity assessment of the Phase 3 trials were:

- To demonstrate that immune responses for the 13 serotypes in the 20vPnC are non-inferior to those of the corresponding serotypes in the 13vPnC group and for the 7 additional serotypes are non-inferior to the lowest among the 13 serotypes in the 13vPnC group (B7471012 and B7471011)
- To demonstrate that immune responses to specific concomitant vaccine antigens when co-administered with 20vPnC are non-inferior to the corresponding responses when co-administered with 13vPnC in infants (B7471012 and B7471011)
- To demonstrate that a single dose of 20vPnC administered to participants ≥15 months to <5 years of age previously immunized with 13vPnC and to participants 5 years to <18 years of age elicits immune responses expected to provide protection against pneumococcal disease due to the 7 additional serotypes (B7471014)

2.4.1. Main studies

Study B7471012, investigating the 2+1 vaccination regimen and study B7471011, investigating the 3+1 vaccination regimen provide the main evidence for immunogenicity and safety in the target paediatric population.

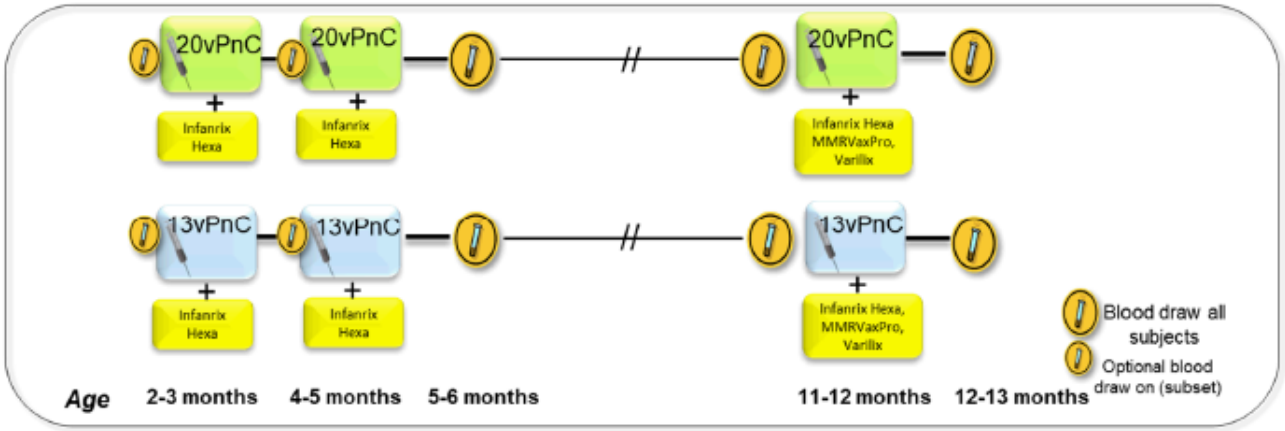
B7471012: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants

B7471012 was a Phase 3, multicentre, randomised, active-controlled, double-blind trial to evaluate the safety, tolerability, and immunogenicity of 20vPnC in healthy infants when administered as a series of 2 infant doses and 1 toddler dose (at 2, 4, and 11-12 months of age). This trial was designed to provide non-inferiority (NI) comparisons of the 20vPnC immune responses with those of 13vPnC to infer effectiveness in infants for the 2+1 vaccination schedule. Data were also generated on key routine paediatric vaccines given concomitantly with 20vPnC or 13vPnC.

Approximately 1200 infants born at >36 weeks of gestation and ≥42 to ≤112 days of age at the time of consent by their parents/legal guardians were planned to be enrolled. Participants were randomised in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at enrolment following a 2+1 schedule (Doses 1, 2, and 3). Participants received the same vaccine (either 20vPnC or 13vPnC) for all 3 doses. The planned duration of study participation was approximately 11 months for each participant. The trial was performed at 59 sites in the EU and Australia and was planned to include approximately 1200 infants.

A separate cohort of approximately 60 infants from Russia was added to the trial for regulatory purposes for the Eurasian Economic Region. Dosing in that cohort is currently in progress and was not designed to be included in the main analysis and not part of this Type II variation. The Russian cohort was not included in the primary study population due to planned earlier completion of study visits in the primary study population than the Russian cohort and differences in concomitant vaccine schedule and visit windows in the Russian participants.

Table 4 Study design B7471012



Visit 1 (Day 1) – Dose 1 of either 20vPnC or 13vPnC administered. Administration of a concomitant vaccine Infanrix hexa.

Visit 2 (42 to 63 Days after Visit 1, ie, Study Day 43 through Study Day 64) - Dose 2 of either 20vPnC or 13vPnC administered. Administration of a concomitant vaccine Infanrix hexa.

Visit 3 (28 to 42 Days After Visit 2) - Dose 2 Follow-up, blood draw for immunogenicity

Visit 4 (335 to 386 Days of Age) – blood draw for immunogenicity prior to vaccination; Dose 3 of either 20vPnC or 13vPnC administered. Administration of concomitant vaccines Infanrix hexa, MMR and varicella vaccines.

Visit 5 (28 to 42 Days After Visit 4) - Dose 3 Follow-up, blood draw for immunogenicity

Methods

Study participants

Inclusion criteria

1. Male or female infants born at >36 weeks of gestation and 2 months of age (≥42 to ≤112 days) at the time of consent (the day of birth is considered day of life 1).
2. Participants whose parent(s)/legal guardian(s) are willing and able to comply with all scheduled visits, treatment plan, and other study procedures.
3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.
4. Expected to be available for the duration of the study and whose parents(s)/legal guardian can be contacted by telephone during study participation.
5. Participants whose parent(s)/legal guardian(s) is capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion criteria

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.

2. Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes.

3. Major known congenital malformation or serious chronic disorder.

4. History of microbiologically proven invasive disease caused by *S pneumoniae*.

5. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus (HIV) infection, leukaemia, lymphoma, or organ or bone marrow transplant.

6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

7. Congenital, functional, or surgical asplenia.

8. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

9. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.

10. Prior receipt of diphtheria, tetanus, pertussis, poliomyelitis, and/or Hib vaccine.

11. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. If systemic corticosteroids have been

administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

12. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) since birth or planned receipt through the last planned blood draw in the study (Visit 5, 1 month after Dose 3).

Prior/Concurrent Clinical Study Experience:

13. Participation in other studies involving investigational drug(s), investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation or intrauterine exposure to investigational vaccines. Participation in purely observational studies is acceptable.

Other Exclusions:

14. Children or grandchildren who are direct descendants of investigator site staff members or Pfizer employees who are directly involved in the conduct of the study.

Treatments

Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC in a 3-dose vaccination schedule at roughly 2-3, 4-5, and 11-12 months of age (hereafter known as a 2+1 schedule). Participants received a single dose (0.5 mL) of 20vPnC or 13vPnC IM into the anterolateral thigh muscle of the left leg at each vaccination visit (Doses 1, 2, and 3 at Visits 1, 2, and 4, respectively). The same vaccine (20vPnC or 13vPnC) was administered for all 3 doses.

Concomitant vaccines

Participants were also to receive 1 dose of DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) concomitantly with all doses of 20vPnC or 13vPnC (Doses 1, 2, and 3 at Visits 1, 2, and 4, respectively). Participants also were to receive MMR (M-M-RVAXPRO) and varicella (Varilrix) vaccines concomitantly with booster dose of 20vPnC or 13vPnC were also (Dose 3 at Visit 4). The MMR and varicella vaccines were intended to be given to all participants. However, some countries and sites did not administer MMR and varicella vaccines as concomitant study vaccines at Dose 3 due to local practices/recommendations. If they were not given at Dose 3, they were to be considered non-study vaccines. All concomitant vaccinations were to be administered into a limb other than the left leg (the site of 20vPnC or 13vPnC injection).

Other concomitant medications

The use of prophylactic antipyretic/pain medication, while permitted, was not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication was allowed.

Objectives

Objectives and estimands

Primary Safety Objective	Estimands
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3
Primary Pneumococcal Immunogenicity Objectives	Estimands
• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for all 13 shared serotypes in the 20vPnC group are non-inferior to those of the corresponding serotypes in the 13vPnC group at 1 month after Dose 2 • To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for all 7 additional serotypes in the 20vPnC group are non-inferior to the lowest among the 13 serotypes* in the 13vPnC group at 1 month after Dose 2. *If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group
• To demonstrate that the serotype-specific IgG GMCs for all 13 serotypes in the 20vPnC group are non-inferior to those for the corresponding serotypes in the 13vPnC group at 1 month after Dose 2 • To demonstrate that the serotype-specific IgG GMCs for all 7 additional serotypes in the 20vPnC group are non-inferior to the lowest among the 13 serotypes* in the 13vPnC group at 1 month after Dose 2 *other than serotype 3 (see above)	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group

• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are non-inferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3 • To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are non-inferior to the lowest among the 13 serotypes* in the 13vPnC group at 1 month after Dose 3. *other than serotype 3 (see above)	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of IgG concentrations from the 20vPnC group to the 13vPnC group • For each of the 7 additional serotypes in 20vPnC: GMR of IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group
Primary Concomitant Immunogenicity Objective	Estimands
To demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are non-inferior to immune responses induced by concomitant vaccine antigens given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib 1 month after Dose 3 between the 20vPnC and the 13vPnC groups • GMRs of antibody levels to measles, mumps, rubella, and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 3
Secondary Pneumococcal Immunogenicity Objective	Estimands
To further describe the immune responses induced by 20vPnC	In evaluable participants: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group at 1 month after Dose 3 • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group at 1 month after Dose 3 • For each of the 20 serotypes in 20vPnC: serotype-specific OPA GMTs 1 month after Dose 2 and 1 month after Dose 3 in each vaccine group • For each of the 20 serotypes in 20vPnC: GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group
Secondary Concomitant Immunogenicity Objective	Estimand
To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2 between the 20vPnC and the 13vPnC groups
Exploratory Objectives	Estimands

To further describe the immunogenicity of 20vPnC	In evaluable participants for each of the 20 serotypes in 20vPnC in each group: • Percentages of participants with the predefined IgG concentration before Dose 1 and before Dose 2 • IgG GMCs before Dose 1 and before Dose 2 • Percentages of participants with ≥4-fold rise in IgG concentrations from before Dose 3 to 1 month after Dose 3 • GMFRs in OPA titres from before Dose 3 to 1 month after Dose 3 • Percentage of participants with ≥4-fold rise in OPA titres from before Dose 3 to 1 month after Dose 3 • Percentages of participants with OPA titres ≥LLOQ at available time points In evaluable participants in each group: • For serotype 15C: IgG GMCs, OPA GMTs, and percentages of participants with OPA titres ≥ LLOQ at available time points • For serotype 6C: IgG GMCs, OPA GMTs, and percentages of participants with OPA titres ≥ LLOQ at available time points
To further describe the immune responses induced by concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with alternative prespecified antibody levels to Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 2 and 1 month after Dose 3 • GMRs of the antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib from the 20vPnC group to the 13vPnC group at 1 month after Dose 3 • GMCs of the antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib at 1 month after Dose 2 for each vaccine group • Differences in percentages of participants with prespecified antibody levels to measles, mumps, rubella, and varicella antigens 1 month after Dose 3 between the 20vPnC and the 13vPnC groups

Outcomes/endpoints

Primary Pneumococcal Immunogenicity Endpoints

- Pneumococcal IgG concentrations 1 month after Dose 2 and classification of IgG concentrations 1 month after Dose 2 (post-toddler dose)
- Pneumococcal IgG concentrations 1 month after Dose 3 (post-toddler dose)

Primary Concomitant Immunogenicity Endpoints

- Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) 1 month after Dose 3
- Antibody levels to HBsAg 1 month after Dose 3
- Antibody levels to poliovirus strains (types 1, 2, and 3) 1 month after Dose 3
- Antibody levels to Hib 1 month after Dose 3

- Antibody levels to MMR and varicella virus 1 month after Dose 3

Antibody concentrations to diphtheria toxoid, tetanus toxoid, and pertussis antigens were determined on sera collected 1 month after Dose 3 for all randomized participants. Antibody concentrations to HBsAg, poliovirus strains (types 1, 2, and 3), Hib, and MMR and varicella were determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes.

Secondary Pneumococcal Immunogenicity Endpoints

- Classification of IgG concentrations 1 month after Dose 3 (post-toddler dose)
- Fold rise of pneumococcal IgG concentrations from before Dose 3 to 1 month after Dose 3
- Pneumococcal OPA titres 1 month after Dose 2
- Pneumococcal OPA titres 1 month after Dose 3

OPA titres were determined on subsets of participants from each vaccine group.

Secondary Concomitant Immunogenicity Endpoints

- Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) 1 month after Dose 2
- Antibody levels to poliovirus strains (types 1, 2, and 3) 1 month after Dose 2
- Antibody levels to Hib 1 month after Dose 2

Antibody concentrations to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) will be determined on sera collected 1 month after Dose 2 from a randomly selected subset of participants with sufficient sera volumes. Antibody concentrations to poliovirus strains and Hib will be determined on sera collected 1 month after Dose 2 from the same subset of participants selected for 1 month after Dose 3 concomitant vaccine assessment.

Other Endpoints

- Pneumococcal IgG concentrations before Dose 1 and before Dose 2
- Fold rises of pneumococcal IgG concentrations from 1 month after Dose 2 to before Dose 3 and from 1 month after Dose 2 to 1 month after Dose 3
- Classification of IgG concentration fold changes as a ≥4-fold rise from before Dose 3 to 1 month after Dose 3
- Pneumococcal OPA titres and fold rises at available time points (1 month after Dose 2, before Dose 3, and 1 month after Dose 3)
- Serotype 15C IgG concentrations and OPA titres at available time points
- Serotype 6C IgG concentrations and OPA titres at available time points

Sample size

The sample size of the study was determined primarily based on considerations of 1) accumulating a sufficient overall safety database for the 20vPnC infant clinical development program,

2) providing robust assessment of the pneumococcal immune responses induced by 20vPnC and 13vPnC, 3) ensuring robust assessment to demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are non-inferior to immune responses induced by concomitant vaccine antigens given with 13vPnC, and 4) practical constraints of available serum volumes from individual study participants with all planned immunogenicity assessments.

The study power for the primary pneumococcal immunogenicity objectives was assessed based on simulations of multivariate log-normal distributed random numbers with assumptions supported by IgG results after 2 and/or 3 infant doses from historical 13vPnC and 7vPnC infant studies, and IgG results after 3 infant doses and the toddler dose of an internal Phase 2 infant study of 20vPnC (B7471003). To accommodate the uncertainties in the assumptions, 3 different assumed GMRs of the 20vPnC to the 13vPnC group 1 month after Dose 2 were explored to evaluate the study power.

With approximately 1200 enrolled participants using a 1:1 randomization ratio, assuming a 10% nonevaluable rate at 1 month after Dose 2, and a 17% nonevaluable rate at 1 month after Dose 3, the study was expected to result in approximately 540 and 500 evaluable participants for each vaccine group at 1 month after Dose 2 and 1 month after Dose 3, respectively. Dependent on the different IgG GMR assumptions, it was estimated that the study had a power of at least 85% when redefining study success to show NI in at least 47 (out of 60 total primary) NI assessments. Thereby, NI of 20vPnC to 13vPnC for percentages of participants with the predefined IgG concentration results for a serotype was considered to be met if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages was greater than –10%. NI of 20vPnC to 13vPnC for serotype-specific IgG GMCs for a serotype as considered to be met if the lower bound of the 2-sided 95% CI for the GMR (20vPnC/13vPnC) was greater than 0.5.

This sample size was considered suitable to also have sufficient power for all NI tests for the (coprimary) concomitant immunogenicity objective, as well as for the primary safety objective.

Randomisation

All eligible participants were planned to be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC. Allocation of participants to vaccine groups was planned to proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]).

The site personnel (study coordinator or specified designee) was planned to be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel were to be provided with a vaccine assignment, randomization number, and dispensable unit (DU) or container numbers when investigational product was supplied via the IRT system. The IRT system was supposed to provide a confirmation report containing the participant number, randomization number, and DU or container numbers assigned. The confirmation report was to be stored in the site's files.

Blinding (masking)

The study was planned to be participant- and investigator-blinded. Sponsor personnel and investigators involved in evaluating participant data in the primary study population were planned to be blinded to vaccine assignment until the analysis at the completion of the primary study population. Laboratory personnel performing the assays were planned to remain blinded until all assays were completed and assay results finalized. Standard proceedings for blind breaking during study conduct were put in place with the study protocol.

Statistical methods

Unless otherwise stated, the descriptive statistics for continuous variables were n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables (e.g. proportions) were the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

All baseline characteristics including demographic data, medical history and participants' disposition and compliance were planned to be analysed in descriptive manner. Subset analyses were planned to be done in descriptive manner, separately by sex and in countries where sufficient numbers were present for the critical safety and immunogenicity endpoints.

In general, standard statistical methodology for reporting all safety data was planned to be used. Details regarding the local tolerance and safety data analyses had been prespecified in the SAP.

Analysis sets

For purposes of analysis, the following participant populations were to be defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Dose 2 evaluable immunogenicity	Any participants who 1. Are eligible and randomized, 2. Are within the protocol-defined age window (ie, 42-112 days of age, inclusive) on the day of Dose 1, 3. Receive the first 2 vaccinations to which they are randomized, 4. Have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 2, and 5. Have no other major protocol deviations as determined by the clinician.

Population	Description
	The Dose 2 evaluable immunogenicity population will be the primary analysis population for the pneumococcal immunogenicity results from the blood collected before Dose 3. The statistical analysis of concomitant immunogenicity results 1 month after Dose 2 will be primarily based on the Dose 2 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines with the first 2 doses. Participants will be grouped as randomized in the immunogenicity analysis.
Dose 3 evaluable immunogenicity	Any participants who 1. Are eligible and randomized, 2. Are within the protocol-defined age window (ie, 42-112 days of age, inclusive) on the day of Dose 1, 3. Receive all 3 vaccinations as randomized, with Dose 3 received within the protocol-defined window (ie, 335-386 days of age, inclusive), 4. Have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 3, and 5. Have no other major protocol deviations as determined by the clinician. The Dose 3 evaluable immunogenicity population will be the primary analysis population for pneumococcal immunogenicity results after Dose 3. The statistical analysis of concomitant immunogenicity results 1 month after Dose 3 will be primarily based on the Dose 3 evaluable immunogenicity populations restricted to those who also receive the appropriate concomitant vaccines at the Dose 3 visit. Participants will be grouped according to their randomized vaccine in the immunogenicity analysis.
All-available immunogenicity	All randomized participants who receive at least 1 dose of the investigational product with at least 1 valid immunogenicity result. Participants will be grouped according to their randomized vaccine in the immunogenicity analysis.

Population	Description
Safety	All participants who receive at least 1 dose of the investigational product and have safety data assessed after any dose. Participants will be grouped according to the vaccine as administered in the safety analysis. Safety data after Dose 3 will be summarized for participants in the safety population who receive Dose 3 with safety follow-up after Dose 3.

For the Dose 2 and Dose 3 evaluable immunogenicity population definitions, the blood collection window has been expanded by 1 extra day before and 14 days after the protocol-specified blood collection window of 28 to 42 days defined in the protocol, for consistency with established rules in the 13vPnC development program.

The major protocol deviations were to be determined by clinical review or medical monitor. A major protocol deviation was a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with a suspected decrease in potency of the vaccine. The sponsor's clinician was to identify those participants with major protocol deviations before any unblinded analysis.

It was planned that if there were less than a 10% difference in the total number of participants between the all-available and evaluable immunogenicity population, only the evaluable immunogenicity population was to be used for the analysis of immunogenicity results.

Immunogenicity analyses

The estimands to evaluate the immunogenicity objectives for NI were planned to be based on evaluable populations. These estimands were supposed to estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimand addressed the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance was considered likely to diminish the observed difference between the 2 groups.

Empirical Reverse Cumulative Distribution Curves (RCDCs) were to be plotted as a step function of proportion of participants with assay results equal to or exceeding a specified value over the full range of the observed assay results.

For immunogenicity results of IgG concentrations, OPA titres, and the antibody levels of the concomitant vaccines, geometric means (GMs) were to be computed along with associated 95% CIs. The GMs and the 95% CIs were planned to be calculated as the means and the CIs of the assay results on the natural log scale and then exponentiating the results. Two-sided 95% CIs were to be calculated based on the t-distribution.

Where appropriate, geometric mean ratios (GMRs) and their 2-sided 95% CIs were to be derived by calculating differences in means (20vPnC – 13vPnC) and CIs on the natural log scale of the concentrations/titres and then exponentiating the results. Two-sided 95% CIs were to be calculated based on the t-distribution (allowing for unequal variances).

Geometric mean fold rises (GMFRs) were planned to be calculated as the mean of the difference of antibody levels (later result minus earlier result) on the natural log scale and exponentiating the results. The associated 2-sided 95% CIs were to be computed by exponentiating the CIs using Student's t-distribution for the mean difference on the natural log scale.

The exact 95% CI for binary endpoints for each group were to be computed using the F distribution (Clopper-Pearson). The 95% CI for the between-group difference for binary endpoints were planned to be calculated using the Miettinen and Nurminen method.

Primary immunogenicity endpoints analysis

1) For the *percentage of participants with pneumococcal IgG concentrations above a prespecified threshold at 1 month after Dose 2*, hypothesis testing was planned to be used to assess the NI of 20vPnC to 13vPnC. The null hypothesis (H0A) for a serotype was

   H_{0A}: $\pi_{20vPnC} - \pi_{13vPnC} \leq -10\%$,

with a 10% margin for NI, where

- π_{20vPnC} is the percentage of participants achieving the predefined IgG antibody concentration for the serotype from the 20vPnC group 1 month after Dose 2;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in 13vPnC, π_{13vPnC} is the percentage of participants achieving the predefined IgG concentration for the serotype from the 13vPnC group 1 month after Dose 2;
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, π_{13vPnC} is the percentage of participants achieving the predefined IgG concentration for the serotype with the lowest percentage among the 13 matched serotypes from the 13vPnC group 1 month after Dose 2, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

The null hypothesis (H_{0A}) was to be rejected, and NI of 20vPnC to 13vPnC for the percentage of participants with a predefined IgG concentration for a serotype was to be declared if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages was greater than –10%.

2) For the *pneumococcal IgG GMCs 1 month after Dose 2* hypothesis testing was planned to assess the NI of 20vPnC to 13vPnC. The null hypothesis (H0B) for a serotype was

   H_{0B}: $\ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$

where ln(0.5) corresponds to a 2-fold margin for NI and

- $\ln(\mu_{20vPnC})$ is the natural log of the geometric mean IgG concentration in the 20vPnC group for that serotype 1 month after Dose 2;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration in the 13vPnC group 1 month after Dose 2;

If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group 1 month after Dose 2, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

3) A similar testing framework was set up to evaluate NI for *pneumococcal IgG GMCs 1 month after Dose 3*. The null hypothesis (H0C) for a serotype was

H_{0C}: $\ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$

The null hypotheses H_{0B} and H_{0C} were to be rejected, and NI of 20vPnC to 13vPnC for the pneumococcal serotype-specific IgG GMC was to be declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC group to the 13vPnC group for the serotype was greater than 0.5 (2-fold NI margin).

4) For the *percentage of participants with antibody levels above prespecified levels for concomitant vaccine antigen at 1 month after Dose 3*, hypothesis testing was planned to assess the NI of the 20vPnC group to the 13vPnC group. For each of the applicable concomitant vaccine antigens (diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib), the null hypothesis was:

   H_{0C}: $\pi_{20vPnC} - \pi_{13vPnC} \leq -10\%$

where

- 10% is the margin for NI.
- π_{20vPnC} is the percentage of participants with a prespecified antibody level to the specific concomitant vaccine antigen at 1 month after Dose 3 in the 20vPnC group.
- π_{13vPnC} is the percentage of participants with a prespecified antibody level to the specific concomitant vaccine antigen at 1 month after Dose 3 in the 13vPnC group.

The null hypothesis was to be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, was greater than –10%.

For the GMCs of Antibody Levels to concomitant vaccine antigens 1 month after

Dose 3, hypothesis testing was planned to assess the NI of the 20vPnC group to the 13vPnC group. For each of the applicable concomitant vaccine antigens, the null hypothesis was:

H_{0D}: $\ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$

where

- $\ln(0.5)$ corresponds to a 2-fold margin for NI.
- $\ln(\mu_{20vPnC})$ is the natural log of the GMCs for antibody levels to the specific concomitant vaccine at 1 month after Dose 3 in the 20vPnC group.
- $\ln(\mu_{13vPnC})$ is the natural log of the GMCs for antibody levels to the specific concomitant vaccine at 1 month after Dose 3 in the 13vPnC group.

The null hypothesis (H_{0D}) testing for NI was to be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the concomitant antibody GMR (20vPnC over 13vPnC) is greater than 0.5 (2-fold NI margin).

Overall, the primary pneumococcal immunogenicity objectives were considered achieved if NI of the immune response induced by 20vPnC compared to 13vPnC based on both percentages of participants with predefined IgG levels and IgG GMCs at 1 month after Dose 2, as well as the IgG GMCs at 1 month after Dose 3, was established for all 20 serotypes, a total of 60 NI evaluations.

Therefore, the overall type I error rate for the primary immunogenicity assessment of the pneumococcal immune response of 20vPnC 1 month after Dose 3 was supposed to be controlled at the 0.05 level.

The primary concomitant immunogenicity objective was considered met if NI is achieved for each concomitant vaccine antigen. Therefore, the type I error rate for the concomitant immunogenicity assessment was supposed to be controlled at the 0.05 level.

Secondary and further immunogenicity endpoints analysis

The following endpoints were planned to be analysed as secondary/additional endpoints using standard statistical methodology, not involving hypothesis testing (for NI):

- Participants with predefined pneumococcal IgG concentrations 1 month after Dose 3
- OPA Titres 1 Month After Dose 2 and 1 Month After Dose 3
- Fold Change of IgG Concentrations From Before Dose 3 to 1 Month After Dose 3
- Participants With Prespecified Antibody Levels to Each Concomitant Vaccine Antigen at 1 Month After Dose 2
- Participants With Predefined Pneumococcal IgG Concentrations Before Dose 1 and Before Dose 2
- IgG Concentrations Before Dose 1 and Before Dose 2
- Fold Change of IgG Concentrations
- Participants With a ≥4-Fold Rise in IgG Concentrations
- Fold Change of OPA Titres
- Participants With a ≥4-Fold Rise in OPA Titres
- Participants With Pneumococcal OPA Titres ≥ LLOQ
- IgG Concentrations and Pneumococcal OPA Titres for Serotypes 15C and 6C
- Participants With Alternative Prespecified Antibody Levels to Hib at 1 Month After Dose 2 and 1 Month After Dose 3
- Antibody Levels to Concomitant Vaccine Antigens at 1 Month After Dose 2 and 1 Month After Dose 3
- Participants With Prespecified Antibody Levels to Measles, Mumps, Rubella, and Varicella Vaccine Antigens 1 Month After Dose 3

Results

Participant flow

Table 5. Disposition of All Participants – All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	**13vPnC n[a] (%)**	**Total n[a] (%)**
Randomized[b]	603 (100.0)	604 (100.0)	1207 (100.0)
Not vaccinated	2 (0.3)	1 (0.2)	3 (0.2)
Vaccinated			
Dose 1	601 (99.7)	603 (99.8)	1204 (99.8)
Dose 2	593 (98.3)	598 (99.0)	1191 (98.7)
Dose 3	588 (97.5)	594 (98.3)	1182 (97.9)
Completed 1-month follow-up after Dose 2	591 (98.0)	598 (99.0)	1189 (98.5)
Completed 1-month follow-up after Dose 3	583 (96.7)	590 (97.7)	1173 (97.2)
Completed all visits per protocol	583 (96.7)	590 (97.7)	1173 (97.2)
Total withdrawn	20 (3.3)	14 (2.3)	34 (2.8)
Withdrawn before Dose 1	2 (0.3)	1 (0.2)	3 (0.2)
Withdrawn after Dose 1 and before 1-month follow-up after Dose 2	10 (1.7)	5 (0.8)	15 (1.2)
Withdrawn after 1-month follow-up after Dose 2 and before Dose 3	3 (0.5)	4 (0.7)	7 (0.6)
Withdrawn after Dose 3 and before 1-month follow-up after Dose 3	5 (0.8)	4 (0.7)	9 (0.7)
Reason for withdrawal			
Withdrawal by parent/guardian	7 (1.2)	5 (0.8)	12 (1.0)
Lost to follow-up	5 (0.8)	4 (0.7)	9 (0.7)
No Longer meets eligibility criteria	3 (0.5)	3 (0.5)	6 (0.5)
Adverse event	3 (0.5)	0	3 (0.2)
Protocol deviation	2 (0.3)	1 (0.2)	3 (0.2)
Other	0	1 (0.2)	1 (0.0)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.

Table 6. Vaccine Administration – All Randomized Participants

Vaccine (as Administered)	Vaccine Group (as Randomized) 20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	N=603	N=604	N=1207
Not vaccinated[c]	2 (0.3)	1 (0.2)	3 (0.2)
Dose 1[d]	N=601	N=603	N=1204
20vPnC or 13vPnC	601 (100.0)	603 (100.0)	1204 (100.0)
DTPa-HBV-IPV/Hib	601 (100.0)	603 (100.0)	1204 (100.0)
Dose 2[d]	N=593	N=598	N=1191
20vPnC or 13vPnC	593 (100.0)	598 (100.0)	1191 (100.0)
DTPa-HBV-IPV/Hib	593 (100.0)	598 (100.0)	1191 (100.0)
Dose 3[d]	N=588	N=594	N=1182
20vPnC or 13vPnC	588 (100.0)	594 (100.0)	1182 (100.0)
DTPa-HBV-IPV/Hib	587 (99.8)	593 (99.8)	1180 (99.8)
MMR[e]	505 (85.9)	514 (86.5)	1019 (86.2)
Varicella[e]	503 (85.5)	513 (86.4)	1016 (86.0)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations for the "not vaccinated" row.
c. Not vaccinated with 20vPnC or 13vPnC.
d. N = number of participants who received the specified dose. This value is the denominator for the percentage calculations for the specified dose.
e. Some sites may not have administered MMR and varicella vaccines to the participants at Dose 3 due to local practice/recommendations, in which case these vaccines were considered nonstudy vaccines.

Compliance With Intervention - Immunogenicity Blood Samples

Table 7. Immunogenicity Blood Samples Drawn – All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Received Dose 1[b]	N=601	N=603	N=1204
Blood sample drawn before Dose 1[c]	214 (35.6)	205 (34.0)	419 (34.8)
Received Dose 2[d]	N=593	N=598	N=1191
Blood sample drawn before Dose 2[c]	212 (35.8)	200 (33.4)	412 (34.6)
Blood sample drawn 1 month after Dose 2	568 (95.8)	565 (94.5)	1133 (95.1)
<28 Days	7 (1.2)	5 (0.8)	12 (1.0)
28 to 42 Days[e]	546 (92.1)	541 (90.5)	1087 (91.3)
>42 Days	15 (2.5)	19 (3.2)	34 (2.9)
Blood sample not obtained at 1 month after Dose 2	25 (4.2)	33 (5.5)	58 (4.9)
Received Dose 3[f]	N=588	N=594	N=1182
Blood sample drawn before Dose 3	566 (96.3)	579 (97.5)	1145 (96.9)
Blood sample drawn 1 month after Dose 3	556 (94.6)	564 (94.9)	1120 (94.8)
<28 Days	3 (0.5)	4 (0.7)	7 (0.6)
28 to 42 Days[e]	523 (88.9)	522 (87.9)	1045 (88.4)
>42 Days	30 (5.1)	38 (6.4)	68 (5.8)
Blood sample not obtained at 1 month after Dose 3	32 (5.4)	30 (5.1)	62 (5.2)

a. n = Number of participants with the specified characteristic.
b. The values in this row are the denominators for the percentage calculations for the "blood sample drawn before Dose 1" row.
c. Only a subset of participants (participants at certain investigator sites) had blood drawn for exploratory immunogenicity assessments prior to Dose 1 and prior to Dose 2.
d. The values in this row are the denominators for the percentage calculations for the "blood sample drawn before Dose 2" row, the "blood sample drawn 1 month after Dose 2" row and associated time frames.
e. Protocol-specified time frame.
f. The values in this row are the denominators for the percentage calculations for the "blood sample drawn before Dose 3" row, the "blood sample drawn 1 month after Dose 3" row and associated time frames.

Recruitment

The study was conducted at 59 sites: 2 sites in Australia, 2 sites in Belgium, 7 sites in the Czech Republic, 1 site in Denmark, 5 sites in Estonia, 10 sites in Finland, 5 sites in Italy, 1 site in Netherlands, 3 sites in Norway, 16 sites in Poland ad 7 sites in Slovakia.

First subject first visit: 09 September 2020, Last subject last visit: 22 April 2022

Conduct of the study

Protocol amendments

There were 2 amendments to the original study protocol (11 February 2020). The most relevant change introduced with the Amendment 1 (13 April July 2020), was addition of serotype-specific IgG concentrations 1 month after Dose 3 to the primary objectives, based on regulatory agency feedback,

Additional changes included modification of the concomitant administration of MMR and varicella vaccines to allow greater flexibility with local practices, clarification to indicate that a fourth dose of Infanrix hexa is not permitted in the study and several editorial updates made to be consistent with other phase 3 studies of 20vPnC. With Amendment 2 (18 June 2021) non-inferiority of IgG GMCs and the percentage of participants with predefined thresholds after second infant doses were added as primary immunogenicity objectives, and the objective for IgG percentage of participants with predefined thresholds after the toddler dose was moved from primary to the secondary objective, based on Scientific Advice from the CHMP. The statistical sections for these objectives were updated accordingly.

Protocol deviations

Protocol Deviation Category Subcategory	Vaccine Group (as Randomized) 20vPnC (N[a]=603) n[b] (%)	 13vPnC (N[a]=604) n[b] (%)	 Total (N[a]=1207) n[b] (%)
Inclusion/exclusion	2 (0.3)	1 (0.2)	3 (0.2)
Entered into study but did not meet inclusion criterion or met exclusion criterion	2 (0.3)	1 (0.2)	3 (0.2)
Investigational product	2 (0.3)	0	2 (0.2)
Incorrect vaccine administered	2 (0.3)	0	2 (0.2)
Procedures/tests	0	1 (0.2)	1 (0.1)
Procedure/Test not performed per protocol	0	1 (0.2)	1 (0.1)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

b. n = Number of participants with the specified characteristic.

There were 51 PDs specifically attributed to COVID-19 that consisted of visits which occurred outside the protocol-specified window (all nonimportant) which was expected given the ongoing COVID-19 pandemic. Regulatory guidance was followed during this trial.

Baseline data

Table 8. Demographic Characteristics – Safety Population

Netherlands	7 (1.2)	7 (1.2)	14 (1.2)
Norway	7 (1.2)	7 (1.2)	14 (1.2)
Poland	274 (45.6)	272 (45.1)	546 (45.3)
Slovakia	17 (2.8)	17 (2.8)	34 (2.8)
Age at Dose 1 (days)			
Mean (SD)	69.2 (17.76)	69.7 (18.32)	69.4 (18.04)
Median	68.0	68.0	68.0
Min, max	(43, 112)	(43, 112)	(43, 112)
Age at Dose 3 (days)			
Mean (SD)	370.3 (16.13)	370.5 (15.94)	370.4 (16.03)
Median	371.0	371.0	371.0
Min, max	(335, 450)	(335, 468)	(335, 468)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

Numbers analysed

Table 9. Analysis population

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	**13vPnC n[a] (%)**	**Total n[a] (%)**
Randomized[b]	603 (100.0)	604 (100.0)	1207 (100.0)
Vaccinated	601 (99.7)	603 (99.8)	1204 (99.8)
Safety population	601 (99.7)	603 (99.8)	1204 (99.8)
Excluded from safety population	2 (0.3)	1 (0.2)	3 (0.2)
Reason for exclusion[c]			
Did not receive any vaccination	2 (0.3)	1 (0.2)	3 (0.2)
All-available immunogenicity population	591 (98.0)	596 (98.7)	1187 (98.3)
Excluded from all-available immunogenicity population	12 (2.0)	8 (1.3)	20 (1.7)
Reason for exclusion[c]			
Did not receive any vaccination	2 (0.3)	1 (0.2)	3 (0.2)
Did not have at least 1 valid immunogenicity result	10 (1.7)	7 (1.2)	17 (1.4)
Dose 2 evaluable immunogenicity population	567 (94.0)	562 (93.0)	1129 (93.5)
Excluded from Dose 2 evaluable immunogenicity population	36 (6.0)	42 (7.0)	78 (6.5)
Reason for exclusion[c]			
Not eligible at randomization/dose[d]	1 (0.2)	1 (0.2)	2 (0.2)
Did not receive first 2 vaccinations as randomized	9 (1.5)	5 (0.8)	14 (1.2)
Did not have blood draw 1 month after Dose 2	25 (4.1)	33 (5.5)	58 (4.8)

No blood drawn within 27 to 56 days after Dose 2	0	3 (0.5)	3 (0.2)
Did not have at least 1 valid immunogenicity result at 1 month after Dose 2	1 (0.2)	0	1 (0.0)
Dose 3 evaluable immunogenicity population	497 (82.4)	504 (83.4)	1001 (82.9)
Excluded from Dose 3 evaluable immunogenicity population	106 (17.6)	100 (16.6)	206 (17.1)
Reason for exclusion[c]			
Not eligible at randomization/dose[d]	1 (0.2)	1 (0.2)	2 (0.2)
Did not receive all 3 vaccinations as randomized	14 (2.3)	9 (1.5)	23 (1.9)
Not 335 to 386 days of age at Dose 3	52 (8.6)	49 (8.1)	101 (8.4)
Did not have blood draw 1 month after Dose 3	29 (4.8)	26 (4.3)	55 (4.6)
No blood drawn within 27 to 56 days after Dose 3	7 (1.2)	14 (2.3)	21 (1.7)
Did not have at least 1 valid immunogenicity result at 1 month after Dose 3	1 (0.2)	1 (0.2)	2 (0.2)
Other major protocol deviation	2 (0.3)	0	2 (0.2)

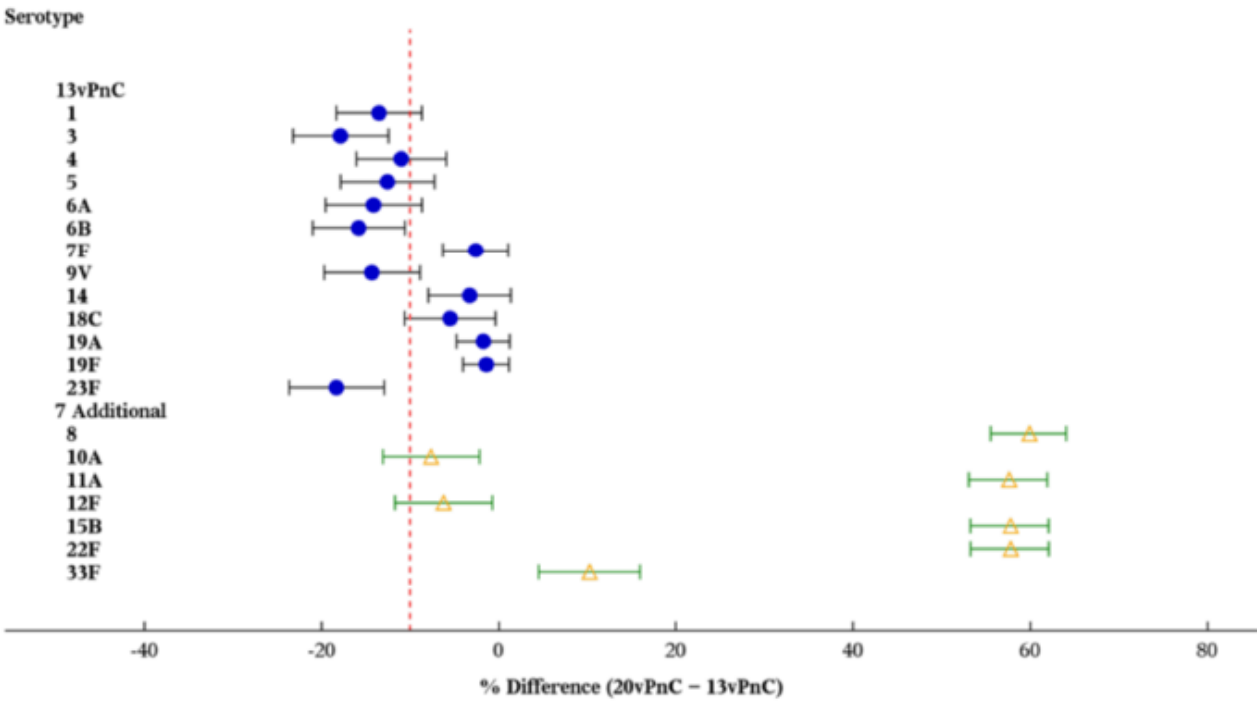
a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Reasons are listed in hierarchical order. Each excluded participant is counted only once under the first applicable reason.
d. Violation of any protocol defined inclusion or exclusion criteria.

Outcomes and estimation

1. Percentages of Participants With Predefined IgG Concentrations After Dose 2 (last infant dose) (primary objective)

Figure 10. Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Predefined Pneumococcal IgG Levels – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

Forest Plot of Differences (20vPnC − 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Predefined Pneumococcal IgG Levels – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population



Abbreviation: IgG = immunoglobulin G.
Note: The predefined pneumococcal IgG level for all serotypes is ≥0.35 µg/mL, except for the following: serotype 5 ≥0.23 µg/mL; serotype 6B ≥0.10 µg/mL; and serotype 19A ≥0.12 µg/mL.
Note: For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 6B (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.
Note: 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

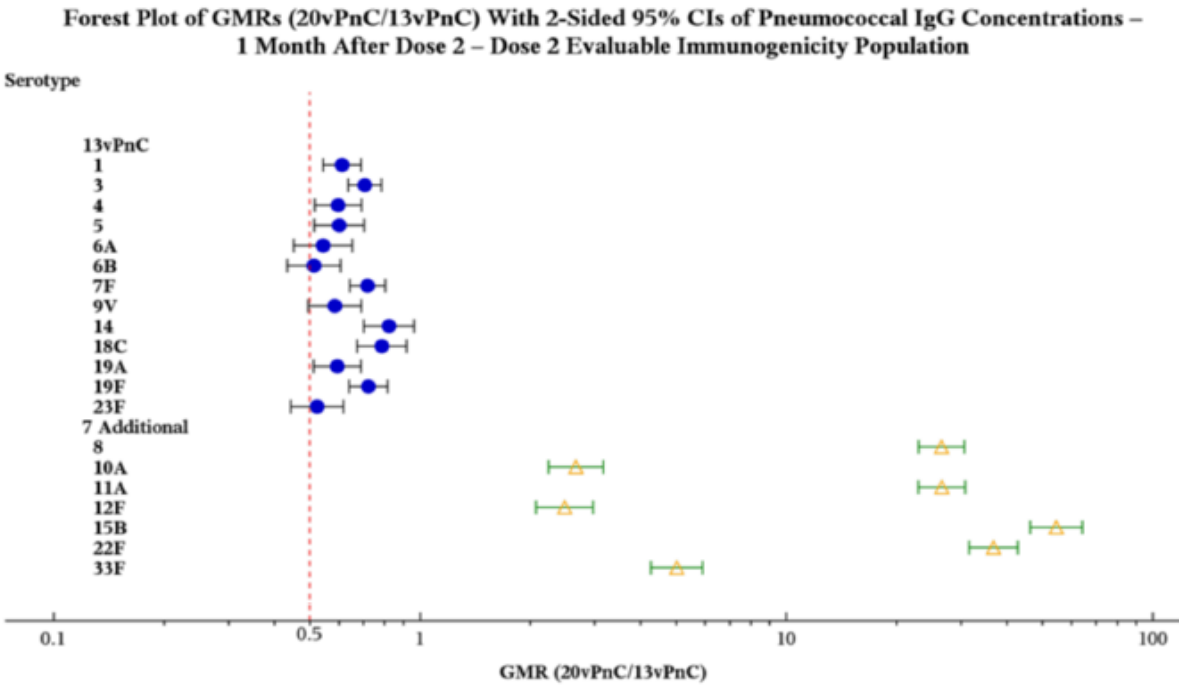
Table 11. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	566	400	70.7	(66.7, 74.4)	562	473	84.2	(80.9, 87.1)	-13.5	(-18.3, -8.7)
3	≥0.35 µg/mL	566	328	58.0	(53.8, 62.1)	562	426	75.8	(72.0, 79.3)	-17.9	(-23.2, -12.4)
4	≥0.35 µg/mL	566	388	68.6	(64.5, 72.4)	562	447	79.5	(76.0, 82.8)	-11.0	(-16.0, -5.9)
5	≥0.23 µg/mL	566	359	63.4	(59.3, 67.4)	562	427	76.0	(72.2, 79.5)	-12.6	(-17.8, -7.2)
6A	≥0.35 µg/mL	566	337	59.5	(55.4, 63.6)	562	414	73.7	(69.8, 77.3)	-14.1	(-19.5, -8.6)
6B	≥0.10 µg/mL	564	117	20.7	(17.5, 24.3)	561	205	36.5	(32.5, 40.7)	-15.8	(-21.0, -10.6)
7F	≥0.35 µg/mL	566	496	87.6	(84.6, 90.2)	562	507	90.2	(87.5, 92.5)	-2.6	(-6.3, 1.1)
9V	≥0.35 µg/mL	566	341	60.2	(56.1, 64.3)	562	419	74.6	(70.7, 78.1)	-14.3	(-19.7, -8.9)
14	≥0.35 µg/mL	565	444	78.6	(75.0, 81.9)	562	460	81.9	(78.4, 85.0)	-3.3	(-7.9, 1.4)
18C	≥0.35 µg/mL	566	402	71.0	(67.1, 74.7)	562	430	76.5	(72.8, 80.0)	-5.5	(-10.6, -0.4)
19A	≥0.12 µg/mL	566	522	92.2	(89.7, 94.3)	562	528	94.0	(91.6, 95.8)	-1.7	(-4.8, 1.3)
19F	≥0.35 µg/mL	566	534	94.3	(92.1, 96.1)	562	538	95.7	(93.7, 97.2)	-1.4	(-4.0, 1.2)
23F	≥0.35 µg/mL	566	133	23.5	(20.1, 27.2)	562	235	41.8	(37.7, 46.0)	-18.3	(-23.6, -12.9)
7 Additional											
8	≥0.35 µg/mL	567	547	96.5	(94.6, 97.8)	561	205	36.5	(32.5, 40.7)	59.9	(55.6, 64.1)
10A	≥0.35 µg/mL	567	164	28.9	(25.2, 32.8)	561	205	36.5	(32.5, 40.7)	-7.6	(-13.1, -2.1)
11A	≥0.35 µg/mL	567	534	94.2	(91.9, 96.0)	561	205	36.5	(32.5, 40.7)	57.6	(53.1, 61.9)
12F	≥0.35 µg/mL	567	172	30.3	(26.6, 34.3)	561	205	36.5	(32.5, 40.7)	-6.2	(-11.7, -0.7)
15B	≥0.35 µg/mL	566	534	94.3	(92.1, 96.1)	561	205	36.5	(32.5, 40.7)	57.8	(53.3, 62.1)
22F	≥0.35 µg/mL	567	535	94.4	(92.1, 96.1)	561	205	36.5	(32.5, 40.7)	57.8	(53.3, 62.1)
33F	≥0.35 µg/mL	566	265	46.8	(42.6, 51.0)	561	205	36.5	(32.5, 40.7)	10.3	(4.5, 16.0)

Abbreviation: IgG = immunoglobulin G.
a. For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 6B (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.
b. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
c. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

2. Pneumococcal Serotype-Specific IgG GMCs After Dose 2 (last infant dose) (primary objective)

Figure 12. Forest Plot of GMRs (20vPnC/13vPnC) With 2–Sided 95% CIs of Pneumococcal IgG Concentrations – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population



Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: For the 13vPnC serotypes, the compared results are from the corresponding serotype in 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 6B (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.
Note: GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC – 13vPnC) and the corresponding CIs (based on the Student t distribution).

Table 13. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC[a]			20vPnC/13vPnC	
Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[a]	(95% CI[d])
13vPnC								
1	566	0.57	(0.52, 0.62)	562	0.93	(0.86, 1.01)	0.61	(0.54, 0.69)
3	566	0.41	(0.38, 0.45)	562	0.58	(0.54, 0.63)	0.71	(0.64, 0.79)
4	566	0.55	(0.50, 0.61)	562	0.92	(0.83, 1.02)	0.60	(0.52, 0.69)
5	566	0.34	(0.30, 0.38)	562	0.56	(0.50, 0.62)	0.60	(0.52, 0.70)
6A	566	0.45	(0.40, 0.52)	562	0.84	(0.73, 0.95)	0.54	(0.45, 0.65)
6B	564	0.03	(0.03, 0.04)	561	0.06	(0.05, 0.07)	0.51	(0.43, 0.61)
7F	566	1.02	(0.94, 1.10)	562	1.41	(1.30, 1.53)	0.72	(0.64, 0.80)
9V	566	0.45	(0.40, 0.51)	562	0.77	(0.68, 0.87)	0.59	(0.50, 0.69)
14	565	1.05	(0.94, 1.18)	562	1.28	(1.14, 1.43)	0.82	(0.70, 0.96)
18C	566	0.69	(0.62, 0.77)	562	0.87	(0.78, 0.98)	0.79	(0.67, 0.92)
19A	566	0.67	(0.61, 0.74)	562	1.13	(1.01, 1.26)	0.59	(0.51, 0.69)
19F	566	2.21	(2.04, 2.40)	562	3.06	(2.80, 3.34)	0.72	(0.64, 0.82)
23F	566	0.13	(0.12, 0.15)	562	0.25	(0.22, 0.28)	0.52	(0.44, 0.62)
7 Additional								
8	567	1.62	(1.51, 1.74)	561	0.06	(0.05, 0.07)	26.55	(22.98, 30.67)
10A	567	0.16	(0.14, 0.18)	561	0.06	(0.05, 0.07)	2.67	(2.25, 3.17)
11A	567	1.62	(1.50, 1.75)	561	0.06	(0.05, 0.07)	26.60	(22.95, 30.82)
12F	567	0.15	(0.13, 0.17)	561	0.06	(0.05, 0.07)	2.48	(2.08, 2.97)
15B	566	3.33	(3.00, 3.70)	561	0.06	(0.05, 0.07)	54.60	(46.35, 64.30)
22F	567	2.25	(2.06, 2.45)	561	0.06	(0.05, 0.07)	36.80	(31.57, 42.89)
33F	566	0.31	(0.28, 0.34)	561	0.06	(0.05, 0.07)	5.03	(4.27, 5.92)

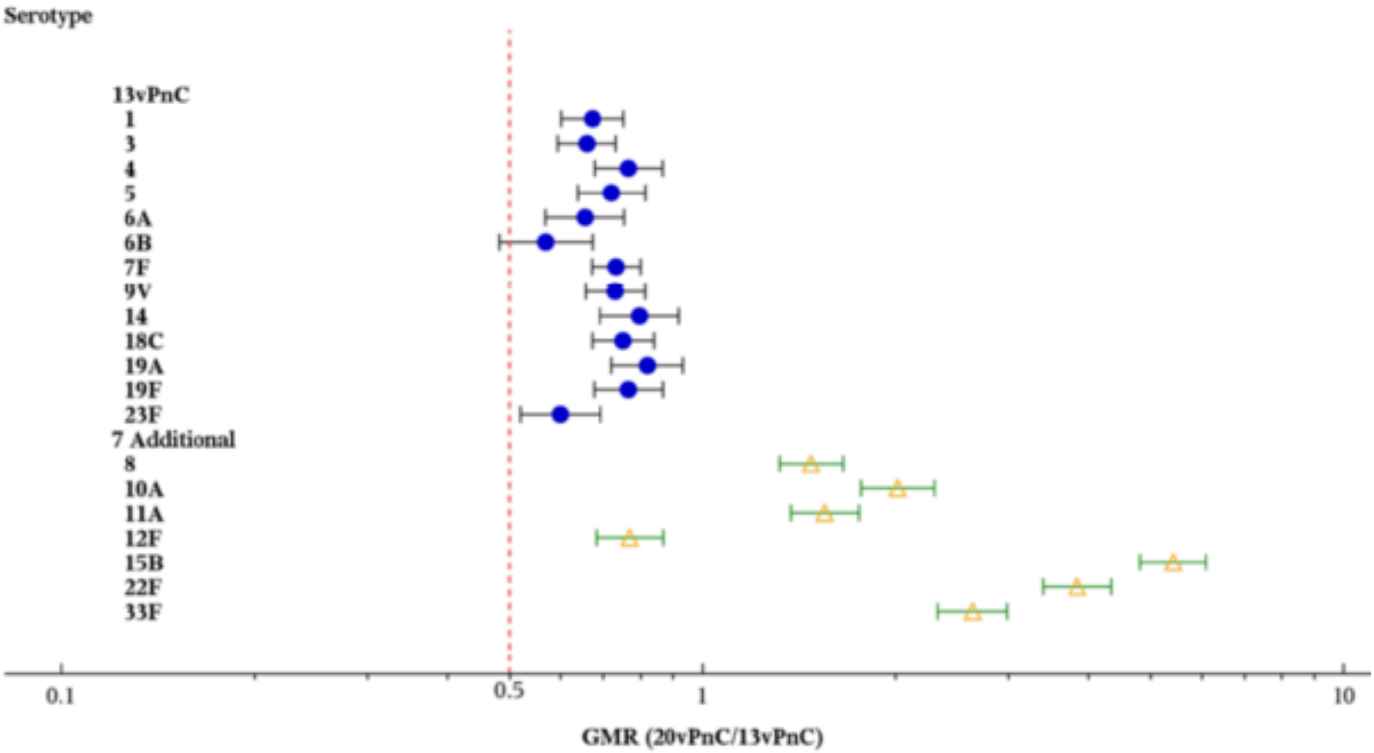
Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. For the 13vPnC serotypes, the GMCs are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the GMCs are from serotype 6B (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.
b. n = Number of participants with valid IgG concentrations for the specified serotype.
c. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
d. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations

Table 14. Pneumococcal IgG GMCs and GMRs for the 7 Additional Serotypes Using the Corresponding GMCs in the 13vPnC Group – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

IG

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR[c]	(95% CI[c])
7 Additional								
8	567	1.62	(1.51, 1.74)	561	0.02	(0.02, 0.02)	91.19	(81.19, 102.43)
10A	567	0.16	(0.14, 0.18)	562	0.02	(0.02, 0.02)	8.38	(7.20, 9.76)
11A	567	1.62	(1.50, 1.75)	562	0.02	(0.02, 0.02)	74.53	(65.99, 84.17)
12F	567	0.15	(0.13, 0.17)	562	0.01	(0.01, 0.01)	17.91	(15.66, 20.48)
15B	566	3.33	(3.00, 3.70)	562	0.04	(0.04, 0.04)	83.56	(71.77, 97.28)
22F	567	2.25	(2.06, 2.45)	562	0.01	(0.01, 0.01)	337.08	(287.86, 394.72)
33F	566	0.31	(0.28, 0.34)	562	0.03	(0.02, 0.03)	12.19	(10.55, 14.09)

Forest Plot of GMRs (20vPnC/13vPnC) With 2-Sided 95% CIs of Pneumococcal IgG Concentrations – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population



Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: For the 13vPnC serotypes, the compared results are from the corresponding serotype in 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 5 (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.
Note: GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC – 13vPnC) and the corresponding CIs (based on the Student t distribution).

Table 15.

Pneumococcal IgG GMCs and GMRs for the 7 Additional Serotypes Using the Corresponding GMCs in the 13vPnC Group – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR[c]	(95% CI[c])
7 Additional								
8	495	3.57	(3.32, 3.83)	501	0.03	(0.03, 0.03)	113.37	(100.05, 128.46)
10A	495	4.86	(4.41, 5.36)	502	0.01	(0.01, 0.01)	423.02	(372.25, 480.73)
11A	495	3.74	(3.44, 4.07)	502	0.02	(0.01, 0.02)	229.66	(199.06, 264.96)
12F	495	1.86	(1.71, 2.01)	502	0.01	(0.01, 0.01)	224.31	(204.73, 245.76)
15B	495	13.09	(12.10, 14.15)	502	0.02	(0.02, 0.03)	527.47	(465.44, 597.77)
22F	495	9.27	(8.52, 10.08)	502	0.00	(0.00, 0.00)	2193.09	(1908.27, 2520.41)
33F	495	6.37	(5.83, 6.95)	501	0.01	(0.01, 0.01)	530.53	(470.15, 598.66)
9V	494	3.68	(3.42, 3.97)	502	5.04	(4.67, 5.43)	0.73	(0.66, 0.81)
14	493	4.52	(4.08, 5.00)	501	5.66	(5.12, 6.26)	0.80	(0.69, 0.92)
18C	494	2.71	(2.52, 2.93)	502	3.61	(3.33, 3.91)	0.75	(0.67, 0.84)
19A	494	4.51	(4.11, 4.94)	502	5.49	(5.02, 6.01)	0.82	(0.72, 0.93)
19F	494	6.19	(5.68, 6.75)	502	8.08	(7.40, 8.83)	0.77	(0.68, 0.87)
23F	494	2.64	(2.40, 2.91)	502	4.40	(3.95, 4.90)	0.60	(0.52, 0.69)
7 Additional								
8	495	3.57	(3.32, 3.83)	502	2.41	(2.21, 2.64)	1.48	(1.32, 1.66)
10A	495	4.86	(4.41, 5.36)	502	2.41	(2.21, 2.64)	2.02	(1.77, 2.30)
11A	495	3.74	(3.44, 4.07)	502	2.41	(2.21, 2.64)	1.55	(1.37, 1.75)
12F	495	1.86	(1.71, 2.01)	502	2.41	(2.21, 2.64)	0.77	(0.68, 0.87)
15B	495	13.09	(12.10, 14.15)	502	2.41	(2.21, 2.64)	5.42	(4.82, 6.10)
22F	495	9.27	(8.52, 10.08)	502	2.41	(2.21, 2.64)	3.84	(3.40, 4.34)
33F	495	6.37	(5.83, 6.95)	502	2.41	(2.21, 2.64)	2.64	(2.33, 2.99)

4. Percentage of Participants With Predefined Serotype-Specific IgG Concentrat

Table 15 bis

Pneumococcal IgG GMCs and GMRs for the 7 Additional Serotypes Using the Corresponding GMCs in the 13vPnC Group – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR[c]	(95% CI[c])
7 Additional								
8	495	3.57	(3.32, 3.83)	501	0.03	(0.03, 0.03)	113.37	(100.05, 128.46)
10A	495	4.86	(4.41, 5.36)	502	0.01	(0.01, 0.01)	423.02	(372.25, 480.73)
11A	495	3.74	(3.44, 4.07)	502	0.02	(0.01, 0.02)	229.66	(199.06, 264.96)
12F	495	1.86	(1.71, 2.01)	502	0.01	(0.01, 0.01)	224.31	(204.73, 245.76)
15B	495	13.09	(12.10, 14.15)	502	0.02	(0.02, 0.03)	527.47	(465.44, 597.77)
22F	495	9.27	(8.52, 10.08)	502	0.00	(0.00, 0.00)	2193.09	(1908.27, 2520.41)
33F	495	6.37	(5.83, 6.95)	501	0.01	(0.01, 0.01)	530.53	(470.15, 598.66)

Table 16. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	494	480	97.2	(95.3, 98.4)	502	493	98.2	(96.6, 99.2)	-1.0	(-3.1, 0.9)
3	≥0.35 µg/mL	494	408	82.6	(79.0, 85.8)	502	468	93.2	(90.7, 95.3)	-10.6	(-14.7, -6.7)
4	≥0.35 µg/mL	494	490	99.2	(97.9, 99.8)	502	498	99.2	(98.0, 99.8)	0.0	(-1.4, 1.3)
5	≥0.23 µg/mL	494	486	98.4	(96.8, 99.3)	502	492	98.0	(96.4, 99.0)	0.4	(-1.4, 2.2)
6A	≥0.35 µg/mL	494	488	98.8	(97.4, 99.6)	501	495	98.8	(97.4, 99.6)	0.0	(-1.6, 1.5)
6B	≥0.10 µg/mL	494	486	98.4	(96.8, 99.3)	501	489	97.6	(95.9, 98.8)	0.8	(-1.1, 2.7)
7F	≥0.35 µg/mL	494	492	99.6	(98.5, 100.0)	502	502	100.0	(99.3, 100.0)	-0.4	(-1.5, 0.4)
9V	≥0.35 µg/mL	494	490	99.2	(97.9, 99.8)	502	496	98.8	(97.4, 99.6)	0.4	(-1.0, 1.9)
14	≥0.35 µg/mL	493	476	96.6	(94.5, 98.0)	501	491	98.0	(96.4, 99.0)	-1.5	(-3.7, 0.6)
18C	≥0.35 µg/mL	494	490	99.2	(97.9, 99.8)	502	493	98.2	(96.6, 99.2)	1.0	(-0.5, 2.7)
19A	>0.12 µg/mL	494	492	99.6	(98.5, 100.0)	502	500	99.6	(98.6, 100.0)	0.0	(-1.1, 1.1)
19F	≥0.35 µg/mL	494	492	99.6	(98.5, 100.0)	502	499	99.4	(98.3, 99.9)	0.2	(-0.9, 1.4)
23F	≥0.35 µg/mL	494	476	96.4	(94.3, 97.8)	502	488	97.2	(95.4, 98.5)	-0.9	(-3.2, 1.4)
7 Additional											
8	≥0.35 µg/mL	495	491	99.2	(97.9, 99.8)	502	488	97.2	(95.4, 98.5)	2.0	(0.4, 3.9)
10A	≥0.35 µg/mL	495	484	97.8	(96.1, 98.9)	502	488	97.2	(95.4, 98.5)	0.6	(-1.5, 2.7)
11A	≥0.35 µg/mL	495	487	98.4	(96.8, 99.3)	502	488	97.2	(95.4, 98.5)	1.2	(-0.7, 3.2)
12F	≥0.35 µg/mL	495	478	96.6	(94.6, 98.0)	502	488	97.2	(95.4, 98.5)	-0.6	(-2.9, 1.6)
15B	≥0.35 µg/mL	495	492	99.4	(98.2, 99.9)	502	488	97.2	(95.4, 98.5)	2.2	(0.7, 4.1)
22F	>0.35 µg/mL	495	491	99.2	(97.9, 99.8)	502	488	97.2	(95.4, 98.5)	2.0	(0.4, 3.9)
33F	≥0.35 µg/mL	495	488	98.6	(97.1, 99.4)	502	488	97.2	(95.4, 98.5)	1.4	(-0.4, 3.4)

Additional endpoints

1. IgG GMFRs From Before to 1 Month After Dose 3, GMFRs From 1 Month After Dose 2 to 1 Month After Dose 3, and GMCs at Each Timepoint

Table 17. Pneumococcal IgG GMFRs – Evaluable Immunogenicity Population

					Sampling Time Point					
					Time Point 1		Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
13vPnC										
1	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.57	(0.52, 0.62)	0.12	(0.11, 0.13)	0.2	(0.2, 0.2)
			13vPnC	550	0.93	(0.86, 1.02)	0.18	(0.17, 0.20)	0.2	(0.2, 0.2)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.56	(0.51, 0.61)	1.71	(1.58, 1.84)	3.0	(2.8, 3.4)
			13vPnC	478	0.90	(0.82, 0.99)	2.53	(2.33, 2.75)	2.8	(2.6, 3.1)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.12	(0.11, 0.13)	1.69	(1.57, 1.83)	13.9	(12.7, 15.3)
			13vPnC	495	0.18	(0.17, 0.19)	2.52	(2.32, 2.74)	13.9	(12.8, 15.1)
3	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.41	(0.38, 0.44)	0.05	(0.05, 0.06)	0.1	(0.1, 0.1)
			13vPnC	550	0.58	(0.54, 0.63)	0.07	(0.07, 0.08)	0.1	(0.1, 0.1)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.41	(0.38, 0.44)	0.72	(0.66, 0.77)	1.8	(1.6, 1.9)
			13vPnC	478	0.60	(0.55, 0.64)	1.09	(1.01, 1.17)	1.8	(1.7, 2.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.05	(0.05, 0.06)	0.71	(0.66, 0.77)	13.7	(12.4, 15.1)
			13vPnC	495	0.07	(0.07, 0.08)	1.09	(1.01, 1.17)	15.2	(13.9, 16.7)
4	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.55	(0.49, 0.61)	0.14	(0.13, 0.15)	0.3	(0.2, 0.3)
			13vPnC	550	0.93	(0.84, 1.04)	0.20	(0.18, 0.21)	0.2	(0.2, 0.2)

	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.53	(0.47, 0.59)	4.11	(3.77, 4.49)	7.8	(6.9, 8.8)
			13vPnC	478	0.90	(0.80, 1.01)	5.34	(4.88, 5.84)	5.9	(5.3, 6.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.14	(0.13, 0.15)	4.10	(3.77, 4.47)	29.8	(27.0, 32.9)
			13vPnC	495	0.19	(0.18, 0.21)	5.34	(4.90, 5.83)	27.7	(25.0, 30.6)
5	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.33	(0.30, 0.37)	0.13	(0.12, 0.14)	0.4	(0.4, 0.4)
			13vPnC	550	0.56	(0.50, 0.62)	0.18	(0.17, 0.20)	0.3	(0.3, 0.4)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.32	(0.29, 0.36)	1.72	(1.59, 1.87)	5.3	(4.8, 6.0)
			13vPnC	478	0.54	(0.48, 0.62)	2.43	(2.22, 2.66)	4.5	(4.0, 5.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.12	(0.11, 0.13)	1.73	(1.59, 1.88)	14.0	(12.9, 15.2)
			13vPnC	495	0.18	(0.16, 0.19)	2.40	(2.19, 2.63)	13.6	(12.6, 14.7)
6A	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.44	(0.39, 0.51)	0.29	(0.26, 0.32)	0.7	(0.6, 0.7)
			13vPnC	549	0.84	(0.74, 0.96)	0.42	(0.38, 0.46)	0.5	(0.5, 0.5)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.44	(0.38, 0.51)	7.69	(6.97, 8.47)	17.4	(15.2, 20.1)
			13vPnC	477	0.80	(0.70, 0.92)	11.88	(10.68, 13.22)	14.8	(12.9, 17.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.29	(0.26, 0.32)	7.71	(7.00, 8.49)	26.9	(24.2, 30.0)
			13vPnC	493	0.41	(0.37, 0.46)	11.89	(10.72, 13.19)	28.7	(25.9, 31.7)
6B	1 Month after Dose 2	Before Dose 3	20vPnC	544	0.03	(0.03, 0.03)	0.07	(0.06, 0.08)	2.3	(2.0, 2.5)
			13vPnC	548	0.06	(0.05, 0.07)	0.12	(0.10, 0.13)	1.9	(1.7, 2.1)

	1 Month after Dose 2	1 Month after Dose 3	20vPnC	479	0.03	(0.03, 0.04)	2.58	(2.30, 2.89)	82.6	(72.6, 94.1)
			13vPnC	477	0.06	(0.05, 0.07)	4.65	(4.09, 5.29)	78.7	(68.3, 90.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	481	0.07	(0.06, 0.08)	2.64	(2.36, 2.96)	36.8	(33.3, 40.6)
			13vPnC	493	0.12	(0.10, 0.13)	4.64	(4.09, 5.26)	40.2	(36.8, 44.0)
7F	1 Month after Dose 2	Before Dose 3	20vPnC	547	1.01	(0.93, 1.09)	0.42	(0.39, 0.45)	0.4	(0.4, 0.4)
			13vPnC	550	1.41	(1.30, 1.53)	0.55	(0.51, 0.59)	0.4	(0.4, 0.4)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.98	(0.90, 1.07)	3.60	(3.38, 3.83)	3.7	(3.4, 4.0)
			13vPnC	478	1.37	(1.26, 1.50)	4.96	(4.65, 5.29)	3.6	(3.3, 3.9)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.42	(0.39, 0.45)	3.60	(3.38, 3.83)	8.5	(7.9, 9.2)
			13vPnC	495	0.53	(0.49, 0.57)	4.92	(4.62, 5.24)	9.3	(8.6, 10.0)
9V	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.44	(0.39, 0.50)	0.17	(0.15, 0.18)	0.4	(0.3, 0.4)
			13vPnC	550	0.77	(0.69, 0.87)	0.26	(0.24, 0.28)	0.3	(0.3, 0.4)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.43	(0.38, 0.49)	3.67	(3.40, 3.96)	8.5	(7.4, 9.7)
			13vPnC	478	0.75	(0.66, 0.85)	5.05	(4.67, 5.46)	6.7	(5.9, 7.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.16	(0.15, 0.18)	3.66	(3.40, 3.95)	22.5	(20.4, 24.7)
			13vPnC	495	0.25	(0.23, 0.27)	5.02	(4.65, 5.42)	19.9	(18.3, 21.6)
14	1 Month after Dose 2	Before Dose 3	20vPnC	545	1.04	(0.93, 1.17)	0.47	(0.42, 0.52)	0.4	(0.4, 0.5)
			13vPnC	550	1.26	(1.13, 1.42)	0.67	(0.60, 0.75)	0.5	(0.5, 0.6)

	1 Month after Dose 2	1 Month after Dose 3	20vPnC	480	1.05	(0.93, 1.19)	4.49	(4.05, 4.98)	4.3	(3.7, 5.0)
			13vPnC	477	1.26	(1.12, 1.43)	5.66	(5.11, 6.27)	4.5	(3.8, 5.2)
	Before Dose 3	1 Month after Dose 3	20vPnC	480	0.47	(0.42, 0.53)	4.55	(4.11, 5.04)	9.7	(8.7, 10.8)
			13vPnC	494	0.67	(0.59, 0.75)	5.65	(5.11, 6.25)	8.4	(7.6, 9.4)
18C	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.68	(0.61, 0.76)	0.17	(0.16, 0.18)	0.3	(0.2, 0.3)
			13vPnC	550	0.87	(0.78, 0.98)	0.21	(0.20, 0.23)	0.2	(0.2, 0.3)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.68	(0.61, 0.77)	2.71	(2.51, 2.93)	4.0	(3.5, 4.5)
			13vPnC	478	0.87	(0.77, 0.98)	3.62	(3.33, 3.93)	4.2	(3.7, 4.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.17	(0.16, 0.19)	2.70	(2.50, 2.91)	15.8	(14.5, 17.1)
			13vPnC	495	0.21	(0.19, 0.23)	3.59	(3.31, 3.90)	17.0	(15.7, 18.4)
19A	1 Month after Dose 2	Before Dose 3	20vPnC	546	0.66	(0.59, 0.73)	0.11	(0.10, 0.13)	0.2	(0.2, 0.2)
			13vPnC	550	1.13	(1.01, 1.26)	0.14	(0.12, 0.15)	0.1	(0.1, 0.1)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.64	(0.58, 0.72)	4.49	(4.09, 4.94)	7.0	(6.2, 7.9)
			13vPnC	478	1.15	(1.02, 1.30)	5.52	(5.04, 6.05)	4.8	(4.2, 5.4)
	Before Dose 3	1 Month after Dose 3	20vPnC	481	0.11	(0.10, 0.13)	4.48	(4.08, 4.92)	39.3	(34.6, 44.7)
			13vPnC	495	0.13	(0.12, 0.15)	5.48	(5.01, 5.99)	40.7	(36.4, 45.5)
19F	1 Month after Dose 2	Before Dose 3	20vPnC	547	2.18	(2.00, 2.37)	0.30	(0.27, 0.32)	0.1	(0.1, 0.1)
			13vPnC	550	3.03	(2.77, 3.32)	0.39	(0.36, 0.42)	0.1	(0.1, 0.1)

	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	2.19	(2.00, 2.40)	6.20	(5.68, 6.77)	2.8	(2.5, 3.2)
			13vPnC	478	2.98	(2.70, 3.28)	8.14	(7.44, 8.90)	2.7	(2.5, 3.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.30	(0.28, 0.33)	6.16	(5.64, 6.72)	20.5	(18.4, 22.9)
			13vPnC	495	0.38	(0.35, 0.41)	8.14	(7.45, 8.89)	21.4	(19.4, 23.7)
23F	1 Month after Dose 2	Before Dose 3	20vPnC	547	0.13	(0.11, 0.14)	0.08	(0.07, 0.09)	0.6	(0.6, 0.7)
			13vPnC	550	0.25	(0.22, 0.28)	0.12	(0.10, 0.13)	0.5	(0.4, 0.5)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.13	(0.11, 0.14)	2.66	(2.41, 2.93)	20.9	(18.5, 23.5)
			13vPnC	478	0.24	(0.21, 0.27)	4.44	(3.98, 4.95)	18.8	(16.6, 21.3)
	Before Dose 3	1 Month after Dose 3	20vPnC	482	0.08	(0.07, 0.09)	2.63	(2.38, 2.90)	32.3	(29.2, 35.7)
			13vPnC	495	0.11	(0.10, 0.13)	4.37	(3.93, 4.87)	38.3	(34.7, 42.4)
7 Additional										
8	1 Month after Dose 2	Before Dose 3	20vPnC	548	1.61	(1.49, 1.73)	0.28	(0.26, 0.30)	0.2	(0.2, 0.2)
			13vPnC	548	0.02	(0.02, 0.02)	0.02	(0.02, 0.03)	1.3	(1.2, 1.5)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	1.62	(1.50, 1.74)	3.56	(3.31, 3.84)	2.2	(2.0, 2.4)
			13vPnC	476	0.02	(0.02, 0.02)	0.03	(0.03, 0.04)	1.8	(1.5, 2.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	483	0.28	(0.26, 0.30)	3.54	(3.30, 3.81)	12.7	(11.6, 13.9)
			13vPnC	493	0.02	(0.02, 0.02)	0.03	(0.03, 0.03)	1.4	(1.3, 1.5)
10A	1 Month after Dose 2	Before Dose 3	20vPnC	549	0.16	(0.14, 0.18)	0.34	(0.30, 0.37)	2.1	(1.9, 2.4)

			13vPnC	550	0.02	(0.02, 0.02)	0.01	(0.01, 0.01)	0.6	(0.5, 0.6)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.15	(0.13, 0.17)	4.87	(4.41, 5.39)	31.9	(27.9, 36.5)
			13vPnC	478	0.02	(0.02, 0.02)	0.01	(0.01, 0.01)	0.6	(0.5, 0.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.33	(0.29, 0.37)	4.81	(4.35, 5.31)	14.8	(13.3, 16.4)
			13vPnC	495	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.1	(1.0, 1.2)
11A	1 Month after Dose 2	Before Dose 3	20vPnC	549	1.62	(1.50, 1.75)	0.27	(0.25, 0.30)	0.2	(0.2, 0.2)
			13vPnC	550	0.02	(0.02, 0.02)	0.01	(0.01, 0.02)	0.7	(0.6, 0.8)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	1.63	(1.50, 1.78)	3.73	(3.42, 4.07)	2.3	(2.0, 2.6)
			13vPnC	478	0.02	(0.02, 0.02)	0.02	(0.01, 0.02)	0.8	(0.7, 0.9)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.27	(0.25, 0.29)	3.72	(3.42, 4.05)	13.8	(12.4, 15.3)
			13vPnC	495	0.01	(0.01, 0.02)	0.02	(0.01, 0.02)	1.1	(1.0, 1.2)
12F	1 Month after Dose 2	Before Dose 3	20vPnC	549	0.15	(0.13, 0.17)	0.11	(0.10, 0.12)	0.8	(0.7, 0.8)
			13vPnC	550	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(0.9, 1.0)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.14	(0.13, 0.17)	1.85	(1.71, 2.01)	12.8	(11.1, 14.8)
			13vPnC	478	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(0.9, 1.0)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.11	(0.10, 0.12)	1.85	(1.71, 2.01)	16.5	(15.0, 18.0)
			13vPnC	495	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(1.0, 1.1)
15B	1 Month after Dose 2	Before Dose 3	20vPnC	548	3.31	(2.97, 3.68)	0.96	(0.88, 1.05)	0.3	(0.3, 0.3)

			13vPnC	550	0.04	(0.04, 0.04)	0.02	(0.02, 0.02)	0.5	(0.4, 0.6)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	480	3.25	(2.89, 3.66)	13.06	(12.05, 14.15)	4.0	(3.5, 4.6)
			13vPnC	478	0.04	(0.03, 0.04)	0.02	(0.02, 0.03)	0.6	(0.5, 0.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.97	(0.89, 1.07)	13.07	(12.08, 14.15)	13.4	(11.9, 15.1)
			13vPnC	495	0.02	(0.02, 0.02)	0.02	(0.02, 0.03)	1.3	(1.2, 1.4)
22F	1 Month after Dose 2	Before Dose 3	20vPnC	549	2.19	(2.01, 2.40)	0.72	(0.67, 0.79)	0.3	(0.3, 0.4)
			13vPnC	550	0.01	(0.01, 0.01)	0.00	(0.00, 0.00)	0.5	(0.5, 0.6)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	2.19	(1.99, 2.41)	9.23	(8.47, 10.06)	4.2	(3.8, 4.7)
			13vPnC	478	0.01	(0.01, 0.01)	0.00	(0.00, 0.00)	0.6	(0.5, 0.7)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.72	(0.66, 0.78)	9.21	(8.46, 10.02)	12.8	(11.5, 14.3)
			13vPnC	495	0.00	(0.00, 0.00)	0.00	(0.00, 0.00)	1.3	(1.1, 1.4)
33F	1 Month after Dose 2	Before Dose 3	20vPnC	548	0.30	(0.27, 0.33)	0.51	(0.46, 0.57)	1.7	(1.5, 1.9)
			13vPnC	549	0.03	(0.02, 0.03)	0.01	(0.01, 0.01)	0.4	(0.4, 0.5)
	1 Month after Dose 2	1 Month after Dose 3	20vPnC	481	0.29	(0.26, 0.33)	6.33	(5.79, 6.93)	21.6	(19.0, 24.5)
			13vPnC	477	0.03	(0.02, 0.03)	0.01	(0.01, 0.01)	0.5	(0.4, 0.5)
	Before Dose 3	1 Month after Dose 3	20vPnC	484	0.49	(0.44, 0.55)	6.33	(5.79, 6.92)	12.9	(11.6, 14.3)
			13vPnC	494	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.1	(1.0, 1.2)

2. OPA GMTs 1 month After Dose 2 and Dose 3

Table 18. **Pneumococcal OPA GMTs – 1 Month after Dose 2 – Dose 2 Evaluable Immunogenicity Population**

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	113	14	(12, 16)	107	23	(19, 28)
3	114	31	(26, 36)	102	40	(34, 47)
4	113	333	(270, 413)	112	391	(314, 486)
5	112	21	(18, 23)	102	27	(23, 31)
6A	112	347	(273, 441)	100	409	(318, 527)
6B	106	54	(42, 71)	97	105	(76, 144)
7F	114	858	(736, 1000)	111	895	(781, 1027)
9V	116	233	(182, 298)	112	285	(228, 358)
14	111	287	(215, 383)	101	360	(264, 489)
18C	114	588	(467, 741)	112	719	(590, 876)
19A	115	57	(43, 75)	111	91	(69, 121)
19F	114	97	(81, 116)	103	117	(94, 146)
23F	105	59	(42, 84)	108	68	(48, 96)
7 Additional						
8	103	164	(133, 203)	118	17	(15, 18)
10A	109	855	(610, 1199)	115	39	(34, 44)
11A	105	327	(253, 423)	116	49	(47, 51)
12F	96	4788	(3779, 6067)	116	26	(23, 28)
15B	104	846	(605, 1183)	117	17	(15, 19)
22F	104	4444	(3666, 5386)	117	10	(9, 11)
33F	102	2373	(1759, 3202)	115	178	(163, 195)

Table 19. **Pneumococcal OPA GMTs – 1 Month after Dose 3 – Dose 3 Evaluable Immunogenicity Population**

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	104	54	(43, 69)	97	101	(79, 129)
3	105	99	(84, 117)	98	129	(111, 150)
4	99	904	(752, 1086)	100	992	(777, 1266)
5	106	60	(50, 72)	98	82	(66, 101)
6A	105	1101	(897, 1350)	96	1304	(1018, 1671)
6B	102	537	(408, 706)	96	864	(664, 1125)
7F	100	1811	(1553, 2112)	103	2197	(1905, 2533)
9V	97	3254	(2596, 4079)	99	4544	(3681, 5610)
14	105	738	(606, 899)	95	926	(751, 1142)
18C	98	1296	(1048, 1602)	102	1870	(1489, 2348)
19A	99	754	(627, 907)	100	707	(558, 896)
19F	105	183	(140, 237)	97	258	(192, 347)
23F	100	697	(530, 917)	101	975	(734, 1296)
7 Additional						
8	92	1398	(1088, 1796)	105	31	(25, 39)
10A	91	3403	(2600, 4455)	107	69	(52, 91)
11A	87	2966	(2212, 3978)	92	66	(51, 85)
12F	88	5501	(4499, 6725)	108	29	(25, 35)
15B	91	2676	(1948, 3677)	109	23	(18, 30)
22F	83	6523	(4848, 8777)	106	17	(13, 24)
33F	72	11315	(8107, 15794)	99	708	(545, 920)

3. Percentages of Participants With a ≥4 Fold Rise in IgG Concentrations From Before Dose 3 to 1 Month After Dose 3

For the 13 matched serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 74.2% (serotype 14) to 98.1% (serotype 6B) in the 20vPnC group and from 71.5% (serotype 14) to 98.2% (serotype 6B) in the 13vPnC group.

For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 83.5% (serotype 15B) to 95.5% (serotype 12F) in the 20vPnC group.

4. Percentage of participants with ≥4-fold rise in OPA titres from before Dose 3 to 1 month after Dose 3

For the 13 matched serotypes, the percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 3 ranged from 48.0% (serotype 7F) to 95.8 (serotype 4) in the 20vPnC group and from 63.8% (serotype 5) to 97.9% (serotype 18C) in the 13vPnC group.
For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 3 ranged from 47.0% (serotype 33F) to 92.2% (serotype 22F) in the 20vPnC group. As would be expected, there were very few participants with a ≥4-fold rise for the 7 additional serotypes in the 13vPnC group.

Concomitant immunogenicity objective

In study B7471012, concomitant vaccine responses were assessed on randomly selected serum subsets with sufficient sera volumes. The NI of the percentages of participants with prespecified antibody levels to diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens, and NI of the GMRs of antibody levels to MMR and varicella vaccine antigens between the 20vPnC group and the 13vPnC group at 1 month after dose 3 (age 12-13 months) were assessed (primary concomitant immunogenicity objectives). The NI criteria for these antigen assessments were the same as those used for the primary pneumococcal endpoints (2-fold criterion for a continuous endpoint and 10% criterion for a binary endpoint).

Table 20 **Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population**

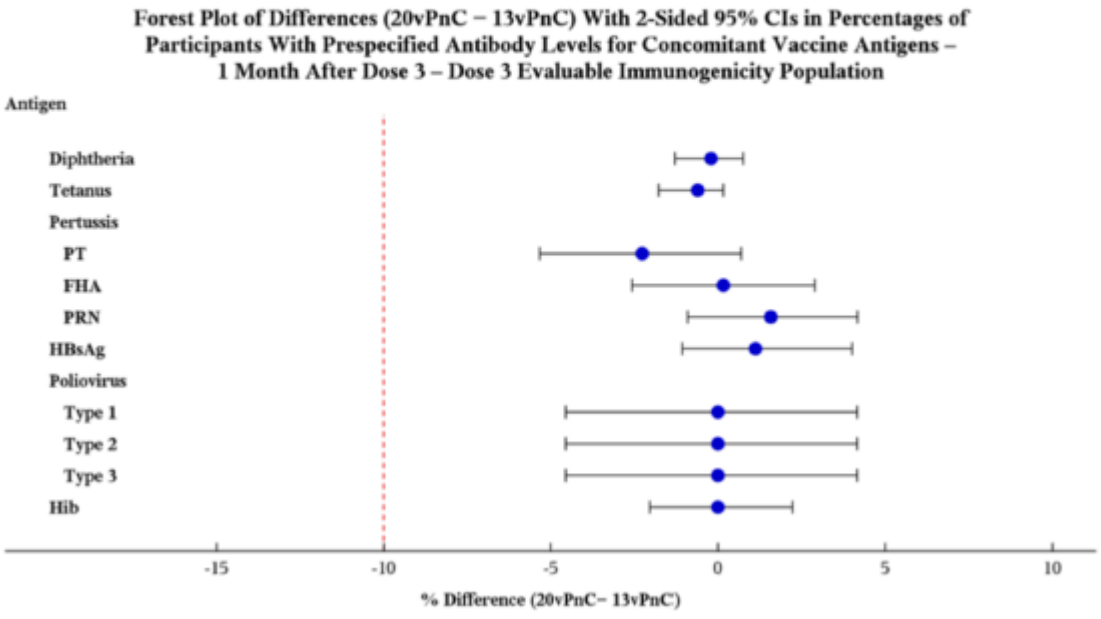


Table 21

Figure 6. Forest Plot of GMRs (20vPnC/13vPnC) With 2-Sided 95% CIs for Concomitant Vaccine Antigens – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

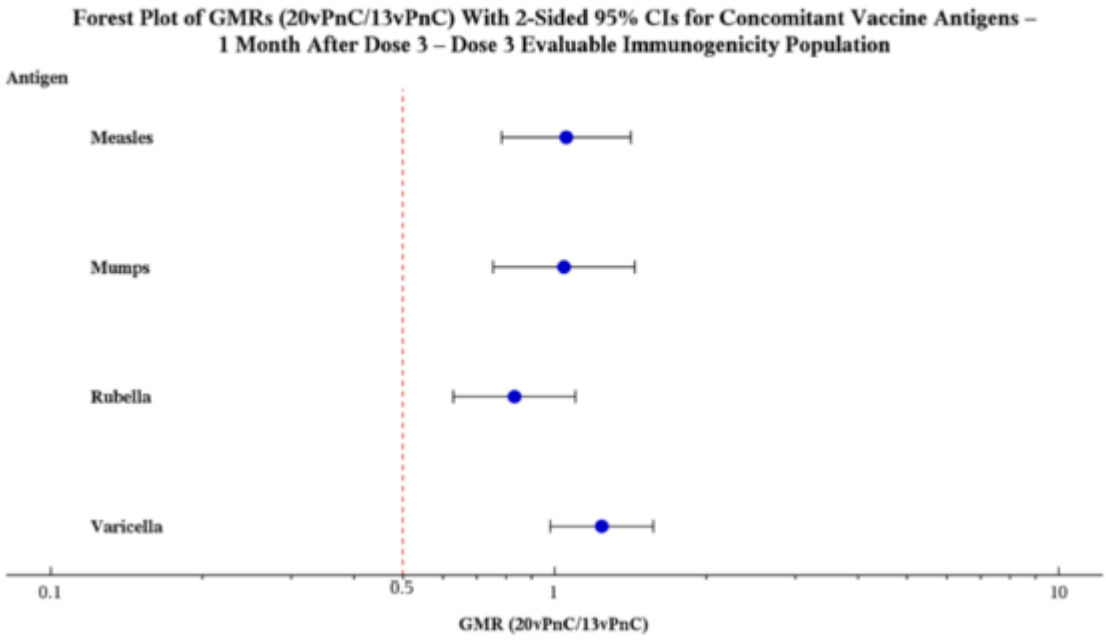


Table 22 **14.31. Concomitant Vaccine Antigens (Measles, Mumps, Rubella, and Varicella) GMs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population**

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Antigen (Units)	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])	GMR[c]	(95% CI[c])
Measles (AU/mL)	128	228.63	(186.34, 280.52)	132	216.72	(174.92, 268.52)	1.05	(0.79, 1.42)
Mumps (AU/mL)	128	36.81	(29.12, 46.54)	133	35.25	(28.14, 44.17)	1.04	(0.76, 1.44)
Rubella (IU/mL)	128	31.81	(25.54, 39.62)	132	38.20	(32.10, 45.45)	0.83	(0.63, 1.10)
Varicella (mIU/mL)	128	195.58	(165.14, 231.62)	132	157.60	(133.57, 185.95)	1.24	(0.98, 1.57)

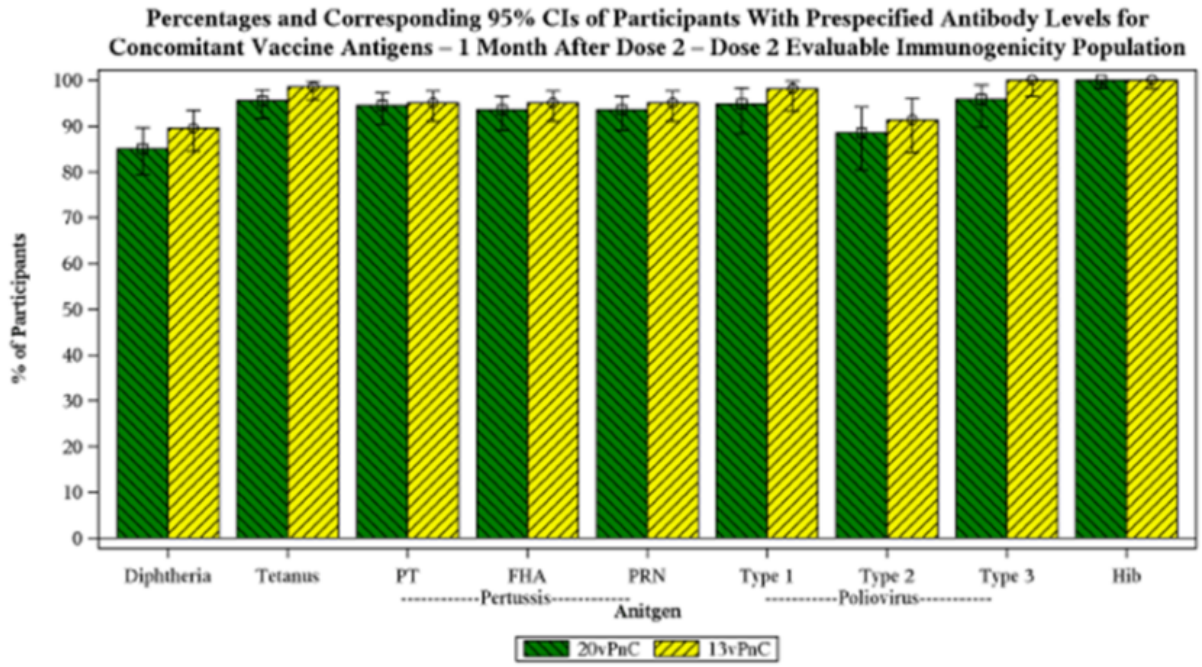
Abbreviations: AU/mL = arbitrary units per milliliter; GM = geometric mean; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; mIU/mL = milli-international units per milliliter.
Note: For this table, the Dose 3 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with Dose 3.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Antibody concentrations to the measles, mumps, rubella, and varicella vaccine antigens were determined on subsets of participants who received the MMR and varicella vaccines.
a. n = Number of participants with valid assay results for the specified antigen.
b. GMs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the concentrations (20vPnC – 13vPnC) and the corresponding CIs (based on the Student t distribution).

Table 23 **Concomitant Vaccine Antigens (Diphtheria, Tetanus, Pertussis, Poliovirus, *H. influenzae* type b, Hepatitis B) GMs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population**

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Antigen (Units)	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])	GMR[c]	(95% CI[c])
Diphtheria (IU/mL)	494	1.59	(1.49, 1.70)	498	2.09	(1.95, 2.23)	0.76	(0.69, 0.84)
Tetanus (IU/mL)	494	3.10	(2.87, 3.35)	498	2.95	(2.73, 3.20)	1.05	(0.94, 1.17)
Pertussis (EU/mL)								
PT	494	115.59	(106.55, 125.40)	498	113.50	(105.12, 122.56)	1.02	(0.91, 1.14)
FHA	494	134.42	(126.17, 143.20)	498	129.04	(121.43, 137.12)	1.04	(0.95, 1.14)
PRN	494	199.37	(182.37, 217.95)	498	195.51	(177.87, 214.90)	1.02	(0.90, 1.16)
HBsAg (mIU/mL)	173	10749.5	(8856.4, 13047.4)	178	7594.2	(5915.3, 9749.6)	1.4	(1.0, 1.9)
Poliovirus (titer)								
Type 1	81	3110.4	(2457.9, 3936.1)	89	3118.9	(2485.4, 3913.8)	1.0	(0.7, 1.4)
Type 2	81	1429.8	(1062.0, 1924.9)	89	1972.5	(1629.2, 2388.2)	0.7	(0.5, 1.0)
Type 3	81	907.8	(833.6, 988.7)	89	928.6	(865.3, 996.5)	1.0	(0.9, 1.1)
Hib (µg/mL)	185	6.12	(4.91, 7.64)	169	6.39	(5.19, 7.88)	0.96	(0.71, 1.30)

Table 24

14.40. Percentages and Corresponding 95% CIs of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population



Abbreviation: PT = pertussis toxoid.

Note: The Dose 2 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with the first 2 doses.

Note: Antibody concentrations to the diphtheria, tetanus, pertussis, poliovirus, and Hib vaccine antigens were determined on sera collected 1 month after Dose 2 from randomly selected subsets of participants with sufficient sera volumes.

Note: The prespecified antibody thresholds for the concomitant vaccine antigens are: diphtheria and tetanus toxoids ≥0.1 IU/mL; PT ≥6.35 EU/mL; FHA ≥10.55 EU/mL; PRN ≥4.35 EU/mL; poliovirus strains (types 1, 2, and 3) ≥1:8; Hib ≥0.15 µg/mL. The prespecified antibody thresholds for the concomitant vaccine antigens PT, FHA, and PRN are the observed antipertussis antibody concentration achieved by 95% of participants receiving 13vPnC.

PFIZER CONFIDENTIAL SDTM Creation: 26AUG2022 (04:13) Source Data: adva Table Generation: 09SEP2022 (04:40)(Database snapshot date : 24AUG2022) Output File: ./B7471012_sec/B7471012_CSR/adva_f007_pcm_1md2_eval

Table 25

14.33. Concomitant Vaccine Antigens (Diphtheria, Tetanus, Pertussis, Poliovirus, *H. influenzae* type b) GMs – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Antigen (Units)	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])
Diphtheria (IU/mL)	200	0.32	(0.27, 0.37)	200	0.38	(0.33, 0.44)
Tetanus (IU/mL)	200	0.45	(0.40, 0.51)	200	0.48	(0.43, 0.54)
Pertussis (EU/mL)						
PT	200	34.95	(30.60, 39.92)	200	33.00	(28.97, 37.59)
FHA	200	35.02	(31.27, 39.22)	200	36.04	(32.60, 39.83)
PRN	200	40.94	(34.16, 49.05)	200	45.96	(38.43, 54.96)
Poliovirus (titer)						
Type 1	96	139.9	(102.5, 191.0)	104	167.4	(122.4, 229.1)
Type 2	96	73.1	(55.7, 95.9)	104	113.5	(84.1, 153.2)
Type 3	96	162.0	(120.3, 218.3)	104	240.0	(185.6, 310.2)
Hib (µg/mL)	207	0.54	(0.46, 0.63)	193	0.56	(0.47, 0.67)

Ancillary analyses

Following subgroup analyses were submitted:

- Pneumococcal IgG GMCs by Sex, 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population
- Pneumococcal IgG GMCs by Sex, 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population
- Comparison of the Percentage of Participants With Predefined Levels for Pneumococcal IgG Concentrations for Vaccine Serotypes, by Sex – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

The Applicant also provided the subgroup analyses by vaccine timing (2, 4, and 11–12 months versus 3, 5, and 11–12 months) for the primary pneumococcal immunogenicity endpoints. These data are provided for exploratory purposes, and it should be noted that the sample sizes of the subgroups are small, these analyses were not powered for noninferiority, and variables other than schedule, including country-specific factors, may be biasing the results. Therefore, conclusions based on these data should be approached with caution.

In general, the observed IgG GMCs 1 month after Dose 2 were numerically higher for all vaccine serotypes in both vaccine groups (20vPnC and 13vPnC) in the subgroup vaccinated at 3 and 5 months of age than those vaccinated at 2 and 4 months of age. However, the point estimates of the IgG GMRs (20vPnC/13vPnC) 1 month after Dose 2 were generally similar or slightly numerically higher in the subgroup vaccinated at 2 and 4 months of age.

There were trends for higher observed point estimates of the percentage of participants with predefined IgG concentrations 1 month after Dose 2 in the subgroup vaccinated at 3 and 5 months of age, for both 20vPnC and 13vPnC groups. However, there was no consistent trend in the percent difference (20vPnC – 13vPnC) between the subgroups based on vaccine timing.

The IgG GMCs and GMRs 1 month after Dose 3 were similar in the 2 subgroups regardless of infant vaccine timing.

In summary, although some numerical differences in the point estimates of the IgG responses 1 month after Dose 2 were observed between the 2 subgroups based on timing of infant vaccination, the trend did not persist after Dose 3, at completion of the vaccine series. The trend was observed in both 20vPnC and 13vPnC groups.

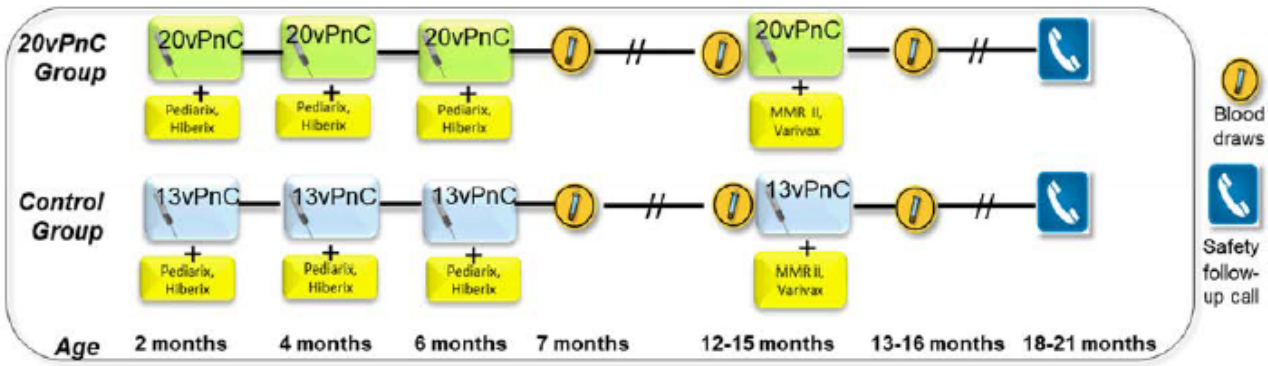
B7471011: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants (4-dose series)

Methods

B7471011 was a Phase 3, multicenter, randomized, active-controlled, double-blind trial conducted in infants born at >36 weeks of gestation and ≥42 to ≤98 days of age at the time of consent. The planned duration of study participation was approximately 16 to 19 months for each infant. The trial was performed at 107 sites in the US and Puerto Rico.

This trial was designed to provide NI comparisons of the 20vPnC immune responses with those of 13vPnC to infer effectiveness in infants when administered as a 4-dose series at 2, 4, 6, and 12-15 months of age. Immunogenicity data were also generated for key routine US paediatric vaccines (DTaP-HBV-IPV/Hib combination vaccine, Pediarix®; Hib vaccine, Hiberix®; MMR vaccine, M-M-R II; and varicella vaccine, Varivax®) given concomitantly with 20vPnC or 13vPnC.

Table 26. Study design B7471011



Visit 1 (Dose 1 Visit, Day 1): administration of Dose 1 (20vPnC or 13vPnC), followed by administration of concomitant vaccines

Visit 2 (Dose 2 Visit, 42 to 63 Days After Dose 1, ie, Study Day 43 Through Study Day 64) – administration of Dose 2 (20vPnC or 13vPnC), followed by administration of concomitant vaccines

Visit 3 (Dose 3 Visit, 42 to 63 Days After Dose 2) - administration of Dose 3 (20vPnC or 13vPnC), followed by administration of concomitant vaccines

Visit 4 (Dose 3 Follow-up Visit, 28 to 42 Days After Dose 3) – blood draw for immunogenicity

Visit 5 (Dose 4 Visit, 365 to 455 Days of Age) – collection of blood sample for immunogenicity prior to vaccination, administration of Dose 4 (20vPnC or 13vPnC) - blood draw for immunogenicity

Visit 6 (Dose 4 Follow-up Visit, 28 to 42 Days After Dose 4) - blood draw for immunogenicity

Visit 7 (Dose 4 6-Month Visit, 168 to 196 Days After Dose 4) – a telephone call 6 months after the last study vaccination (for safety assessment)

Study participants

Inclusion criteria

1. Male or female infants born at >36 weeks of gestation and 2 months of age (≥42 to ≤98 days) at the time of consent (the day of birth is considered day of life 1).
2. Participants whose parent(s)/legal guardian(s) are willing and able to comply with all scheduled visits, treatment plan, and other study procedures.
3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.
4. Expected to be available for the duration of the study and whose parents(s)/legal guardian can be contacted by telephone during study participation.
5. Participants whose parent(s)/legal guardian(s) is capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion criteria

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.
2. Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic- hyporesponsive episodes.
3. Major known congenital malformation or serious chronic disorder.
4. History of microbiologically proven invasive disease caused by *S pneumoniae.*
5. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.
6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
7. Congenital, functional, or surgical asplenia.
8. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

9. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
10. Prior receipt of diphtheria, tetanus, pertussis, poliomyelitis, and/or Hib vaccine.
11. Previous receipt of >1 dose of hepatitis B vaccine; or receipt of a single hepatitis B vaccine dose administered at >30 days old.
12. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.
13. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) since birth or planned receipt through the last planned blood draw in the study (Visit 5, 1 month after Dose 3).

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving investigational drug(s), investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation or intrauterine exposure to investigational vaccines. Participation in purely observational studies is acceptable.

Other Exclusions:

15. Children or grandchildren who are direct descendants of investigator site staff members or Pfizer employees who are directly involved in the conduct of the study.

Treatments

Participants were to be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively). Participants were to receive a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg at each vaccination visit (Doses 1, 2, 3, and 4 at Visits 1, 2, 3, and 5, respectively). Participants were to receive the same vaccine (20vPnC or 13vPnC) for all 4 doses.

Concomitant vaccines

Participants also received a dose of a DTaP-containing vaccine in combination with other antigens (including poliovirus and hepatitis B) (PEDIARIX) and a dose of a Hib vaccine (HIBERIX) at Visits 1, 2, and 3. MMR (M-M-RII) and varicella (VARIVAX) vaccines were administered concomitantly with 20vPnC or 13vPnC at Visit 5 with Dose 4. All concomitant vaccinations were administered into a limb other than the left leg (the site of 20vPnC or 13vPnC injection).

Other concomitant medications

The use of prophylactic antipyretic/pain medication, while permitted, was not recommended on the day of investigational product administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication was allowed.

Objectives

Primary objectives and estimands

Primary Safety Objective	Estimands
• To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentages of participants reporting SAEs up to 6 months after Dose 4 in each group • The percentages of participants reporting NDCMCs up to 6 months after Dose 4 in each group
Primary Pneumococcal Immunogenicity Objectives	**Estimands**
• To demonstrate that the percentages of participants with predefined serotype- specific IgG concentrations for the 13 serotypes in the 20vPnC group are non-inferior to the percentages for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC group and the 13vPnC group
• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are non-inferior to the lowest percentage among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined serotype-specific IgG concentrations, between the 20vPnC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC group
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are non-inferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group

• To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are non-inferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group
Primary Concomitant Immunogenicity Objective	Estimand
• To demonstrate that percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens when given with 20vPnC are non-inferior to the corresponding percentages when the antigens are given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3
Key Secondary Pneumococcal Immunogenicity Objectives	Estimands
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are non-inferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group
• To demonstrate that the serotype-specific IgG GMC for the 7 additional serotypes in the 20vPnC group are non-inferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group
Secondary Pneumococcal Immunogenicity Objective	Estimands
• To further describe the immunogenicity of 20vPnC	In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentages of participants with the predefined serotype-specific IgG concentration in each group In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group
Secondary Concomitant Immunogenicity Objectives	Estimands

• To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC • To demonstrate that GMCs to specific concomitant vaccine antigens when given with 20vPnC are non-inferior to the corresponding GMCs when the antigens are given with 13vPnC at 1 month after Dose 4	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with alternative prespecified antibody levels to Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3 • GMRs of antibody levels to measles, mumps, rubella, and varicella viruses from the 20vPnC group to the 13vPnC group at 1 month after Dose 4
Exploratory Concomitant Immunogenicity Objective	Estimands
• To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive the appropriate concomitant vaccines: • GMRs of the antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib from the 20vPnC group to the 13vPnC group at 1 month after Dose 3 • Differences in percentages of participants with prespecified antibody levels to measles, mumps, rubella, and varicella antigens 1 month after Dose 4 between the 20vPnC and the 13vPnC group

Outcomes/endpoints

Primary Pneumococcal Immunogenicity Endpoints

- Percentage of Participants With Predefined Pneumococcal Serotype-Specific IgG Concentration 1 Month After Dose 3
- Pneumococcal serotype-specific IgG concentration 1 month after Dose 4

Same assays and same reference concentrations were used in this study as in B7471012 study (see above).

Primary Concomitant Immunogenicity Endpoints

- Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) 1 month after Dose 3
- Antibody levels to HBsAg 1 month after Dose 3
- Antibody levels to poliovirus strains (types 1, 2, and 3) 1 month after Dose 3
- Antibody levels to Hib 1 month after Dose 3

Antibody concentrations to each concomitant vaccine were determined on sera collected 1 month after Dose 3 from a randomly selected subset of participants with sufficient sera volumes.

Antibody concentrations were classified based on the same prespecified antibody thresholds for the concomitant vaccine antigens, as used in the -012 study (see above).

Key Secondary Pneumococcal Immunogenicity Endpoints

- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 3

Secondary Pneumococcal Immunogenicity Endpoints

- Pneumococcal serotype-specific OPA titres 1 month after Dose 3, before Dose 4, and 1 month after Dose 4
- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4 and change from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4

OPA titres were determined on serum from randomly selected subsets of participants.

Secondary Concomitant Immunogenicity Endpoints

- Antibody levels to Hib 1 month after Dose 3
- Antibody levels to measles, mumps, rubella, and varicella viruses at 1 month after Dose 4

Antibody concentrations to each concomitant vaccine antigen (measles, mumps, rubella, and varicella) were to be determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes.

Other Endpoints

Exploratory Pneumococcal Immunogenicity Endpoints

- Pneumococcal serotype-specific OPA titres and changes in titres at available time points (1 month after Dose 3, before Dose 4, and 1 month after Dose 4)
- Pneumococcal serotype-specific IgG concentrations and fold-changes in concentrations at available time points (1 month after Dose 3, before Dose 4, and 1 month after Dose 4)
- Serotype 15C IgG concentrations and OPA titres at available time points
- Serotype 6C IgG concentrations and OPA titres at available time points

Sample size

A total of approximately 2000 enrolled participants was considered to yield approximately 1600 evaluable participants assuming a 20% non-evaluable rate for the study, resulting in approximately 800 evaluable participants for each vaccine group with a 1:1 randomization ratio between the 20vPnC and 13vPnC groups. Sample size and power for the primary pneumococcal immunogenicity objectives associated with IgG concentration results at 1 month after Dose 3 and 1 month after Dose 4 were assessed based on simulations with assumptions supported by IgG results from an internal Pfizer Phase 2 infant study of 20vPnC (B7471003) following multivariate log-normal distributions.

Assuming the true GMCs and variance-covariance matrices for the 20 serotype-specific IgG

concentrations from both 20vPnC and 13vPnC groups are the same as those observed from Study B7471003, with 800 evaluable participants from each vaccine group, simulations showed that the study had approximately 93% probability to show at least 37 (out of 40 total) positive non-inferiority assessments comparing IgG results between the 20vPnC and 13vPnC groups, based on percentages of

participants with predefined serotype specific IgG concentration levels at 1 month after Dose 3 and serotype-specific IgG GMCs 1 month after Dose 4 for the 20 serotypes.

This sample size was considered suitable to also have sufficient power for all NI tests for the (coprimary) concomitant immunogenicity objective, as well as for the primary safety objective.

Randomisation

All eligible participants were planned to be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC. Allocation of participants to vaccine groups was planned to proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]).

The site personnel (study coordinator or specified designee) was planned to be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel was to be provided with a vaccine assignment, randomization number, and dispensable unit (DU) or container numbers when investigational product was supplied via the IRT system. The IRT system was supposed to provide a confirmation report containing the participant number, randomization number, and DU or container numbers assigned. The confirmation report was to be stored in the site's files.

Blinding (masking)

The study was planned to be participant- and investigator-blinded. Sponsor personnel and investigators involved in evaluating participant data in the primary study population were planned to be blinded to vaccine assignment until the analysis at the completion of the primary study population.

The protocol foresaw a 'Primary Analysis 1', when complete safety and immunogenicity data through 1 month after Dose 3 from all participants were available; The study team was planned to remain blinded up to this Primary Analysis 1. However, according to the SAP, Primary analysis 1 was planned to be omitted because of internal business decisions. The first of the planned statistical analyses was then to be carried out when the safety and immunogenicity data through 1 month after Dose 4 were available and released. For this reason, the study team was planned to be unblinded after the last participant completes Visit 6 (1 month after Dose 4). The investigator site staff was to remain blinded to participant vaccine group until the last participant completed the final visit and the database has been locked for final analysis. Laboratory personnel performing the assays was to remain blinded until all assays are completed and assay results finalized.

Standard proceedings for blind breaking during study conduct were put in place with the study protocol.

Statistical methods

Unless otherwise stated, descriptive statistics for continuous variables were n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables (eg, proportions) were the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CI where applicable.

All baseline characteristics including demographic data, medical history and participants' disposition and compliance were planned to be analysed in descriptive manner. Subset analyses were planned to be done in descriptive manner for the critical safety and immunogenicity endpoints, separately by sex and race.

A separate exploratory analysis of primary safety endpoints (prompted local reactions, prompted systemic events, and AEs) was planned to be performed for the subsets of participants who received pneumococcal conjugate vaccine administered at the same visit with and without influenza vaccine, if the number of participants included in a subset was large enough. Otherwise, these data was planned to be listed.

In general, standard statistical methodology for reporting all safety data was planned to be used. Details regarding the local tolerance and safety data analyses had been prespecified in the SAP.

According to protocol, statistical analyses were planned to be carried out when the final data for the specified analyses were available:

- Primary Analysis 1: complete safety and immunogenicity data through 1 month after Dose 3 from all participants;
- Primary Analysis 2: complete safety and immunogenicity data from 1 month after Dose 3 through 1 month after Dose 4 from all participants;
- Final safety analysis: complete safety data from 1 month after Dose 4 through the visit occurring 6 months after Dose 4 from all participants.

However, according to the SAP, Primary analysis 1 was not to be conducted because of internal business decisions. The first of the planned statistical analyses was then planned to be carried out when the safety and immunogenicity data through 1 month after Dose 4 were available and released.

Analysis sets
Analysis populations were defined for the statistical analysis of safety and immunogenicity data according to the table:

Population	Description
All-available immunogenicity	All randomized participants who receive at least 1 dose of the investigational product with at least 1 valid immunogenicity result. Participants will be grouped according to their randomized vaccine in the immunogenicity analysis.
Safety	All participants who receive at least 1 dose of the investigational product with safety follow-up after any dose. Participants will be grouped according to the vaccine as administered in the safety analysis. Safety data after Dose 4 will be summarized on the subset of the safety population who also receive Dose 4 with safety follow-up after Dose 4. The statistical analysis of e-diary results will be based on the safety population among those with any e-diary data collected after the specified vaccination.

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Dose 3 evaluable immunogenicity	All participants who 1. are eligible and randomized, 2. are 42 to 98 days of age, inclusive, on the day of Dose 1, 3. receive the first 3 vaccinations to which they are randomized, 4. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 3, and 5. have no other major protocol deviations as determined by the clinician. The Dose 3 evaluable immunogenicity population will be the primary analysis population for the pneumococcal immunogenicity results from the blood collected up to before Dose 4. The statistical analysis of concomitant immunogenicity results 1 month after Dose 3 will be primarily based on the Dose 3 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines with the first 3 doses. Participants will be grouped as randomized in the immunogenicity analysis.
Dose 4 evaluable immunogenicity	All participants who 1. are eligible and randomized, 2. are 42 to 98 days of age, inclusive, on the day of Dose 1, 3. receive all 4 vaccinations as randomized, and are 365 to 455 days of age, inclusive, on the day of Dose 4, 4. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 4, and 5. have no other major protocol deviations as determined by the clinician. The Dose 4 evaluable immunogenicity population will be the primary analysis population for the pneumococcal immunogenicity results after Dose 4. The statistical analysis of concomitant immunogenicity results 1 month after Dose 4 will be primarily based on the Dose 4 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines at the Dose 4 visit. Participants will be grouped as randomized in the immunogenicity analysis.

For the Dose 3 and Dose 4 evaluable immunogenicity population definition, the blood collection window has been expanded by 1 extra day before, and 14 days after, the protocol-specified blood collection window of 28 to 42 days defined in the protocol, for consistency with established rules in the Prevnar 13 program.

Immunogenicity analyses

The estimands to evaluate the immunogenicity objectives for non-inferiority were planned to be based on evaluable populations. These estimands were supposed to estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimand addressed the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups.

Empirical Reverse Cumulative Distribution Curves (RCDCs) were to be plotted as a step function of proportion of participants with assay results equal to or exceeding a specified value versus the indicated assay value, for all observed assay values.

For immunogenicity results of IgG concentrations, OPA titres, and the antibody levels of the concomitant vaccines, geometric means (GMs) were to be computed along with associated 95% CIs. The GMs and the 95% CIs were planned to be calculated as the means and the CIs of the assay results on the natural log scale and then exponentiating the results. Two-sided 95% CIs were to be calculated based on the t-distribution.

Where appropriate, geometric mean ratios (GMRs) and their 2-sided 95% CIs were to be derived by calculating differences in means and CIs on the natural log scale of the concentrations/titres and then exponentiating the results.

Geometric mean fold rises (GMFRs) were planned to be calculated as the mean of the difference of antibody levels (later result minus earlier result) on the natural log scale and exponentiating the results. The associated 2-sided 95% CIs were to be computed by exponentiating the CIs using Student's t-distribution for the mean difference on the natural log scale.

The exact 95% CI for binary endpoints for each group were to be computed using the F distribution (Clopper-Pearson). The 95% CI for the between-group difference for binary endpoints were planned to be calculated using the Miettinen and Nurminen method.

Primary immunogenicity endpoints analysis

For the percentage of participants with pneumococcal IgG concentrations above a prespecified threshold at 1 month after Dose 3, hypothesis testing was planned to be used to assess the NI of 20vPnC to 13vPnC. The null hypothesis (H0A) for a serotype was

$$H_{0A}: \pi_{20vPnC} - \pi_{13vPnC} \leq -10\%,$$

with a 10% margin for NI, where

- π_{20vPnC} is the percentage of participants achieving the predefined IgG antibody concentration for the serotype from the 20vPnC group 1 month after Dose 3;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in 13vPnC, π_{13vPnC} is the percentage of participants achieving the predefined IgG concentration for the serotype from the 13vPnC group 1 month after Dose 3;
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, π_{13vPnC} is the percentage of participants achieving the predefined IgG concentration for the serotype with the lowest percentage among the 13 matched serotypes from the 13vPnC group 1 month after Dose 3, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

The null hypothesis (H_{0A}) was to be rejected, and NI of 20vPnC to 13vPnC for the percentage of participants with a predefined IgG concentration for a serotype was to be declared if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages was greater than –10%.

For the pneumococcal IgG GMCs 1 month after Dose 4 hypothesis testing was planned to assess the NI of 20vPnC to 13vPnC. The null hypothesis (H_{0B}) for a serotype was

$$H_{0B}: \ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$$

where ln(0.5) corresponds to a 2-fold margin for NI and

- $\ln(\mu_{20vPnC})$ is the natural log of the geometric mean IgG concentration in the 20vPnC group for that serotype 1 month after Dose 4;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration in the 13vPnC group 1 month after Dose 4;
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group 1 month after Dose 4, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

The null hypotheses H_{0B} was to be rejected, and NI of 20vPnC to 13vPnC for the pneumococcal serotype-specific IgG GMC was to be declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC group to the 13vPnC group for the serotype was greater than 0.5 (2-fold NI margin).

For the percentage of participants with antibody levels above prespecified levels for concomitant vaccine antigen at 1 month after Dose 3, hypothesis testing was planned to assess the NI of the 20vPnC group to the 13vPnC group. For this a very similar methodological approach as described above for the percentage of participants with predefined serotype-specific IgG concentrations was planned.

The null hypothesis was to be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, was greater than –10%.

Overall, the primary pneumococcal immunogenicity objectives were considered to be achieved if NI of the immune response induced by 20vPnC compared to 13vPnC based on both percentages of participants with predefined IgG levels and IgG GMCs at 1 month after Dose 3, as well as the IgG GMCs at 1 month after Dose 4, was established for all 20 serotypes, a total of 40 NI evaluations.

Therefore, the overall type I error rate for the primary immunogenicity assessment of the pneumococcal immune response of 20vPnC was supposed to controlled at the 0.05 level.

The primary concomitant immunogenicity objective was considered to be met if NI is achieved for each concomitant vaccine antigen. Therefore, the type I error rate for the concomitant immunogenicity assessment was supposed to controlled at the 0.05 level.

Secondary and further immunogenicity endpoints analysis

A similar testing framework as described for the primary analyses was set up to evaluate NI for pneumococcal IgG GMCs 1 month after Dose 3 as key secondary endpoint.

A similar testing framework as described for the primary analyses was set up to evaluate NI for GMCs of Antibody Levels to Concomitant Vaccine Antigen at 1 Month After Dose 4 as secondary endpoint.

The following endpoints were planned to be analyses as secondary/additional endpoints using standard statistical methodology, not involving hypothesis testing (for NI):

- OPA Titres 1 Month After Dose 3 and 1 Month After Dose 4

- Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations at 1 Month After Dose 4
- Fold Change of IgG Concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 until 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4
- Participants With Prespecified Antibody Levels to Each Concomitant Vaccine Antigen at 1 Month After Dose 3
- Antibody Levels to Concomitant Vaccine Antigens 1 Month After Dose 3 and After Dose 4
- Participants With Pneumococcal OPA Titres ≥ LLOQ
- Participants With a ≥4-Fold Rise in OPA Titres From Before Dose 4 to 1 Month After Dose 4
- Fold Changes in Pneumococcal Serotype-Specific OPA Titres From 1 Month After Dose 3 to Before Dose 4, From Before Dose 4 to 1 Month After Dose 4, and From 1 Month After Dose 3 to 1 Month After Dose 4
- Participants With a ≥4-Fold Rise in Serotype-Specific IgG Concentrations From Before Dose 4 to 1 Month After Dose 4
- Pneumococcal Serotype-Specific IgG Concentrations and Pneumococcal OPA Titres for Serotypes 15C and 6C
- Participants With Prespecified Antibody Levels to Measles, Mumps, Rubella, and Varicella Viruses 1 Month After Dose 4

Results

Participant flow

Table 27. Disposition of All Participants – All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	1004 (100.0)	993 (100.0)	1997 (100.0)
Not vaccinated	3 (0.3)	3 (0.3)	6 (0.3)
Vaccinated			
Dose 1	1001 (99.7)	990 (99.7)	1991 (99.7)
Dose 2	966 (96.2)	949 (95.6)	1915 (95.9)
Dose 3	934 (93.0)	926 (93.3)	1860 (93.1)
Dose 4	853 (85.0)	844 (85.0)	1697 (85.0)
Completed 1-month follow-up after Dose 3	930 (92.6)	924 (93.1)	1854 (92.8)
Completed 1-month follow-up after Dose 4	851 (84.8)	839 (84.5)	1690 (84.6)
Completed 6-month follow-up telephone contact[c]	885 (88.1)	842 (84.8)	1727 (86.5)
Completed all visits per protocol	821 (81.8)	802 (80.8)	1623 (81.3)
Total withdrawn	183 (18.2)	191 (19.2)	374 (18.7)
Withdrawn before Dose 1	3 (0.3)	3 (0.3)	6 (0.3)
Withdrawn after Dose 1 and before 1-month follow-up after Dose 3	71 (7.1)	66 (6.6)	137 (6.9)
Withdrawn after 1-month follow-up after Dose 3 and before Dose 4	77 (7.7)	80 (8.1)	157 (7.9)

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Withdrawn after Dose 4 and before 1-month follow-up after Dose 4	2 (0.2)	5 (0.5)	7 (0.4)
Withdrawn after 1-month follow-up after Dose 4 through 6-month follow-up telephone contact	30 (3.0)	37 (3.7)	67 (3.4)
Reason for withdrawal			
Lost to follow-up	48 (4.8)	63 (6.3)	111 (5.6)
Withdrawal by parent/guardian	50 (5.0)	56 (5.6)	106 (5.3)
No longer meets eligibility criteria	51 (5.1)	44 (4.4)	95 (4.8)
Protocol deviation	29 (2.9)	23 (2.3)	52 (2.6)
Adverse event	2 (0.2)	4 (0.4)	6 (0.3)
Physician decision	0	1 (0.1)	1 (0.1)
Other	3 (0.3)	0	3 (0.2)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. The number of participants in the 6-month follow-up telephone contact includes participants who had previously withdrawn from vaccination but whose parent(s)/legal guardian(s) consented to the safety follow-up.

Table 28.

Immunogenicity Blood Samples Drawn – All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Received Dose 3[b]	N=934	N=926	N=1860
Blood sample drawn 1 month after Dose 3	868 (92.9)	848 (91.6)	1716 (92.3)
<28 Days	4 (0.4)	11 (1.2)	15 (0.8)
28 to 42 Days[c]	802 (85.9)	764 (82.5)	1566 (84.2)
>42 Days	62 (6.6)	73 (7.9)	135 (7.3)
Blood sample not obtained at 1 month after Dose 3	66 (7.1)	78 (8.4)	144 (7.7)
Received Dose 4[d]	N=853	N=844	N=1697
Blood sample drawn before Dose 4	825 (96.7)	807 (95.6)	1632 (96.2)
Blood sample drawn 1 month after Dose 4	788 (92.4)	774 (91.7)	1562 (92.0)
<28 Days	6 (0.7)	4 (0.5)	10 (0.6)
28 to 42 Days[c]	718 (84.2)	712 (84.4)	1430 (84.3)
>42 Days	64 (7.5)	58 (6.9)	122 (7.2)
Blood sample not obtained at 1 month after Dose 4	65 (7.6)	70 (8.3)	135 (8.0)

a. n = Number of participants with the specified characteristic.
b. The values in this row are the denominators for the percentage calculations for the "blood sample drawn 1 month after Dose 3" row and associated time frames.
c. Protocol-specified time frame.
d. The values in this row are the denominators for the percentage calculations for the "blood sample drawn before Dose 4" row, the "blood sample drawn 1 month after Dose 4" row and associated time frames.

Recruitment

This trial was conducted at 107 sites in the United States and Puerto Rico.

First subject first visit 20 May 2020. The date of last participant last visit was 02 September 2022.

Conduct of the study

Protocol amendments

There were 2 amendments to the original study protocol (19 February 2020).

With the Amendment 1 (23 April 2020), the primary objective to compare IgG GMCs at the time point 1 month after the third dose has been changed to a key secondary endpoint. Sections describing objectives, estimands, and statistical methods have been updated accordingly.

Amendment 2 (1 April 2022) included addition of text specifying the end date for Visit 5, specifying the latest date for Visit 6 blood collection, text specifying the latest date for Visit 7, and modifying study visit windows based on the calendar date of the last vaccine dose, changes to the timing for unblinding of sponsor personnel from 1 month after Dose 3 to 1 month after Dose 4 and addition of text describing follow-up for participants discontinued prior to completing all 4 doses of study intervention.

Protocol deviations

Table 29.

Important Protocol Deviations – All Randomized Participants

Protocol Deviation Category Subcategory	Vaccine Group (as Randomized) 20vPnC (N[a]=1004) n[b] (%)	 13vPnC (N[a]=993) n[b] (%)	 Total (N[a]=1997) n[b] (%)
Concomitant Medications	17 (1.7)	11 (1.1)	28 (1.4)
Receipt of commercial pneumococcal vaccine.	17 (1.7)	10 (1.0)	27 (1.4)
Took permitted vaccine, but not as specified per protocol	0	1 (0.1)	1 (0.1)
Inclusion/Exclusion	8 (0.8)	2 (0.2)	10 (0.5)
Entered into study but did not meet inclusion criterion or met exclusion criterion	8 (0.8)	2 (0.2)	10 (0.5)
Investigational Product	2 (0.2)	2 (0.2)	4 (0.2)
Incorrect vaccine administered	0	1 (0.1)	1 (0.1)
Storage Error - IP administered but deemed not fit for use	2 (0.2)	1 (0.1)	3 (0.2)
Procedures/Tests	1 (0.1)	1 (0.1)	2 (0.1)
Met temporary delay criteria and was vaccinated	1 (0.1)	1 (0.1)	2 (0.1)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

Baseline data

Table 30. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)		
	20vPnC (N^a=1001) n^b (%)	13vPnC (N^a=987) n^b (%)	Total (N^a=1988) n^b (%)
Sex			
Male	518 (51.7)	505 (51.2)	1023 (51.5)
Female	483 (48.3)	482 (48.8)	965 (48.5)
Race			
White	754 (75.3)	742 (75.2)	1496 (75.3)
Black or African American	110 (11.0)	108 (10.9)	218 (11.0)
Asian	16 (1.6)	16 (1.6)	32 (1.6)
American Indian or Alaska Native	4 (0.4)	3 (0.3)	7 (0.4)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.2)	4 (0.2)
Multiracial	68 (6.8)	73 (7.4)	141 (7.1)
Not reported	47 (4.7)	43 (4.4)	90 (4.5)
Ethnicity			
Hispanic/Latino	312 (31.2)	293 (29.7)	605 (30.4)
Non-Hispanic/non-Latino	661 (66.0)	659 (66.8)	1320 (66.4)
Not reported	28 (2.8)	35 (3.5)	63 (3.2)
Geographic region			
USA	893 (89.2)	881 (89.3)	1774 (89.2)
Puerto Rico	108 (10.8)	106 (10.7)	214 (10.8)
Age at Dose 1 (days)			
Mean (SD)	65.9 (7.98)	65.6 (7.13)	65.8 (7.57)
Median	64.0	64.0	64.0
Min, max	(42, 97)	(43, 96)	(42, 97)
Age at Dose 4 (days)			
Mean (SD)	378.4 (15.75)	378.7 (15.47)	378.5 (15.61)
Median	372.0	373.0	372.0
Min, max	(365, 460)	(366, 455)	(365, 460)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. Participants who received any incorrect study vaccination during the study are excluded.
b. n = Number of participants with the specified characteristic.

Numbers analysed

Table 31. Analysis Populations

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	1004 (100.0)	993 (100.0)	1997 (100.0)
Vaccinated	1001 (99.7)	990 (99.7)	1991 (99.7)
Safety population[c]	1001 (99.7)	990 (99.7)	1991 (99.7)
Excluded from safety population	3 (0.3)	3 (0.3)	6 (0.3)
Reason for exclusion[d]			
Did not receive any vaccination	3 (0.3)	3 (0.3)	6 (0.3)
All-available immunogenicity population	908 (90.4)	889 (89.5)	1797 (90.0)
Excluded from all-available immunogenicity population	96 (9.6)	104 (10.5)	200 (10.0)
Reason for exclusion[d]			
Did not receive any vaccination	3 (0.3)	3 (0.3)	6 (0.3)
Did not have at least 1 valid immunogenicity result	93 (9.3)	101 (10.2)	194 (9.7)
Dose 3 evaluable immunogenicity population	833 (83.0)	803 (80.9)	1636 (81.9)
Excluded from Dose 3 evaluable immunogenicity population	171 (17.0)	190 (19.1)	361 (18.1)
Reason for exclusion[d]			
Not eligible at randomization/dose[e]	6 (0.6)	5 (0.5)	11 (0.6)
Not 42 to 98 days of age at Dose 1	2 (0.2)	3 (0.3)	5 (0.3)
Did not receive first 3 vaccinations as randomized	64 (6.4)	64 (6.4)	128 (6.4)
No blood drawn within 27 to 56 days after Dose 3	93 (9.3)	112 (11.3)	205 (10.3)
Did not have at least 1 valid immunogenicity result within 27 to 56 days after Dose 3	5 (0.5)	8 (0.8)	13 (0.7)
Other major protocol deviation	3 (0.3)	1 (0.1)	4 (0.2)
Dose 4 evaluable immunogenicity population	755 (75.2)	745 (75.0)	1500 (75.1)
Excluded from Dose 4 evaluable immunogenicity population	249 (24.8)	248 (25.0)	497 (24.9)
Reason for exclusion[d]			
Not eligible at randomization/dose[e]	6 (0.6)	5 (0.5)	11 (0.6)
Not 42 to 98 days of age at Dose 1	2 (0.2)	3 (0.3)	5 (0.3)
Did not receive all 4 vaccinations as randomized	145 (14.4)	147 (14.8)	292 (14.6)
Not 365 to 455 days of age at Dose 4	1 (0.0)	0	1 (0.0)
No blood drawn within 27 to 56 days after Dose 4	91 (9.1)	91 (9.2)	182 (9.1)
Did not have at least 1 valid immunogenicity result within 27 to 56 days after Dose 4	4 (0.4)	4 (0.4)	8 (0.4)
Other major protocol deviation	2 (0.2)	1 (0.1)	3 (0.2)

Outcomes and estimation

1. Percentages of participants with predefined serotype-specific IgG concentrations at 1 month after Dose 3 (last infant dose) (co-primary objective)

Table 32.

Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentage of Participants With Predefined Pneumococcal IgG Levels – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

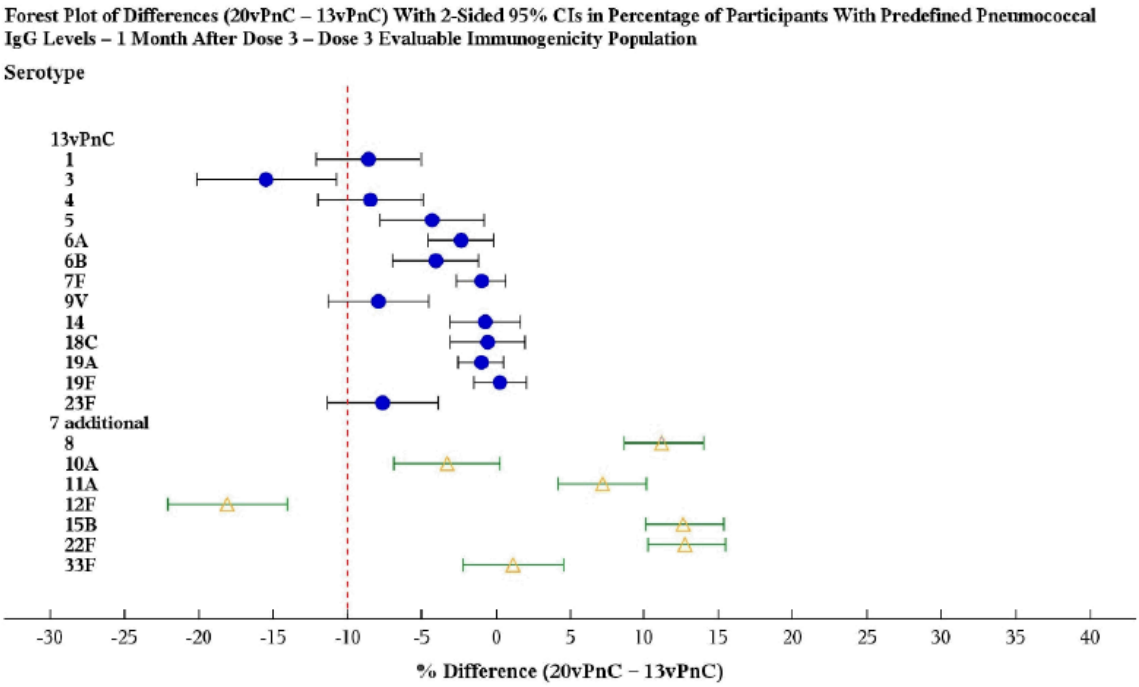


Table 33. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	833	665	79.8	(76.9, 82.5)	802	709	88.4	(86.0, 90.5)	-8.6	(-12.1, -5.1)
3	≥0.35 µg/mL	833	434	52.1	(48.6, 55.5)	802	542	67.6	(64.2, 70.8)	-15.5	(-20.1, -10.8)
4	≥0.35 µg/mL	833	664	79.7	(76.8, 82.4)	802	707	88.2	(85.7, 90.3)	-8.4	(-12.0, -4.9)
5	≥0.23 µg/mL	833	687	82.5	(79.7, 85.0)	802	696	86.8	(84.2, 89.1)	-4.3	(-7.8, -0.8)
6A	≥0.35 µg/mL	833	779	93.5	(91.6, 95.1)	802	769	95.9	(94.3, 97.2)	-2.4	(-4.6, -0.2)
6B	≥0.10 µg/mL	831	734	88.3	(85.9, 90.4)	801	740	92.4	(90.3, 94.1)	-4.1	(-7.0, -1.2)
7F	≥0.35 µg/mL	833	805	96.6	(95.2, 97.8)	802	783	97.6	(96.3, 98.6)	-1.0	(-2.7, 0.7)
9V	≥0.35 µg/mL	833	682	81.9	(79.1, 84.4)	802	720	89.8	(87.5, 91.8)	-7.9	(-11.3, -4.6)
14	≥0.35 µg/mL	832	777	93.4	(91.5, 95.0)	802	755	94.1	(92.3, 95.7)	-0.8	(-3.1, 1.6)
18C	≥0.35 µg/mL	833	771	92.6	(90.6, 94.2)	802	747	93.1	(91.2, 94.8)	-0.6	(-3.1, 1.9)
19A	>0.12 µg/mL	833	809	97.1	(95.7, 98.1)	802	787	98.1	(96.9, 98.9)	-1.0	(-2.6, 0.5)
19F	≥0.35 µg/mL	833	807	96.9	(95.5, 98.0)	802	775	96.6	(95.1, 97.8)	0.2	(-1.5, 2.0)
23F	≥0.35 µg/mL	833	649	77.9	(74.9, 80.7)	802	686	85.5	(82.9, 87.9)	-7.6	(-11.4, -3.9)
7 Additional											
8	≥0.35 µg/mL	833	806	96.8	(95.3, 97.9)	802	686	85.5	(82.9, 87.9)	11.2	(8.6, 14.0)
10A	≥0.35 µg/mL	833	685	82.2	(79.5, 84.8)	802	686	85.5	(82.9, 87.9)	-3.3	(-6.9, 0.3)
11A	≥0.35 µg/mL	833	772	92.7	(90.7, 94.4)	802	686	85.5	(82.9, 87.9)	7.1	(4.2, 10.2)
12F	≥0.35 µg/mL	833	562	67.5	(64.2, 70.6)	802	686	85.5	(82.9, 87.9)	-18.1	(-22.1, -14.0)

15B	≥0.35 µg/mL	833	818	98.2	(97.0, 99.0)	802	686	85.5	(82.9, 87.9)	12.7	(10.2, 15.4)
22F	≥0.35 µg/mL	833	819	98.3	(97.2, 99.1)	802	686	85.5	(82.9, 87.9)	12.8	(10.3, 15.5)
33F	≥0.35 µg/mL	833	722	86.7	(84.2, 88.9)	802	686	85.5	(82.9, 87.9)	1.1	(-2.2, 4.5)

Abbreviation: IgG = immunoglobulin G.

a. For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 23F (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.

b. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.

c. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.

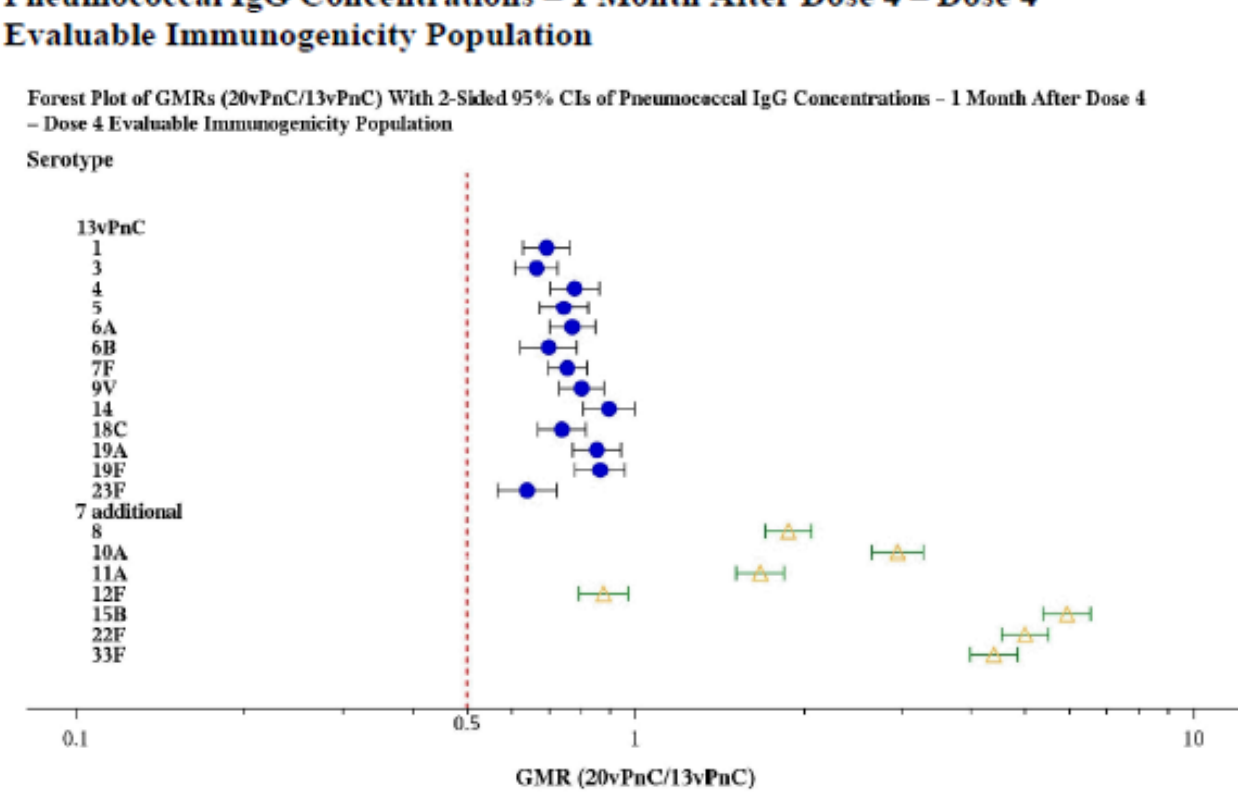
d. Exact 2-sided CI, based on the Clopper and Pearson method.

e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

2. Serotype-specific IgG GMCs at 1 month after Dose 4 (toddler dose) (co-primary objective)

Table 34.

Forest Plot of GMRs (20vPnC / 13vPnC) With 2-Sided 95% CIs of Pneumococcal IgG Concentrations – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population



Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Note: For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 1 (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.

Note: GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC − 13vPnC) and the corresponding CIs (based on the Student t distribution).

Table 35. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC[a]			20vPnC/13vPnC	
Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[a]	(95% CI[d])
13vPnC								
1	755	1.47	(1.37, 1.57)	744	2.12	(1.97, 2.27)	0.69	(0.63, 0.76)
3	755	0.56	(0.53, 0.60)	745	0.85	(0.80, 0.90)	0.66	(0.61, 0.73)
4	754	3.77	(3.52, 4.04)	745	4.84	(4.50, 5.22)	0.78	(0.70, 0.86)
5	755	1.87	(1.74, 2.00)	745	2.51	(2.33, 2.70)	0.74	(0.67, 0.82)
6A	755	9.01	(8.45, 9.61)	745	11.69	(10.91, 12.53)	0.77	(0.70, 0.85)
6B	753	4.01	(3.70, 4.35)	744	5.74	(5.27, 6.24)	0.70	(0.62, 0.79)
7F	755	3.91	(3.70, 4.14)	745	5.18	(4.88, 5.49)	0.76	(0.70, 0.82)
9V	755	3.44	(3.23, 3.67)	744	4.30	(4.02, 4.59)	0.80	(0.73, 0.88)
14	755	5.68	(5.27, 6.12)	745	6.34	(5.88, 6.83)	0.90	(0.81, 1.00)
18C	755	3.46	(3.24, 3.70)	745	4.69	(4.34, 5.05)	0.74	(0.67, 0.82)
19A	754	3.53	(3.30, 3.77)	745	4.13	(3.84, 4.45)	0.85	(0.77, 0.94)
19F	755	5.01	(4.68, 5.36)	745	5.79	(5.36, 6.25)	0.86	(0.78, 0.96)
23F	755	3.95	(3.63, 4.31)	745	6.18	(5.66, 6.75)	0.64	(0.57, 0.72)
7 Additional								
8	755	3.97	(3.73, 4.22)	744	2.12	(1.97, 2.27)	1.87	(1.71, 2.06)
10A	755	6.22	(5.75, 6.72)	744	2.12	(1.97, 2.27)	2.94	(2.64, 3.26)
11A	755	3.53	(3.31, 3.78)	744	2.12	(1.97, 2.27)	1.67	(1.51, 1.84)
12F	755	1.85	(1.73, 1.99)	744	2.12	(1.97, 2.27)	0.88	(0.79, 0.97)
15B	755	12.59	(11.78, 13.45)	744	2.12	(1.97, 2.27)	5.95	(5.39, 6.55)
22F	755	10.60	(9.92, 11.33)	744	2.12	(1.97, 2.27)	5.01	(4.54, 5.52)
33F	755	9.31	(8.71, 9.96)	744	2.12	(1.97, 2.27)	4.40	(3.99, 4.85)

3. Serotype-specific IgG GMCs at 1 month after Dose 3 (last infant dose) (key secondary objective)

Figure 36.

Forest Plot of GMRs (20vPnC / 13vPnC) With 2-Sided 95% CIs of Pneumococcal IgG Concentrations – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

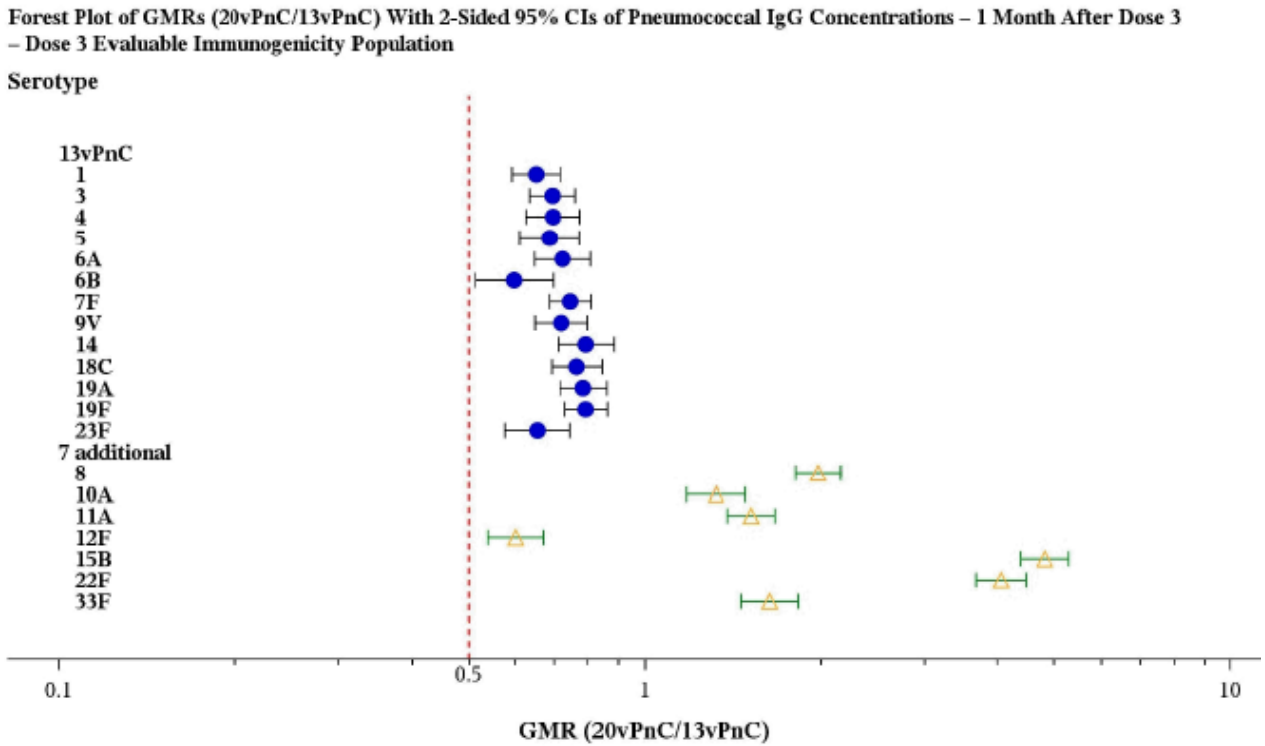


Table 37. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC[a]			20vPnC/13vPnC	
Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[a]	(95% CI[d])
13vPnC								
1	833	0.74	(0.70, 0.79)	802	1.14	(1.06, 1.22)	0.65	(0.59, 0.72)
3	833	0.36	(0.33, 0.38)	802	0.51	(0.48, 0.55)	0.70	(0.64, 0.76)
4	833	0.75	(0.70, 0.81)	802	1.08	(1.00, 1.17)	0.70	(0.63, 0.78)
5	833	0.66	(0.61, 0.71)	802	0.96	(0.88, 1.04)	0.69	(0.61, 0.77)
6A	833	1.95	(1.81, 2.10)	802	2.69	(2.48, 2.92)	0.72	(0.65, 0.81)
6B	831	0.61	(0.55, 0.68)	801	1.02	(0.91, 1.14)	0.60	(0.51, 0.70)
7F	833	1.71	(1.62, 1.81)	802	2.29	(2.16, 2.43)	0.75	(0.69, 0.81)
9V	833	0.87	(0.81, 0.93)	802	1.21	(1.12, 1.30)	0.72	(0.65, 0.80)
14	832	2.16	(2.01, 2.33)	802	2.72	(2.51, 2.95)	0.79	(0.71, 0.89)
18C	833	1.31	(1.23, 1.39)	802	1.71	(1.59, 1.84)	0.77	(0.70, 0.84)
19A	833	0.72	(0.67, 0.76)	802	0.91	(0.85, 0.97)	0.79	(0.72, 0.86)
19F	833	1.59	(1.50, 1.67)	802	2.00	(1.88, 2.12)	0.79	(0.73, 0.86)
23F	833	0.82	(0.75, 0.90)	802	1.25	(1.14, 1.37)	0.66	(0.58, 0.75)
7 Additional								
8	833	1.80	(1.70, 1.91)	802	0.91	(0.85, 0.97)	1.98	(1.81, 2.16)
10A	833	1.21	(1.09, 1.33)	802	0.91	(0.85, 0.97)	1.32	(1.18, 1.49)
11A	833	1.39	(1.30, 1.48)	802	0.91	(0.85, 0.97)	1.52	(1.39, 1.67)
12F	833	0.55	(0.50, 0.60)	802	0.91	(0.85, 0.97)	0.60	(0.54, 0.67)
15B	833	4.40	(4.11, 4.71)	802	0.91	(0.85, 0.97)	4.82	(4.39, 5.30)

Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[a]	(95% CI[d])
22F	833	3.71	(3.45, 3.99)	802	0.91	(0.85, 0.97)	4.06	(3.68, 4.48)
33F	833	1.49	(1.36, 1.64)	802	0.91	(0.85, 0.97)	1.64	(1.46, 1.83)

Table 38. Pnewmococcal IgG GMCs and GMRs for the 7 Additional Serotypes Using the Corr Group – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR[c]	(95% CI[c])
7 Additional								
8	833	1.80	(1.70, 1.91)	794	0.02	(0.02, 0.02)	100.54	(91.58, 110.38)
10A	833	1.21	(1.09, 1.33)	803	0.01	(0.01, 0.01)	99.64	(88.87, 111.70)
11A	833	1.39	(1.30, 1.48)	803	0.02	(0.01, 0.02)	91.03	(82.79, 100.09)
12F	833	0.55	(0.50, 0.60)	803	0.01	(0.01, 0.01)	68.42	(62.47, 74.94)
15B	833	4.40	(4.11, 4.71)	803	0.03	(0.02, 0.03)	169.40	(154.01, 186.33)
22F	833	3.71	(3.45, 3.99)	803	0.01	(0.00, 0.01)	730.84	(651.36, 820.01)
33F	833	1.49	(1.36, 1.64)	802	0.02	(0.01, 0.02)	97.45	(86.96, 109.21)

4. Percentage of Participants With Predefined Serotype-Specific IgG Concentrations 1 Month After Dose 4 (toddler dose) (secondary objective)

Table 39. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 4 – Dose 4 Evaluable immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	755	712	94.3	(92.4, 95.8)	744	723	97.2	(95.7, 98.2)	-2.9	(-5.0, -0.8)
3	≥0.35 µg/mL	755	556	73.6	(70.3, 76.8)	745	639	85.8	(83.1, 88.2)	-12.1	(-16.2, -8.1)
4	≥0.35 µg/mL	754	746	98.9	(97.9, 99.5)	745	738	99.1	(98.1, 99.6)	-0.1	(-1.3, 1.0)
5	≥0.23 µg/mL	755	739	97.9	(96.6, 98.8)	745	728	97.7	(96.4, 98.7)	0.2	(-1.4, 1.7)
6A	≥0.35 µg/mL	755	751	99.5	(98.6, 99.9)	745	743	99.7	(99.0, 100.0)	-0.3	(-1.1, 0.5)
6B	≥0.10 µg/mL	753	746	99.1	(98.1, 99.6)	744	740	99.5	(98.6, 99.9)	-0.4	(-1.4, 0.6)
7F	≥0.35 µg/mL	755	751	99.5	(98.6, 99.9)	745	744	99.9	(99.3, 100.0)	-0.4	(-1.2, 0.3)
9V	≥0.35 µg/mL	755	744	98.5	(97.4, 99.3)	744	736	98.9	(97.9, 99.5)	-0.4	(-1.6, 0.8)
14	≥0.35 µg/mL	755	747	98.9	(97.9, 99.5)	745	741	99.5	(98.6, 99.9)	-0.5	(-1.6, 0.4)
18C	≥0.35 µg/mL	755	747	98.9	(97.9, 99.5)	745	735	98.7	(97.5, 99.4)	0.3	(-0.9, 1.5)
19A	≥0.12 µg/mL	754	753	99.9	(99.3, 100.0)	745	743	99.7	(99.0, 100.0)	0.1	(-0.5, 0.9)
19F	≥0.35 µg/mL	755	746	98.8	(97.7, 99.5)	745	737	98.9	(97.9, 99.5)	-0.1	(-1.3, 1.1)
23F	≥0.35 µg/mL	755	734	97.2	(95.8, 98.3)	745	731	98.1	(96.9, 99.0)	-0.9	(-2.5, 0.7)
7 Additional											
8	≥0.35 µg/mL	755	751	99.5	(98.6, 99.9)	744	723	97.2	(95.7, 98.2)	2.3	(1.1, 3.8)
10A	≥0.35 µg/mL	755	738	97.7	(96.4, 98.7)	744	723	97.2	(95.7, 98.2)	0.6	(-1.1, 2.3)
11A	≥0.35 µg/mL	755	746	98.8	(97.7, 99.5)	744	723	97.2	(95.7, 98.2)	1.6	(0.2, 3.2)
12F	≥0.35 µg/mL	755	719	95.2	(93.5, 96.6)	744	723	97.2	(95.7, 98.2)	-1.9	(-4.0, 0.0)

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
15B	≥0.35 µg/mL	755	753	99.7	(99.0, 100.0)	744	723	97.2	(95.7, 98.2)	2.6	(1.4, 4.0)
22F	≥0.35 µg/mL	755	752	99.6	(98.8, 99.9)	744	723	97.2	(95.7, 98.2)	2.4	(1.3, 3.9)
33F	≥0.35 µg/mL	755	751	99.5	(98.6, 99.9)	744	723	97.2	(95.7, 98.2)	2.3	(1.1, 3.8)

Abbreviation: IgG = immunoglobulin G.

a. For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 1 (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.

b. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.

c. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.

d. Exact 2-sided CI, based on the Clopper and Pearson method.

e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

5. IgG GMFRs From 1 Month After Dose 3 to Before Dose 4, Before Dose 4 to 1 Month After Dose 4, and From 1 Month After Dose 3 to 1 Month After Dose 4

Table 40. Pneumococcal IgG GMFRs – Evaluable immunogenicity Population

					Sampling Time Point					
					Time Point 1		Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
13vPnC										
1	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.74	(0.69, 0.79)	0.20	(0.19, 0.21)	0.3	(0.3, 0.3)
			13vPnC	733	1.16	(1.08, 1.25)	0.30	(0.28, 0.32)	0.3	(0.2, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.73	(0.68, 0.78)	1.44	(1.35, 1.54)	2.0	(1.9, 2.1)
			13vPnC	685	1.14	(1.05, 1.23)	2.07	(1.92, 2.22)	1.8	(1.7, 1.9)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.20	(0.19, 0.21)	1.47	(1.37, 1.57)	7.3	(6.9, 7.8)
			13vPnC	720	0.30	(0.28, 0.32)	2.12	(1.97, 2.28)	7.1	(6.7, 7.6)
3	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.35	(0.32, 0.37)	0.07	(0.06, 0.07)	0.2	(0.2, 0.2)
			13vPnC	733	0.52	(0.48, 0.55)	0.09	(0.09, 0.10)	0.2	(0.2, 0.2)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.34	(0.32, 0.36)	0.56	(0.52, 0.59)	1.6	(1.5, 1.7)
			13vPnC	686	0.50	(0.47, 0.54)	0.83	(0.78, 0.89)	1.7	(1.6, 1.8)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.07	(0.06, 0.07)	0.56	(0.53, 0.60)	8.5	(7.9, 9.1)
			13vPnC	721	0.09	(0.09, 0.10)	0.85	(0.80, 0.91)	9.0	(8.4, 9.6)
4	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.74	(0.69, 0.80)	0.25	(0.23, 0.27)	0.3	(0.3, 0.4)
			13vPnC	733	1.09	(1.01, 1.19)	0.34	(0.31, 0.36)	0.3	(0.3, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	703	0.73	(0.67, 0.79)	3.73	(3.47, 4.01)	5.1	(4.8, 5.5)
			13vPnC	686	1.07	(0.98, 1.16)	4.73	(4.38, 5.11)	4.4	(4.1, 4.8)

				Sampling Time Point						
					Time Point 1		Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
	Before Dose 4	1 Month after Dose 4	20vPnC	731	0.25	(0.23, 0.26)	3.77	(3.52, 4.05)	15.4	(14.3, 16.6)
			13vPnC	721	0.34	(0.32, 0.37)	4.83	(4.48, 5.21)	14.2	(13.1, 15.3)
5	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.65	(0.59, 0.70)	0.21	(0.20, 0.23)	0.3	(0.3, 0.3)
			13vPnC	733	0.97	(0.89, 1.06)	0.30	(0.27, 0.32)	0.3	(0.3, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.64	(0.58, 0.69)	1.84	(1.72, 1.98)	2.9	(2.7, 3.1)
			13vPnC	686	0.94	(0.86, 1.03)	2.46	(2.28, 2.66)	2.6	(2.4, 2.8)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.21	(0.19, 0.23)	1.86	(1.74, 2.00)	8.9	(8.4, 9.5)
			13vPnC	721	0.30	(0.27, 0.32)	2.51	(2.33, 2.71)	8.5	(8.0, 9.0)
6A	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.91	(1.77, 2.07)	0.59	(0.55, 0.64)	0.3	(0.3, 0.3)
			13vPnC	732	2.72	(2.50, 2.96)	0.80	(0.74, 0.85)	0.3	(0.3, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.90	(1.76, 2.06)	8.97	(8.41, 9.57)	4.7	(4.4, 5.0)
			13vPnC	686	2.70	(2.47, 2.94)	11.56	(10.75, 12.43)	4.3	(4.0, 4.6)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.59	(0.55, 0.64)	9.01	(8.44, 9.62)	15.2	(14.3, 16.2)
			13vPnC	720	0.81	(0.75, 0.87)	11.71	(10.91, 12.57)	14.5	(13.5, 15.5)
6B	1 Month after Dose 3	Before Dose 4	20vPnC	754	0.59	(0.53, 0.66)	0.22	(0.21, 0.24)	0.4	(0.4, 0.4)
			13vPnC	730	1.04	(0.93, 1.17)	0.33	(0.31, 0.37)	0.3	(0.3, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	700	0.59	(0.53, 0.66)	3.99	(3.67, 4.34)	6.8	(6.2, 7.4)
			13vPnC	685	1.02	(0.91, 1.15)	5.62	(5.15, 6.14)	5.5	(5.0, 6.0)

Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	Sampling Time Point: Time Point 1 GMC[b]	Time Point 1 (95% CI[b])	Time Point 2 GMC[b]	Time Point 2 (95% CI[b])	Fold Rise GMFR[b]	Fold Rise (95% CI[b])
	Before Dose 4	1 Month after Dose 4	20vPnC	727	0.22	(0.20, 0.24)	4.02	(3.70, 4.37)	18.0	(16.8, 19.3)
			13vPnC	718	0.34	(0.31, 0.37)	5.76	(5.28, 6.27)	17.0	(15.8, 18.2)
7F	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.68	(1.59, 1.79)	0.65	(0.61, 0.69)	0.4	(0.4, 0.4)
			13vPnC	733	2.33	(2.19, 2.48)	0.82	(0.77, 0.87)	0.4	(0.3, 0.4)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.69	(1.59, 1.79)	3.89	(3.68, 4.12)	2.3	(2.2, 2.4)
			13vPnC	686	2.30	(2.16, 2.45)	5.06	(4.76, 5.39)	2.2	(2.1, 2.3)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.65	(0.61, 0.69)	3.91	(3.69, 4.13)	6.0	(5.7, 6.3)
			13vPnC	721	0.81	(0.77, 0.86)	5.19	(4.89, 5.52)	6.4	(6.0, 6.8)
9V	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.86	(0.80, 0.93)	0.29	(0.27, 0.31)	0.3	(0.3, 0.4)
			13vPnC	733	1.23	(1.14, 1.33)	0.38	(0.36, 0.41)	0.3	(0.3, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.86	(0.80, 0.93)	3.41	(3.19, 3.64)	4.0	(3.7, 4.3)
			13vPnC	685	1.21	(1.12, 1.30)	4.16	(3.88, 4.46)	3.4	(3.2, 3.7)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.29	(0.27, 0.31)	3.43	(3.21, 3.66)	11.8	(11.1, 12.6)
			13vPnC	720	0.38	(0.36, 0.41)	4.30	(4.02, 4.60)	11.2	(10.5, 11.9)
14	1 Month after Dose 3	Before Dose 4	20vPnC	757	2.13	(1.97, 2.30)	0.98	(0.90, 1.06)	0.5	(0.4, 0.5)
			13vPnC	733	2.82	(2.60, 3.06)	1.29	(1.20, 1.40)	0.5	(0.4, 0.5)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	703	2.16	(2.00, 2.33)	5.67	(5.25, 6.12)	2.6	(2.4, 2.9)
			13vPnC	686	2.73	(2.51, 2.98)	6.12	(5.66, 6.61)	2.2	(2.0, 2.5)

				Sampling Time Point						
					Time Point 1		Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.96	(0.88, 1.05)	5.64	(5.23, 6.09)	5.9	(5.4, 6.3)
			13vPnC	721	1.26	(1.17, 1.36)	6.26	(5.80, 6.75)	5.0	(4.6, 5.3)
18C	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.29	(1.21, 1.38)	0.30	(0.29, 0.32)	0.2	(0.2, 0.2)
			13vPnC	733	1.77	(1.64, 1.91)	0.41	(0.38, 0.44)	0.2	(0.2, 0.2)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.29	(1.21, 1.38)	3.43	(3.21, 3.66)	2.7	(2.5, 2.8)
			13vPnC	686	1.73	(1.60, 1.87)	4.57	(4.22, 4.94)	2.6	(2.5, 2.8)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.31	(0.29, 0.33)	3.45	(3.22, 3.69)	11.3	(10.6, 12.0)
			13vPnC	721	0.41	(0.39, 0.44)	4.70	(4.35, 5.08)	11.4	(10.7, 12.1)
19A	1 Month after Dose 3	Before Dose 4	20vPnC	757	0.71	(0.66, 0.76)	0.14	(0.13, 0.15)	0.2	(0.2, 0.2)
			13vPnC	733	0.92	(0.86, 0.99)	0.16	(0.15, 0.17)	0.2	(0.2, 0.2)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	703	0.72	(0.67, 0.77)	3.51	(3.27, 3.76)	4.9	(4.6, 5.2)
			13vPnC	686	0.89	(0.83, 0.96)	4.08	(3.78, 4.40)	4.6	(4.2, 4.9)
	Before Dose 4	1 Month after Dose 4	20vPnC	731	0.14	(0.13, 0.15)	3.51	(3.29, 3.76)	25.6	(23.8, 27.6)
			13vPnC	721	0.16	(0.15, 0.17)	4.14	(3.85, 4.47)	25.6	(23.6, 27.7)
19F	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.55	(1.46, 1.64)	0.38	(0.36, 0.41)	0.2	(0.2, 0.3)
			13vPnC	733	2.00	(1.87, 2.13)	0.46	(0.43, 0.49)	0.2	(0.2, 0.2)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.55	(1.47, 1.65)	4.99	(4.66, 5.35)	3.2	(3.0, 3.4)
			13vPnC	686	1.96	(1.83, 2.09)	5.71	(5.27, 6.19)	2.9	(2.7, 3.1)

				Sampling Time Point						
				Time Point 1			Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.38	(0.36, 0.41)	5.02	(4.68, 5.38)	13.1	(12.2, 14.1)
			13vPnC	721	0.46	(0.43, 0.49)	5.79	(5.35, 6.26)	12.5	(11.6, 13.5)
23F	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.80	(0.73, 0.87)	0.21	(0.20, 0.24)	0.3	(0.3, 0.3)
			13vPnC	733	1.27	(1.16, 1.40)	0.33	(0.30, 0.36)	0.3	(0.2, 0.3)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.80	(0.73, 0.88)	3.91	(3.58, 4.26)	4.9	(4.5, 5.3)
			13vPnC	686	1.24	(1.12, 1.37)	6.08	(5.55, 6.66)	4.9	(4.5, 5.3)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.22	(0.20, 0.24)	3.95	(3.62, 4.32)	18.1	(16.8, 19.5)
			13vPnC	721	0.32	(0.29, 0.35)	6.18	(5.65, 6.76)	19.2	(17.9, 20.6)
7 Additional										
8	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.78	(1.67, 1.89)	0.43	(0.40, 0.46)	0.2	(0.2, 0.3)
			13vPnC	706	0.02	(0.02, 0.02)	0.02	(0.02, 0.03)	1.4	(1.3, 1.5)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.79	(1.68, 1.91)	3.92	(3.68, 4.17)	2.2	(2.0, 2.3)
			13vPnC	659	0.02	(0.02, 0.02)	0.03	(0.03, 0.04)	1.8	(1.6, 2.0)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.43	(0.41, 0.46)	3.96	(3.72, 4.22)	9.1	(8.5, 9.8)
			13vPnC	692	0.02	(0.02, 0.03)	0.03	(0.03, 0.04)	1.3	(1.2, 1.4)
10A	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.17	(1.05, 1.29)	0.78	(0.72, 0.85)	0.7	(0.6, 0.7)
			13vPnC	732	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	0.9	(0.9, 1.0)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.18	(1.06, 1.31)	6.29	(5.81, 6.80)	5.3	(4.9, 5.8)

				Sampling Time Point						
				Time Point 1			Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
			13vPnC	686	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(0.9, 1.1)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.76	(0.70, 0.83)	6.17	(5.70, 6.68)	8.1	(7.6, 8.7)
			13vPnC	718	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.1	(1.0, 1.1)
11A	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.37	(1.28, 1.47)	0.36	(0.34, 0.39)	0.3	(0.2, 0.3)
			13vPnC	732	0.02	(0.01, 0.02)	0.02	(0.02, 0.02)	1.1	(1.0, 1.2)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.37	(1.27, 1.47)	3.52	(3.28, 3.77)	2.6	(2.4, 2.8)
			13vPnC	687	0.02	(0.01, 0.02)	0.02	(0.02, 0.02)	1.1	(1.0, 1.3)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.36	(0.34, 0.39)	3.55	(3.32, 3.80)	9.8	(9.1, 10.6)
			13vPnC	719	0.02	(0.01, 0.02)	0.02	(0.02, 0.02)	1.1	(1.0, 1.2)
12F	1 Month after Dose 3	Before Dose 4	20vPnC	758	0.54	(0.49, 0.59)	0.19	(0.17, 0.20)	0.3	(0.3, 0.4)
			13vPnC	732	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(1.0, 1.1)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	0.55	(0.51, 0.61)	1.85	(1.72, 1.99)	3.3	(3.1, 3.6)
			13vPnC	687	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(1.0, 1.1)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	0.19	(0.17, 0.20)	1.85	(1.72, 1.99)	10.0	(9.4, 10.6)
			13vPnC	719	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.0	(1.0, 1.1)
15B	1 Month after Dose 3	Before Dose 4	20vPnC	758	4.33	(4.03, 4.66)	1.55	(1.45, 1.67)	0.4	(0.3, 0.4)
			13vPnC	732	0.03	(0.02, 0.03)	0.02	(0.02, 0.02)	0.8	(0.7, 0.8)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	4.45	(4.15, 4.78)	12.56	(11.76, 13.42)	2.8	(2.6, 3.0)

				Sampling Time Point						
				Time Point 1			Time Point 2		Fold Rise	
Serotype	Time Point 1	Time Point 2	Vaccine Group (as Randomized)	n[a]	GMC[b]	(95% CI[b])	GMC[b]	(95% CI[b])	GMFR[b]	(95% CI[b])
			13vPnC	687	0.03	(0.02, 0.03)	0.02	(0.02, 0.03)	1.0	(0.9, 1.1)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	1.56	(1.45, 1.68)	12.58	(11.76, 13.46)	8.1	(7.5, 8.7)
			13vPnC	719	0.02	(0.02, 0.02)	0.02	(0.02, 0.03)	1.2	(1.2, 1.3)
22F	1 Month after Dose 3	Before Dose 4	20vPnC	758	3.63	(3.36, 3.92)	1.25	(1.15, 1.35)	0.3	(0.3, 0.4)
			13vPnC	732	0.01	(0.00, 0.01)	0.00	(0.00, 0.00)	0.8	(0.7, 0.9)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	3.65	(3.38, 3.94)	10.48	(9.79, 11.21)	2.9	(2.7, 3.1)
			13vPnC	687	0.00	(0.00, 0.01)	0.00	(0.00, 0.01)	1.0	(0.9, 1.1)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	1.25	(1.15, 1.35)	10.53	(9.84, 11.26)	8.4	(7.9, 9.1)
			13vPnC	719	0.00	(0.00, 0.00)	0.00	(0.00, 0.01)	1.2	(1.1, 1.3)
33F	1 Month after Dose 3	Before Dose 4	20vPnC	758	1.46	(1.32, 1.61)	1.07	(0.99, 1.16)	0.7	(0.7, 0.8)
			13vPnC	731	0.02	(0.01, 0.02)	0.01	(0.01, 0.01)	0.8	(0.7, 0.8)
	1 Month after Dose 3	1 Month after Dose 4	20vPnC	704	1.44	(1.30, 1.59)	9.19	(8.58, 9.85)	6.4	(5.9, 7.0)
			13vPnC	686	0.02	(0.01, 0.02)	0.01	(0.01, 0.01)	0.8	(0.8, 0.9)
	Before Dose 4	1 Month after Dose 4	20vPnC	732	1.06	(0.98, 1.14)	9.31	(8.70, 9.97)	8.8	(8.2, 9.4)
			13vPnC	719	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.1	(1.0, 1.1)

6. OPA GMTs after dose 3 and after dose 4

Table 41. Pneumococcal OPA GMTs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	103	26	(21, 33)	98	34	(27, 42)
3	105	51	(43, 61)	97	63	(53, 76)
4	97	339	(252, 455)	90	280	(207, 378)
5	103	32	(27, 39)	98	39	(32, 47)
6A	104	910	(763, 1084)	96	936	(757, 1156)
6B	99	318	(242, 419)	91	516	(409, 651)
7F	91	1222	(1020, 1465)	87	1149	(926, 1424)
9V	94	661	(482, 906)	87	594	(421, 838)
14	103	415	(323, 535)	97	420	(330, 535)
18C	95	1153	(910, 1460)	87	996	(754, 1317)
19A	93	108	(78, 149)	84	109	(79, 151)
19F	102	84	(67, 105)	97	116	(90, 149)
23F	96	255	(186, 350)	86	295	(215, 406)
7 Additional						
8	100	665	(503, 880)	112	18	(17, 20)
10A	101	2558	(1869, 3501)	109	37	(33, 42)
11A	100	289	(212, 395)	108	50	(46, 55)
12F	92	7677	(5952, 9901)	110	28	(24, 33)
15B	97	1560	(1090, 2233)	110	18	(16, 22)
22F	97	6797	(5170, 8936)	113	9	(9, 9)
33F	85	7388	(4803, 11365)	111	198	(177, 220)

Table 42. Pneumococcal OPA GMTs – 1 Month After Dose 4 – Dose 4 Evaluable immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	94	36	(27, 48)	91	66	(50, 87)
3	92	62	(49, 78)	88	102	(86, 120)
4	85	621	(435, 887)	82	961	(714, 1294)
5	94	55	(45, 67)	91	69	(54, 87)
6A	93	1384	(1092, 1753)	91	1767	(1329, 2348)
6B	92	666	(489, 906)	88	1211	(861, 1703)
7F	84	2022	(1673, 2444)	81	2099	(1741, 2531)
9V	85	2609	(1913, 3558)	79	3210	(2500, 4123)
14	92	667	(523, 850)	91	593	(462, 761)
18C	84	1973	(1472, 2643)	83	2425	(1914, 3072)
19A	85	844	(622, 1145)	78	1357	(1007, 1829)
19F	93	246	(179, 337)	91	373	(272, 513)
23F	84	827	(554, 1235)	77	1532	(1118, 2100)
7 Additional						
8	89	1228	(901, 1673)	97	26	(21, 31)
10A	99	3674	(2746, 4916)	102	57	(44, 74)
11A	90	2728	(1975, 3768)	89	69	(53, 89)
12F	86	9320	(7037, 12343)	103	31	(26, 37)
15B	92	3035	(2138, 4308)	100	23	(17, 30)
22F	86	11077	(7956, 15422)	101	15	(11, 20)
33F	80	19216	(13193, 27990)	97	363	(292, 451)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups.
a. n = Number of participants with valid OPA titers for the specified serotype.
b. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).

7. Percentages of Participants With a ≥4 Fold Rise in IgG Concentrations From Before Dose 4 to 1 Month After Dose 4

For the 13 matched serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 4 ranged from 61.5% (serotype 14) to 96.2% (serotype 6A) in the 20vPnC group and from 56.6% (serotype 14) to 95.7% (serotype 19A) in the 13vPnC group.
For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 4 ranged from 77.6% (serotype 15B) to 90.6% (serotype 12F) in the

20vPnC group. Very few participants (≤7.8%) had a ≥4-fold rise for the 7 additional serotypes in the 13vPnC group.

8. Percentages of Participants With a ≥4-Fold Rise in Serotype-Specific OPA Titres From Before Dose 4 to 1 Month After Dose 4

For the 13 matched serotypes, the percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 4 ranged from 38.0% (serotype 7F) to 94.1% (serotype 6A) in the 20vPnC group and from 56.3% (serotype 5) to 98.6% (serotypes 18C and 19A) in the 13vPnC group.

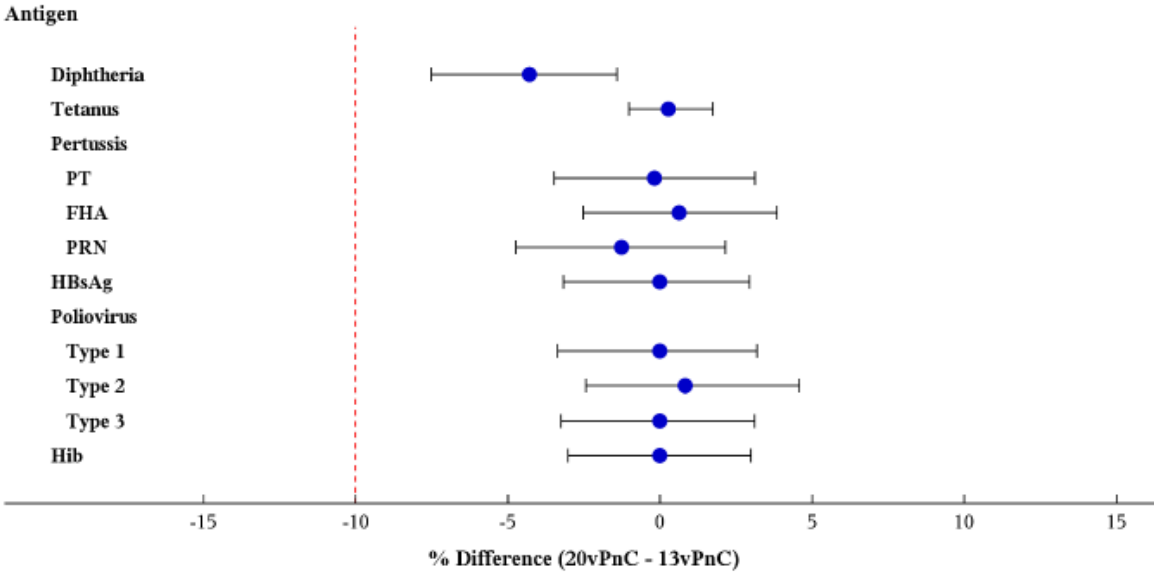
For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 4 of 20vPnC ranged from 57.8% (serotype 33F) to 86.8% (serotype 22F). There were no or very few participants with a ≥4-fold rise for the 7 additional serotypes in the 13vPnC group.

Concomitant immunogenicity objectives

In study B7471011, the concomitant vaccine responses were assessed on randomly selected serum subsets with sufficient sera volumes. The NI of the percentages of participants with prespecified antibody levels to diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens between the 20vPnC group and the 13vPnC group at 1 month after dose 3 (age 7 months; primary concomitant immunogenicity objectives), as well as the NI of the GMRs of antibody levels to MMR and varicella vaccine antigens between the 20vPnC group and the 13vPnC group at 1 month after dose 4 (age 13-16 months; secondary concomitant immunogenicity objectives) were assessed using the same NI criteria as for the primary pneumococcal endpoints (2-fold criterion for a continuous endpoint and 10% criterion for a binary endpoint).

Table 43. **Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population**

Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population



Abbreviations: HBsAg = hepatitis B surface antigen; mIU/mL = milli-international units per milliliter; PT = pertussis toxoid.

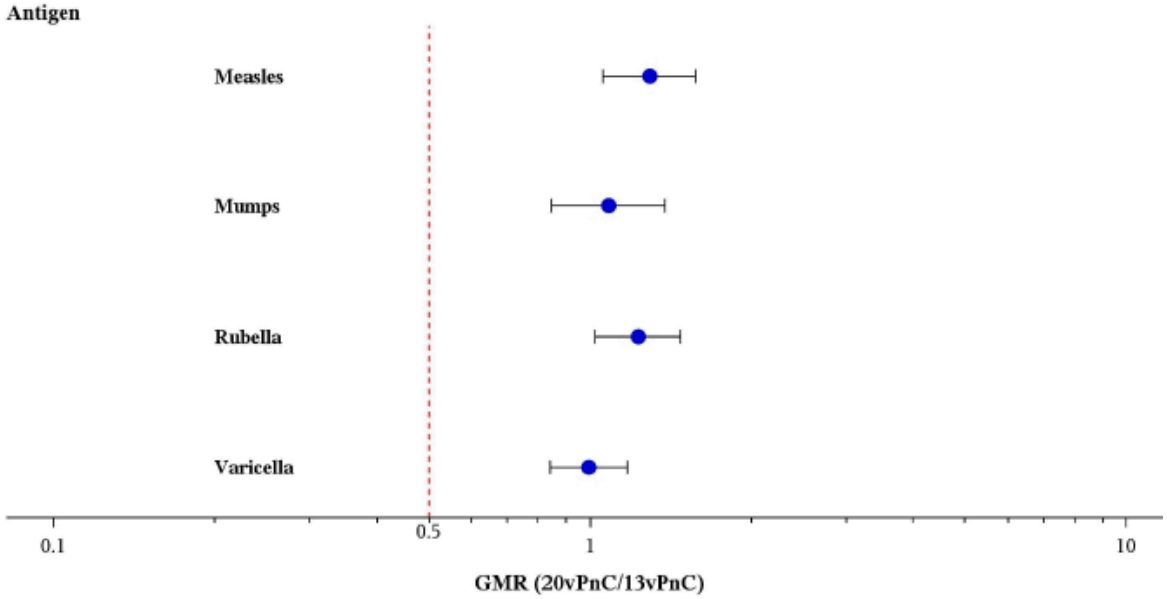
Note: The Dose 3 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with the first 3 doses.

Note: Antibody concentrations to the diphtheria, tetanus, pertussis, hepatitis B, poliovirus and Hib vaccine antigens were determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes.

Note: The prespecified antibody thresholds for the concomitant vaccine antigens are: diphtheria and tetanus toxoids ≥0.1 IU/mL; PT ≥14.40 EU/mL; FHA ≥26.60 EU/mL; PRN ≥13.00 EU/mL; HBsAg ≥10 mIU/mL; Poliovirus strains (types 1, 2, and 3) ≥1:8; Hib ≥0.15 µg/mL. The prespecified antibody thresholds for the concomitant vaccine antigens PT, FHA, and PRN are the observed antipertussis antibody concentration achieved by 95% of participants receiving 13vPnC.

Table 44. Forest Plot of GMRs (20vPnC) With 20Sided 95% Cis for Concomitant Vaccine Antigens – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

Forest Plot of GMRs (20vPnC/13vPnC) With 2-Sided 95% CIs for Concomitant Vaccine Antigens – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population



Abbreviations: GMR = geometric mean ratio; LLOQ = lower limit of quantitation.
Note: The Dose 4 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with Dose 4.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Antibody concentrations to the measles, mumps, rubella, and varicella vaccine antigens were determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes.
Note: GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of each specific concomitant vaccine antibody level (20vPnC − 13vPnC) and the corresponding CIs (based on the Student t distribution).

14.32. Concomitant Vaccine Antigen GMs and GMRs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Antigen (Units)	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])	GMR	(95% CI[c])
Measles (AU/mL)	234	277.74	(243.88, 316.30)	232	215.41	(184.61, 251.35)	1.29	(1.05, 1.58)
Mumps (AU/mL)	234	36.96	(30.82, 44.33)	232	34.19	(28.94, 40.39)	1.08	(0.85, 1.38)
Rubella (IU/mL)	234	49.63	(43.88, 56.13)	232	40.44	(35.19, 46.48)	1.23	(1.02, 1.48)
Varicella (mIU/mL)	231	233.05	(207.25, 262.06)	229	234.78	(208.84, 263.94)	0.99	(0.84, 1.17)

Abbreviations: AU/mL = arbitrary units per milliliter; GM = geometric mean; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; mIU/mL = milli-international units per milliliter.
Note: For this table, the Dose 4 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with Dose 4.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Antibody concentrations to the measles, mumps, rubella, and varicella vaccine antigens were determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes.
a. n = Number of participants with valid assay results for the specified antigen.
b. GMs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. CIs for the ratio are exponentiations of a CI, based on the Student t distribution for the mean difference of the logarithms of the measures (20vPnC – 13vPnC).

14.33. Concomitant Vaccine Antigen GMs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC			20vPnC/13vPnC	
Antigen (Units)	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])	GMR	(95% CI[c])
Diphtheria (IU/mL)	370	0.52	(0.47, 0.58)	363	0.64	(0.58, 0.71)	0.81	(0.71, 0.94)
Tetanus (IU/mL)	370	0.96	(0.89, 1.04)	363	0.96	(0.88, 1.04)	1.00	(0.89, 1.13)
Pertussis (EU/mL)								
PT	370	63.50	(58.50, 68.93)	363	66.74	(61.32, 72.64)	0.95	(0.85, 1.07)
FHA	370	89.49	(83.46, 95.96)	363	86.03	(80.12, 92.37)	1.04	(0.94, 1.15)
PRN	370	66.17	(59.81, 73.20)	363	60.55	(54.99, 66.69)	1.09	(0.95, 1.26)
HBsAg (mIU/mL)	118	2535.3	(2108.7, 3048.3)	127	3077.3	(2597.4, 3645.8)	0.82	(0.64, 1.06)
Poliovirus (Titer)								
Type 1	111	1721.2	(1458.0, 2032.1)	117	1824.5	(1540.7, 2160.5)	0.94	(0.75, 1.19)
Type 2	115	931.7	(774.9, 1120.2)	120	851.1	(695.0, 1042.4)	1.09	(0.83, 1.44)
Type 3	115	801.9	(721.5, 891.4)	120	723.1	(632.3, 827.0)	1.11	(0.94, 1.31)
Hib (µg/mL)	124	2.12	(1.66, 2.71)	125	2.04	(1.61, 2.58)	1.04	(0.74, 1.46)

Abbreviations: GM = geometric mean; GMR = geometric mean ratio; HBsAg = hepatitis B surface antigen; LLOQ = lower limit of quantitation; mIU/mL = milli-international units per milliliter; PT = pertussis toxoid; ULOQ = upper limit of quantitation.
Note: For this table, the Dose 3 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with the first 3 doses.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: For Hib assay values reported as >7.9 mg/L that could not be quantified precisely, a value of 8.0 mg/L was used. For HBsAg assay values reported as >10,000 mIU/mL that could not be quantified precisely, a value of 10,001 mIU/mL was used. For polio assay values >ULOQ, a value of ULOQ +1 was used, except where the plate range was < ULOQ, in which case values > plate range used a value of plate range +1.
Note: Antibody concentrations to the diphtheria, tetanus, pertussis, hepatitis B, poliovirus, and Hib vaccine antigens were determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes.
a. n = Number of participants with valid assay results for the specified antigen.
b. GMs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. CIs for the ratio are exponentiations of a CI, based on the Student t distribution for the mean difference of the logarithms of the measures (20vPnC – 13vPnC).

Ancillary analyses

In B7471011, subgroup analyses were performed separately by sex and by race for the primary and key secondary pneumococcal immunogenicity endpoints: IgG GMCs at 1 month after the toddler dose (Dose 4), the percentages of participants with predefined pneumococcal IgG concentrations at 1 month after the last infant dose (Dose 3), and IgG GMCs at 1 month after the last infant dose (Dose 3).

Robust immune responses to all 20 vaccine serotypes 1 month after Dose 3 and 1 month after Dose 4 in the 20vPnC group were observed for each of the sex and race subgroups based on percentage of participants with predefined IgG concentrations and IgG GMCs. There was a trend of slightly higher observed responses in female and Black or African American subgroups, but the sample sizes were small for the non-White population. The trends were consistent between the vaccine groups, so the relative responses between 20vPnC and 13vPnC groups within the subgroups were generally similar.

Summary of main studies

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

Table 45. Summary of Efficacy for trial B7471012 (3-dose series)

Title: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants (3-dose series)			
Study identifier	Protocol number: B7471012, EudraCT number: 2019-003306-27		
Design	Phase 3, multicentre, randomised, double-blind study conducted at investigator sites in Europe and Australia (results from a separate, small, Russian cohort are not included in this Type II variation)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 11 months not applicable not applicable
Hypothesis	Noninferiority to 13vPnC. For the 13 shared serotypes, NI comparisons were made to the corresponding serotypes in the 13vPnC group. For the 7 additional serotypes, NI comparisons were made to the lowest among the 13 serotypes (except for serotype 3) in the 13vPnC group.		
Vaccine groups	20vPnC		603 participants randomized to receive 3 doses of 20vPnC
	13vPnC		604 participants randomized to receive 3 doses of 13vPnC
			In both groups the first dose was given at 42 to 112 days of age, the second dose 42 to 63 days later, and the third dose given at 11 to 12 months of age
Endpoints and definitions	Primary pneumococcal endpoints	IgG conc	• % diff with predefined IgG conc PD2*: difference in the percentages of participants with the predefined IgG concentration 1 month after Dose 2 (last infant dose) • IgG GMR PD2**: geometric mean ratio of IgG concentrations 1 month after Dose 2 (last infant dose) • IgG GMR PD3**: geometric mean ratio of IgG concentrations 1 month after Dose 3 (toddler dose) *NI criterion for % diff: lower bound of the 2-sided 95% CI (20vPnC group – 13vPnC group) >-10% **NI criterion for IgG GMR: lower bound of the 2-sided 95% confidence interval (CI) for the IgG GMR (20vPnC group/13vPnC group) >0.5 (2-fold NI criterion)
	Secondary pneumococcal endpoints	IgG conc	• % diff with predefined IgG conc PD3: difference (20vPnC group – 13vPnC group) in the percentages of participants with the predefined IgG concentration 1 month after Dose 3 • IgG GMFR PD3: geometric mean fold-rise in IgG concentrations from before to 1 month after Dose 3
		OPA titres	• OPA GMT PD2: opsonophagocytic activity geometric mean titre 1 month after Dose 2 • OPA GMT PD3: OPA geometric mean titre 1 month after Dose 3

	Other supportive pneumococcal endpoints/ estimands	IgG conc	• % diff with alt predefined IgG conc PD2: difference (20vPnC group – 13vPnC group) in the percentages of participants with the alternate predefined IgG concentration 1 month after Dose 2 • IgG GMFR PD2 to PD3: geometric mean fold-rise in IgG concentrations from 1 month after Dose 2 to 1 month after Dose 3
	Exploratory pneumococcal endpoints/ estimands	IgG conc	• % with ⩾4 fold rise in IgG conc: percentage of participants with ⩾4-fold rise in IgG concentration from before to 1 month after Dose 3
		OPA titres	• % with OPA titres ⩾ LLOQ PD2: percentage of participants with OPA titres ⩾ the lower limit of quantitation 1 month after Dose 2 • % with OPA titres ⩾ LLOQ PD3: percentage of participants with OPA titres ⩾ LLOQ 1 month after Dose 3 • OPA GMFR PD3: geometric mean fold-rise in OPA titres from before to 1 month after Dose 3 • % with ⩾4 fold rise in OPA titres: percentage of participants with ⩾4-fold rise in OPA titres from before to 1 month after Dose 3
	Primary concomitant antigen endpoints	Antibody levels to PT, FHA, PRN, HBsAg, poliovirus strains, and Hib PD3	• % diff with prespecified Ab levels PD3: difference in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), hepatitis B surface antigen, poliovirus strains, and *Haemophilus influenzae* type B at 1 month after Dose 3 between the 20vPnC and the 13vPnC groups *NI criterion for % diff: lower bound of the 2-sided 95% CI (20vPnC group–13vPnC group) >-10%
		Antibody levels to MMR and varicella PD3	• GMR of Ab levels PD3: geometric mean ratio of antibody levels to measles, mumps, rubella, and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 3 *NI criterion for GMR: lower bound of the 2-sided 95% CI for the GMR (20vPnC group/13vPnC group) >0.5 (2-fold NI criterion)
Database lock	Date: 24 Aug 2022		
Results and Analysis			
Analysis description	Co-Primary Analysis: Non-inferiority of 20vPnC to 13vPnC based on difference in % of participants with the predefined IgG concentration (⩾0.35 µg/mL for all serotypes except 5 [⩾0.23 µg/mL], 6B [⩾0.10 µg/mL], and 19A [⩾0.12 µg/mL]) 1 month after Dose 2 (last infant dose)		

Analysis population and time point description	Dose 2 evaluable immunogenicity population: All eligible randomized participants who received the vaccines to which they were randomly assigned at the first 2 doses, had at least 1 valid immunogenicity result from the blood sample collection at the 1-month-after-Dose 2 visit within an appropriate window, and had no other major protocol deviations
Results	• 4 of the 13 matched serotypes met the 10% statistical NI criterion. • 9 of the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 9V, 18C and 23F) missed the statistical NI criterion. • 5 of the 7 additional serotypes met the 10% statistical NI criterion compared with the lowest percentage among the 13 serotypes (serotype 6B) in the 13vPnC group. • 2 of the 7 additional serotypes (10A and 12F) missed the statistical NI criterion CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation
Notes	Non-inferiority criterion was met for 4/13 shared serotypes, however the response rates were numerically lower with 20vPnC compared to 13vPnC. The percentage of participants with predefined serotype-specific IgG concentrations ranged from 20.7% (serotype 6B) to 94.3% (serotype 19F) in the 20vPnC group, and from 36.5% (serotype 6B) to 95.7% (serotype 19F) in the 13vPnC group. For the additional 7 serotypes, the percentage of participants with predefined serotype-specific IgG concentrations ranged from 28.9% (serotype 10A) to 96.5% (serotype 8) in the 20vPnC group.
Analysis description	Co-Primary Analysis: Non-inferiority of 20vPnC to 13vPnC based on IgG GMRs 1 month after Dose 2 (last infant dose)
Analysis population and time point description	Dose 2 evaluable immunogenicity population: All eligible randomized participants who received the vaccines to which they were randomly assigned at the first 2 doses, had at least 1 valid immunogenicity result from the blood sample collection at the 1-month-after-Dose 2 visit within an appropriate window, and had no other major protocol deviations
Results	• 9 of the 13 matched serotypes met the NI criterion. • 4 of the 13 matched serotypes (6A, 6B, 9V, and 23F) missed the NI criterion. • all of the 7 additional serotypes met the 2-fold statistical NI criterion compared with the lowest IgG GMC (serotype 6B) among the 13 serotypes in the 13vPnC group. CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation.
Notes	Non-inferiority to 13vPnC was shown for 9/13 shared serotypes, however, numerically lower IgG GMCs were observed with 20vPnC compared to 13vPnC. Point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.51 (serotype 6B) to 0.82 (serotype 14). The upper bound of 95% CIs for IgG GMR did not include unity for any serotype. For the shared serotypes, the IgG GMCs 1 month after Dose 2 ranged from 0.03 µg/mL (serotype 6B) to 2.21 µg/mL (serotype 19F) in the 20vPnC group and from 0.06 µg/mL (serotype 6B) to 3.06 µg/mL (serotype 19F) in the 13vPnC group. For the majority of serotypes in 20vPnC group, the IgG GMCs were very close to or even below the pre-defined cut-offs. For the 7 additional serotypes, the IgG GMCs ranged from 0.15 µg/mL (serotype 12F) to 3.33 µg/mL (serotype 15B) in the 20vPnC group 1 month after Dose 2. Pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in the 13vPnC group.
Analysis description	Co-Primary Analysis: Non-inferiority of 20vPnC to 13vPnC based on IgG GMRs 1 month after Dose 3 (toddler dose)

Analysis population and time point description	Dose 3 evaluable immunogenicity population: All eligible randomized participants who received all 3 randomized vaccinations, with Dose 3 received within the protocol-defined age window; had at least 1 valid immunogenicity result from the blood collection at the 1 month-after-Dose 3 visit within an appropriate window; and had no other major protocol deviations.
Results	• 12 of the 13 matched serotypes met the 2-fold statistical NI criterion. • Serotype 6B missed the NI criterion • All of the 7 additional serotypes met the 2-fold statistical NI criterion compared with the lowest IgG geometric mean concentration (GMC; serotype 5) among the 13 serotypes (excluding serotype 3) in the 13vPnC group. CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation
Notes	Serotype 6B missed the NI criterion for IgG GMCs 1 month after Dose 3 with a GMR of 0.57 and 2-sided 95% CI from 0.48 to 0.67. Although the non-inferiority margin of ⩾0.5 was met for 12/13 shared serotypes, numerically lower IgG GMCs were observed with 20vPnC compared to 13vPnC. The point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.57 (serotype 6B) to 0.82 (serotype 19A). The upper bound of 95% CIs for IgG GMR did not include unity for any serotype. For the shared serotypes, IgG GMCs ranged from 0.72 µg/mL (serotype 3) to 6.19 µg/mL (serotype 19F) in the 20vPnC group and from 1.09 µg/mL (serotype 3) to 11.82 µg/mL (serotype 6A) in the 13vPnC group. For the majority of shared serotypes, the IgG GMCs were well above the pre-defined cut-offs. For the 7 additional serotypes, IgG GMCs ranged from 1.86 µg/mL (serotype 12F) to 13.09 µg/mL (serotype 15B) in the 20vPnC group 1 month after Dose 3. Pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in the 13vPnC group.
Analysis description	Secondary analysis: Difference in % of participants with the predefined IgG concentration 1 month after Dose 3 (toddler dose)
Analysis population and time point description	Dose 3 evaluable immunogenicity population: All eligible randomized participants who received all 3 randomized vaccinations, with Dose 3 received within the protocol-defined age window; had at least 1 valid immunogenicity result from the blood collection at the 1 month-after-Dose 3 visit within an appropriate window; and had no other major protocol deviations
Results	• For the 13 matched serotypes, the observed differences (20vPnC–13vPnC) ranged from -10.6% (2-sided 95% CI: -14.7%, -6.7%) for serotype 3 to 1.0% (2-sided 95% CI: -0.5%, 2.7%) for serotype 18C). • For the 7 additional serotypes, the observed differences (20vPnC– lowest 13vPnC) ranged from -0.6% for serotype 12F (2-sided 95% CI: -2.9%, 1.6%) to 2.2% for serotype 15B (2-sided 95% CI: 0.7%, 4.1%). CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation
Notes	For the shared serotypes, the percentage of participants with predefined IgG concentrations ranged from 82.6% (serotype 3) to 99.6% (serotypes 7F, 14, 19A and 19F) in the 13vPnC group, and from 93.2% (serotype 3) to 100% (serotype 7F) in the 13vPnC group. Although non-inferiority was not formally tested for the response rate after Dose3, for serotype 3 the point estimate for the difference in response rate was below -10% (-10.6% (95% CI -14.7%, -6.7%).

Table 46. Summary of Efficacy for trial B7471011 (4-dose series)

Title: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants			
Study identifier	Protocol number: B7471011, EudraCT number: 2019-003305-10		
Design	Phase 3, multicenter, randomized, double-blind trial conducted at investigator sites in the continental United States and the US territory of Puerto Rico		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 16 to 19 months Not applicable Not applicable
Hypothesis	Noninferiority to 13vPnC. For the 13 shared serotypes, NI comparisons were made to the corresponding serotypes in the 13vPnC group. For the 7 additional serotypes, NI comparisons were made to the lowest among the 13 serotypes (except for serotype 3) in the 13vPnC group.		
Vaccine groups	20vPnC		1004 participants randomized to receive 4 doses of 20vPnC
	13vPnC		993 participants randomized to receive 4 doses of 13vPnC
			Vaccines were given at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively)
Endpoints and definitions	Primary pneumococcal endpoints	IgG conc	• % diff with predefined IgG conc PD3**: difference (20vPnC–13vPnC) in the percentages of participants with the predefined IgG concentration 1 month after Dose 3 (last infant dose) • IgG GMR PD4*: geometric mean ratio (20vPnC/13vPnC) of IgG concentrations 1 month after Dose 4 (toddler dose)
	Key Secondary pneumococcal endpoints/ estimands	IgG concs	• IgG GMR PD3*: geometric mean ratio (20vPnC/13vPnC) of IgG concentrations 1 month after Dose 3 (last infant dose) *NI criterion for IgG GMR: lower bound of the 2-sided 95% confidence interval (CI) for the IgG GMR (20vPnC group/13vPnC group) >0.5 (2-fold NI criterion) **NI criterion for % diff: lower bound of the 2-sided 95% CI (20vPnC group – 13vPnC group) >-10%
		OPA titres	• OPA GMT PD3: OPA geometric mean titre 1 month after Dose 3 • OPA GMT PD4: OPA geometric mean titre 1 month after Dose 4
	Primary concomitant antigen endpoints/estimand	Antibody levels to PT, FHA, PRN, HBsAg, poliovirus strains, and Hib PD3	Antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), hepatitis B surface antigen, poliovirus strains, and *Haemophilus influenzae* type B 1 month after Dose 3 % diff with prespecified Ab levels PD3: difference in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib at 1 month after Dose 3 between the 20vPnC and the 13vPnC groups *NI criterion for % diff: lower bound of the 2-sided 95% CI (20vPnC group – 13vPnC group) >-10%
Database lock	Date: 09 Sep 2022		
Results and Analysis			
Analysis description	Co-primary Analysis: Non-inferiority of 20vPnC to 13vPnC based on difference in % of participants with the predefined IgG concentration (≥0.35 µg/mL for all serotypes except 5 [≥0.23 µg/mL], 6B [≥0.10 µg/mL], and 19A [≥0.12 µg/mL]) 1 month after Dose 3 (last infant dose)		

Analysis population and time point description	Dose 3 evaluable immunogenicity population: All eligible randomized participants who received the vaccines to which they were randomly assigned at the first 3 doses, had at least 1 valid and determinate immunogenicity result from the 1-month-after-Dose 3 visit, had blood collection within an appropriate window after Dose 3, and had no other major protocol deviations.
Results	• 8 of the 13 matched serotypes met the 10% statistical NI criterion. • 5 of the 13 serotypes (1, 3, 4, 9V, and 23F) missed the statistical NI criterion • 6 of the 7 additional serotypes met the 10% statistical NI criterion compared with the lowest percentage among the 13 serotypes (serotype 6B) in the 13vPnC group. • Serotype 12F missed the statistical NI criterion. CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation.
Notes	For serotype 3, the 95% CI lay entirely below the NI margin of -10%. Even for the 8/13 shared serotypes for which NI criterion was met, numerically lower response rates were observed with 20vPnC compared to 13vPnC. The percentage of participants with predefined serotype-specific IgG concentrations ranged from 52.1% (serotype 3) to 97.1% (serotype 19A) in the 20vPnC group, and from 67.6% (serotype 3) to 98.1% (serotype 19A) in the 13vPnC group. Of 7 additional serotypes, serotype 12F missed the NI criterion, as the percentage point difference (20vPnC-13vPnC) was -18.1 and the entire 95% CI lay below the NI margin (95% CI -22.1%, -14.0%). For the additional 7 serotypes, the response rate ranged from 67.5% (serotype 12F) to 98.3% (serotype 22F) in the 20vPnC group.
Analysis description	Key Secondary Analysis: Non-inferiority of 20vPnC to 13vPnC based on IgG GMRs 1 month after Dose 3 (last infant dose)
Analysis population and time point description	Dose 3 evaluable immunogenicity population: All eligible randomized participants who received the vaccines to which they were randomly assigned at the first 3 doses, had at least 1 valid and determinate immunogenicity result from the 1-month-after-Dose 3 visit, had blood collection within an appropriate window after Dose 3, and had no other major protocol deviations.
Results	• All of the 13 matched serotypes met the 2-fold statistical NI criterion. • All of the 7 additional serotypes met the 2-fold statistical NI criterion compared with the lowest IgG GMC (serotype 19A) among the 13 serotypes (excluding serotype 3) in the 13vPnC group. CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation.
Notes	Although the NI criterion of ≥0.5 was met for all shared serotypes, numerically lower IgG GMCs were observed with 20vPnC compared to 13vPnC. For shared serotypes, the point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.60 (serotype 6B) to 0.79 (serotypes 14, 19A and 19F). The upper bound of 95% CIs for IgG GMR did not include unity for any serotype. The IgG GMCs ranged from 0.36 µg/mL (serotype 3) to 2.16 µg/mL (serotype 14) in the 20vPnC group and from 0.51 µg/mL (serotype 3) to 2.72 µg/mL (serotype 14) in the 13vPnC group. For the majority of serotypes, the IgG GMCs were above the pre-defined cut-offs. Only for serotype 3, the lower bound of the 95% CI of IgG GMC was at 0.33 µg/mL, which is below the cut-off of 0.35 µg/mL. The IgG GMCs of 7 additional serotypes 1 month after Dose 3 ranged from 0.55 µg/mL (serotype 12F) to 4.40 µg/mL (serotype 15B) in the 20vPnC group and from 0.01 µg/mL to 0.03 µg/mL in the 13vPnC group. Pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in the 13vPnC group.
Analysis description	Co-primary Analysis: Non-inferiority of 20vPnC to 13vPnC based on IgG GMRs 1 month after Dose 4 (toddler dose)
Analysis population and time point description	Dose 4 evaluable immunogenicity population: All eligible randomized participants who received all 4 randomized vaccinations, with Dose 4 received within the defined window (365 455 days of age); had at least 1 valid and determinate immunogenicity result after Dose 4; had blood collection within an appropriate window after Dose 4; and had no other major protocol deviations.

Results	• All of the 13 matched serotypes met the 2-fold statistical NI criterion. • All of the 7 additional serotypes met the 2-fold statistical NI criterion compared with the lowest IgG geometric mean concentration (GMC; serotype 1) among the 13 serotypes (excluding serotype 3) in the 13vPnC group. CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation.
Notes	The NI criterion for IgG GMRs after Dose 4 was met for all shared serotypes. Nonetheless, numerically lower IgG GMCs were observed with 20vPnC compared to 13vPnC for the 13 shared serotypes. For the shared serotypes, the point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.66 (serotype 3) to 0.90 (serotype 14). The upper bound of 95% CIs for IgG GMR did not include unity, except for the serotype 14 (95% CI 0.81, 1.00). For the shared serotypes, the IgG GMCs 1 month after Dose 4 ranged from 0.56 µg/mL (serotype 3) to 9.01 µg/mL (serotype 6A) in the 20vPnC group and from 0.85 µg/mL (serotype 3) to 11.69 µg/mL (serotype 6A) in the 13vPnC group. For the majority of shared serotypes in both groups, the IgG GMCs were well above the pre-defined cut-offs. For 7 additional serotypes, the IgG GMCs 1 month after Dose 4 ranged from 1.85 µg/mL (serotype 12F) to 12.59 µg/mL (serotype 15B) in the 20vPnC group. Pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in the 13vPnC group.
Analysis description	Difference in % of participants with the predefined IgG concentration 1 month after Dose 4 (toddler dose)
Analysis population and time point description	Dose 4 evaluable immunogenicity population: All eligible randomized participants who received all 4 randomized vaccinations, with Dose 4 received within the defined window (365 455 days of age); had at least 1 valid and determinate immunogenicity result after Dose 4; had blood collection within an appropriate window after Dose 4; and had no other major protocol deviations.
Results	• For the 13 matched serotypes, the observed differences (20vPnC – 13vPnC) in percentages of participants with predefined serotype-specific IgG concentrations 1 month after Dose 4 ranged from -12.1% (serotype 3) to 0.3% (serotype 18C) • For the 7 additional serotypes, the observed differences in percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 4 ranged from -1.9% (serotype 12F) to 2.6% (serotype 15B), between the 20vPnC group and the lowest percentage among the 13 serotypes (serotype 1, excluding serotype 3) in the 13vPnC group CAVE: For the 7 additional serotypes, comparison was made to the lowest response in the control arm; such comparison has the potential to mislead interpretation of the IgG response due to systematic overestimation.
Notes	For the 13 shared serotypes, the response rate ranged between 73.6% (serotype 3) and 99.9% (serotype 7F) in the 20vPnC group and between 85.8% (serotype 3) and 99.9% (serotype 7F) in the 13vPnC group. Although NI was not formally tested for this endpoint, for serotype 3 the point estimate for the difference in response rate was below -10% (-12.1% (95% CI -16.2, -8.1%)). For the 7 additional serotypes, the observed percentages of participants with predefined serotype-specific IgG concentration ranged from 95.2% (serotype 12F) to 99.7% (serotype 15B) in the 20vPnC group.

Clinical studies in special populations

There were no studies in special populations with 20vPnC. During a scientific advice procedure, the CHMP agreed that, given the experience with Prevenar 13 in special populations (sickle cell disease, HIV infection, or with an hematopoietic stem cell transplant, preterm), a successful demonstration of comparable immune responses for the 20-valent vaccine vs. Prevenar 13 could allow similar statements to appear in the SmPC for the 20-valent vaccine. However, the SmPC would clarify that the statement is based on data with Prevenar 13. This agreement is upheld.

Supportive studies

The data presented below regarding the percentage of participants with pre-defined IgG concentrations are based on the thresholds initially pprovided by the Applicant, which were not endorsed by the CHMP. However, as the results in the main studies are comparable between the initially submitted analysis and the post-hoc analyses, no updated analyses were requested for the supportive studies.

Phase 3 Trial in US Participants ≥15 Months to <18 Years of Age (B7471014)

B7471014 is a Phase 3, multicentre, open-label, single-arm trial in participants ≥15 months to <18 years of age at the time of consent. The trial was conducted at 40 sites in the US. Participants 15 months to <5 years of age were required to have documentation of at least 3 doses of 13vPnC prior to enrolment. The information on the most recent dose of pneumococcal vaccine was also collected if available in participants ≥5 years of age (Cohorts 3 and 4). This trial was performed to provide 20vPnC immunogenicity data in children in the setting of a well-established national infant pneumococcal conjugate immunization program, where direct protection against the 7 additional serotypes may offer benefit, and to support an indication for 20vPnC in children up to <18 years of age.

Study Participants: The study population consisted of healthy male or female children ≥15 months to <18 years of age at the time of consent (Cohort 1: ≥15 to <24 months, Cohort 2: ≥2 to <5 years, Cohort 3: ≥5 to <10 years, and Cohort 4: ≥10 to <18 years; approximately 200 participants in each cohort).

For children ≥15 months to <5 years of age (Cohorts 1 and 2): written documentation of receipt of at least 3 doses of 13vPnC; the last dose of 13vPnC was to have been administered >2 months before enrollment into the trial.

Subjects with a history of microbiologically proven invasive disease caused by *S. pneumoniae*, adverse reactions to vaccination, significant neurological disorders or with known/suspected immunodeficiency or under immunosuppressive therapy were excluded from the study population. In addition, previous vaccination with any investigational pneumococcal vaccine or with PPSV23, or planned receipt through trial participation resulted in exclusion.

Treatments Participants received a single dose of 20vPnC on Day 1 (Visit 1). Participants returned for Visit 2, approximately 1 month (28 to 42 days) after Visit 1. Participants' parents/legal guardians were contacted via telephone for safety follow-up Visit 3, approximately 6 months (168 to 196 days) after Visit 1. The duration of this trial for each participant was approximately 6 months.

Objectives: The objectives of this study were (1) to demonstrate that the serotype-specific IgG concentrations for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC (Cohort 1 and Cohort 2), (2) to demonstrate that the serotype-specific OPA titres for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding OPA titres before 20vPnC (Cohort 3 and Cohort 4), (3) to further describe the immune responses to 20vPnC in Cohorts 1, 2, 3 and 4.

Endpoints

Primary Immunogenicity Endpoint(s)

- Cohorts 1 and 2: Pneumococcal serotype-specific IgG concentrations for the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) before and 1 month after 20vPnC

- Cohorts 3 and 4: Pneumococcal serotype-specific OPA titres for the 7 additional serotypes before and 1 month after 20vPnC

Secondary Endpoint(s)

- Pneumococcal serotype-specific IgG concentrations before and 1 month after 20vPnC
  Fold changes in IgG concentrations will be calculated for each participant by taking the ratio of assay results from the later visit to the earlier visit for the 13vPnC serotypes in Cohorts 1 and 2 and for all 20 serotypes in Cohorts 3 and 4.
- Pneumococcal serotype-specific OPA titres before and 1 month after 20vPnC
  - Fold changes in OPA titres for all 20 serotypes in Cohorts 1 and 2 and for the 13vPnC serotypes in Cohorts 3 and 4
  - Classification of fold changes as a $\geqslant$4-fold rise for the 7 additional serotypes in Cohorts 2, 3, and 4. The 4-fold rise in OPA titres is being performed on children traditionally considered to have a more mature immune response to polysaccharide antigens ($\geqslant$2 years of age)

Prior pneumococcal vaccination

Participants' age at the time of their last 13vPnC or 7vPnC vaccination will be categorized as <1 year of age or $\geqslant$1 year of age. Additionally, time since the last 13vPnC or 7vPnC vaccination will be categorized in the following intervals: 2 to<6 months, 6 to<12 months, 1 to<5 years, 5 to<10 years, and 10 years or more.

Hypotheses and Decision Rules

Cohort 1 and Cohort 2

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the IgG concentrations for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the IgG concentrations before 20vPnC within each cohort. The null hypothesis (H0) for a serotype is

H_0: $\mu_{\text{fold rise}} \leqslant 1.0$

where

- $\mu_{\text{fold rise}}$ is the geometric mean of the fold rise in IgG concentration from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI calculated based on the Student's t-distribution for the IgG GMFR is greater than 1.0.

Cohort 3 and Cohort 4

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the OPA titres for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the OPA titres before 20vPnC within each cohort. The null hypothesis (H0) for a serotype is

H_0: $\mu_{\text{fold rise}} \leqslant 1.0$

where

- $\mu_{\text{fold rise}}$ is the geometric mean of the fold change in OPA titre from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI calculated based on the Students t-distribution for the OPA GMFR is greater than 1.0.

Disposition of participants

A total of 839 participants were enrolled — between 203 and 219 participants in each of the 4 age cohorts. Approximately 99% of participants in each cohort were vaccinated (831 participants in total). Greater than 95.0% of participants in each age cohort completed all visits per protocol.

A small percentage (≤4.1% in each age cohort) of participants were withdrawn from the trial; the most common reason for withdrawal was lost to follow-up. The one participant (≥10 years of age; Cohort 4) in the "other" category was withdrawn per physician decision for non-safety reasons (Appendix 16.2.1.1). No participant discontinued from the trial due to an AE or specifically for COVID-19-related reasons.

Populations analysed

The number of participants included in the all-available and evaluable immunogenicity populations were similar. Since the difference between the numbers of participants in the evaluable immunogenicity population and the all-available immunogenicity population was <10%, no analyses were performed for the all-available immunogenicity population per the study SAP.

Baseline characteristics

Demographic and baseline characteristics of sex, race, and ethnicity for the safety population were generally similar across the 4 age cohorts. There were somewhat more male participants in each age cohort, except in participants ⩾2 to <5 years of age (Cohort 2, which had an approximately equal distribution). The majority of the study population was White (80.1% to 86.8%/cohort), and non-Hispanic/non-Latino (78.5% to 83.6%/cohort) across all age cohorts.

Table 47

Table 5. Timing of Last Prior Dose of 13vPnC or 7vPnC – All Vaccinated Participants

	20vPnC			
	≥15 to <24 Months (N[a]=209) n[b] (%)	≥2 to <5 Years (N[a]=216) n[b] (%)	≥5 to <10 Years (N[a]=201) n[b] (%)	≥10 to <18 Years (N[a]=205) n[b] (%)
Age at the time of last dose of 13vPnC	209 (100.0)	216 (100.0)	NA	NA
<1 Year	52 (24.9)	25 (11.6)	NA	NA
≥1 Year	157 (75.1)	191 (88.4)	NA	NA
Time since last dose of 13vPnC or 7vPnC				
2 to <6 Months	80 (38.3)	4 (1.9)	0	0
6 to <12 Months	125 (59.8)	11 (5.1)	0	0
1 to <5 Years	4 (1.9)	201 (93.1)	34 (16.9)	4 (2.0)
5 to <10 Years	NA	NA	145 (72.1)	42 (20.5)
≥10 Years	NA	NA	NA	138 (67.3)

Abbreviation: NA = not applicable

Immunogenicity results:

Participants ⩾15 to <24 Months of Age (Cohorts 1 and 2)

IgG GMFRs for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

Substantial increases in IgG concentrations were observed 1 month after 20vPnC for all 7 additional serotypes. The IgG concentrations for all 7 additional serotypes after 20vPnC were superior to those

before vaccination in participants ≥15 to <24 months of age, as demonstrated by the lower bound of the 2-sided 95% CI for each of the IgG GMFRs >1.0. The observed IgG GMFRs ranged from 27.9 (serotype 12F) to 1847.7 (serotype 22F), with lower 2-sided 95% CIs of 22.9-fold (serotype 12F) or higher.

The IgG GMCs for the 7 additional serotypes were low (≤0.04 µg/mL) before 20vPnC in participants ≥15 to <24 months of age. GMCs increased substantially after 20vPnC, ranging from 1.17 µg/mL (serotype 15B) to 9.57 µg/mL (serotype 22F) for 6 of the 7 additional serotypes and was 0.22 µg/mL for serotype 12F.

Table 48. **Pneumococcal IgG GMFRs for the 7 Additional Serotypes – Participants ≥15 Months to <5 Years of Age – Evaluable Immunogenicity Population**

			Sampling Time Point					
			Before Vaccination		1 Month After Vaccination		Fold Rise	
Serotype	Age Cohort	n[a]	GMC[b]	95% CI[b]	GMC[b]	95% CI[b]	GMFR[b]	95% CI[b]
8	≥15 to <24 Months	186	0.04	(0.03, 0.05)	4.67	(4.16, 5.24)	113.4	(93.2, 137.9)
	≥2 to <5 Years	178	0.05	(0.04, 0.06)	5.04	(4.41, 5.76)	107.0	(86.1, 133.0)
10A	≥15 to <24 Months	188	0.01	(0.01, 0.02)	1.23	(1.02, 1.48)	83.2	(69.1, 100.2)
	≥2 to <5 Years	181	0.03	(0.02, 0.03)	2.76	(2.28, 3.34)	106.7	(86.2, 132.0)
11A	≥15 to <24 Months	188	0.03	(0.02, 0.03)	1.61	(1.39, 1.86)	62.7	(49.9, 78.8)
	≥2 to <5 Years	182	0.06	(0.04, 0.08)	2.64	(2.25, 3.09)	43.6	(33.2, 57.1)
12F	≥15 to <24 Months	188	0.01	(0.01, 0.01)	0.23	(0.19, 0.28)	27.9	(22.9, 34.1)
	≥2 to <5 Years	182	0.01	(0.01, 0.01)	0.38	(0.31, 0.46)	36.6	(30.1, 44.7)
Serotype	Age Cohort	n[a]	GMC[b]	95% CI[b]	GMC[b]	95% CI[b]	GMFR[b]	95% CI[b]
15B	≥15 to <24 Months	188	0.02	(0.02, 0.03)	1.16	(0.97, 1.39)	52.1	(43.2, 62.8)
	≥2 to <5 Years	180	0.05	(0.04, 0.07)	3.99	(3.14, 5.06)	73.3	(58.7, 91.5)
22F	≥15 to <24 Months	188	0.01	(0.00, 0.01)	9.61	(8.13, 11.35)	1847.7	(1481.3, 2304.5)
	≥2 to <5 Years	182	0.02	(0.01, 0.02)	12.46	(10.82, 14.35)	796.2	(577.1, 1098.4)
33F	≥15 to <24 Months	188	0.02	(0.01, 0.02)	1.90	(1.59, 2.26)	113.5	(92.5, 139.2)
	≥2 to <5 Years	182	0.04	(0.03, 0.05)	3.16	(2.63, 3.79)	78.3	(61.6, 99.5)

Percentage of Participants With Predefined IgG Concentrations for the 7 Additional Serotypes 1 Month After 20vPnC

Table 49. **Number (%) of Participants ≥15 to <24 Months of Age With Predefined Levels for Pneumococcal IgG Concentrations for the 7 Additional Serotypes – 1 Month After Vaccination – Evaluable Immunogenicity Population**

			20vPnC ≥15 to <24 Months		
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])

Participants ⩾2 to <5 Years of Age (Cohort 2)

Percentage of Participants With a ⩾4-Fold Rise in OPA Titres for the 7 Additional Serotypes From Before to 1 Month After 20vPnC (Key Secondary Objective)

Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])
11A	≥0.35 µg/mL	190	177	93.2	(88.6, 96.3)
12F	≥0.35 µg/mL	190	76	40.0	(33.0, 47.3)
15B	≥0.35 µg/mL	190	159	83.7	(77.6, 88.6)
22F	≥0.35 µg/mL	190	188	98.9	(96.2, 99.9)
33F	≥0.35 µg/mL	190	176	92.6	(87.9, 95.9)

Table 50.

Number (%) of Participants ≥2 to <18 Years of Age With a ≥4-Fold Rise in Pneumococcal OPA Titers for the 7 Additional Serotypes From Before to 1 Month After Vaccination – Evaluable Immunogenicity Population

	20vPnC											
	≥2 to <5 Years				≥5 to <10 Years				≥10 to <18 Years			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
8	74	69	93.2	(84.9, 97.8)	153	141	92.2	(86.7, 95.9)	174	155	89.1	(83.5, 93.3)
10A	73	62	84.9	(74.6, 92.2)	134	108	80.6	(72.9, 86.9)	142	116	81.7	(74.3, 87.7)
11A	52	45	86.5	(74.2, 94.4)	136	90	66.2	(57.6, 74.1)	155	97	62.6	(54.5, 70.2)
12F	74	70	94.6	(86.7, 98.5)	154	149	96.8	(92.6, 98.9)	164	155	94.5	(89.8, 97.5)
15B	76	67	88.2	(78.7, 94.4)	142	127	89.4	(83.2, 94.0)	164	154	93.9	(89.1, 97.0)
22F	68	59	86.8	(76.4, 93.8)	137	120	87.6	(80.9, 92.6)	168	136	81.0	(74.2, 86.6)
33F	73	52	71.2	(59.4, 81.2)	144	115	79.9	(72.4, 86.1)	158	119	75.3	(67.8, 81.8)

OPA GMTs and GMFRs

OPA titres for the 7 additional and 13vPnC serotypes were determined on serum samples from randomly selected subsets of participants ⩾2 to <5 years of age.

For the 7 additional serotypes, substantial increases in OPA GMTs were observed 1 month after 20vPnC in participants ⩾2 to <5 years of age. GMTs before vaccination ranged from 37 (serotype 12F) to 2179 (serotype 33F). GMTs after 20vPnC ranged from 4428 (serotype 8) to 28,076 (serotype 33F). OPA GMFRs ranged from 12.4 (serotype 33F) to 319.9 (serotype 12F).

IgG GMFRs for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

Substantial increases in IgG concentrations were observed 1 month after 20vPnC for all 7 additional serotypes. The IgG concentrations for all 7 additional serotypes after 20vPnC were superior to those before vaccination in participants ≥2 to <5 years of age, as demonstrated by the lower bound of the 2-sided 95% CI for each of the IgG GMFRs >1.0. The observed IgG GMFRs ranged from 36.6 (serotype 12F) to 796.2 (serotype 22F), with lower 2-sided 95% CIs of 30.1-fold (serotype 12F) or higher.

Participants **≥5** to <10 Years of Age (Cohort 3)

Percentage of Participants With a ≥4-Fold Rise in OPA Titres for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

The percentage of participants ≥5 to <10 years of age with a ≥4-fold rise in OPA titres for the 7 additional serotypes from before to 1 month after 20vPnC ranged from 66.2% (serotype 11A) to 96.8% (serotype 12F) (Table 48). The serotypes with relatively low percentages of participants with a ≥4-fold rise in OPA titres (serotypes 11A and 33F) were also the serotypes with high OPA GMTs before vaccination.

OPA GMFRs for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

Table 51.

Pneumococcal OPA GMFRs for the 7 Additional Serotypes – Participants ≥5 to <18 Years of Age – Evaluable Immunogenicity Population

			Sampling Time Point					
			Before Vaccination		1 Month After Vaccination		Fold Rise	
Serotype	Age Cohort	n[a]	GMT[b]	95% CI[b]	GMT[b]	95% CI[b]	GMFR[b]	95% CI[b]
8	≥5 to <10 Years	153	35	(28, 44)	3755	(3152, 4473)	106.5	(79.9, 142.0)
	≥10 to <18 Years	174	36	(29, 44)	3091	(2628, 3635)	86.3	(64.2, 115.9)
10A	≥5 to <10 Years	134	657	(446, 968)	20127	(16036, 25261)	30.6	(20.1, 46.6)
	≥10 to <18 Years	142	459	(316, 667)	15360	(12424, 18989)	33.5	(22.3, 50.1)
11A	≥5 to <10 Years	136	1423	(1006, 2013)	16464	(13074, 20733)	11.6	(7.6, 17.7)
	≥10 to <18 Years	155	808	(570, 1145)	12021	(9882, 14624)	14.9	(10.2, 21.8)
12F	≥5 to <10 Years	154	50	(39, 65)	23210	(18292, 29451)	463.6	(332.3, 646.7)
	≥10 to <18 Years	164	43	(34, 55)	19645	(16245, 23756)	454.1	(333.3, 618.7)
15B	≥5 to <10 Years	142	68	(47, 100)	26060	(19565, 34712)	380.8	(228.3, 635.2)
	≥10 to <18 Years	164	44	(31, 60)	21780	(16729, 28355)	499.0	(338.7, 735.3)
22F	≥5 to <10 Years	137	270	(171, 426)	34717	(27258, 44216)	128.5	(76.7, 215.3)
	≥10 to <18 Years	168	240	(155, 370)	26678	(21494, 33112)	111.2	(67.1, 184.3)
33F	≥5 to <10 Years	144	3210	(2699, 3818)	45518	(36088, 57411)	14.2	(10.9, 18.4)
	≥10 to <18 Years	158	2896	(2426, 3456)	33315	(26730, 41522)	11.5	(8.9, 14.9)

Participants **≥10** to <18 Years of Age (Cohort 4)

Percentage of Participants With a ≥4-Fold Rise in OPA Titres for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

For the 7 additional serotypes, the percentage of participants ≥10 to <18 years of age with a ≥4-fold rise in OPA titres from before to 1 month after 20vPnC ranged from 62.6% (serotype 11A) to 94.5% (serotype 12F) (Table 48). The serotypes with relatively low percentages of participants with a ≥4-fold rise in OPA titres (serotypes 11A and 33F) were also the serotypes with high OPA GMTs before vaccination.

OPA GMFRs for the 7 Additional Serotypes From Before to 1 Month After 20vPnC

Substantial increases in OPA titres were observed 1 month after 20vPnC for all 7 additional serotypes. The OPA GMTs for all 7 additional serotypes after 20vPnC were superior to those before vaccination in participants ≥10 to <18 years of age, as demonstrated by the lower bound of the 2-sided 95% CI for each of the OPA GMFRs >1.0 (Table 49). The observed OPA GMFRs ranged from 11.5 (serotype 33F) to 499.0 (serotype 15B), with lower 2-sided CIs of 8.9 (serotype 33F) or higher. The serotypes with relatively low GMFRs (serotypes 11A and 33F) were also the serotypes with high OPA GMTs before vaccination.

The observed OPA GMTs for the 7 additional serotypes were low before 20vPnC in participants ≥10 to <18 years of age. GMTs before vaccination ranged from 35 (serotype 8) to 2895 (serotype 33F) and increased substantially after 20vPnC, ranging from 3125 (serotype 8) to 32,363 (serotype 33F).

OPA GMTs and GMFRs for the 13vPnC Serotypes

OPA titres for the 13vPnC serotypes were determined on serum samples from a randomly selected subset of participants ≥10 to <18 years of age.

Increases in OPA GMTs were observed for all 13vPnC serotypes 1 month after 20vPnC in participants ≥10 to <18 years of age. GMTs before vaccination ranged from 11 (serotype 1) to 516 (serotype 7F). GMTs after 20vPnC ranged from 105 (serotype 3) to 10,085 (serotype 6B) (Supplemental Table 14.8). OPA GMFRs for the 13vPnC serotypes ranged from 5.8 (serotype 3) to 147.9 (serotype 6A) (Table 12).

Subgroup Analyses

Subgroup Analyses by Sex and Race

For the 7 additional serotypes, IgG GMFRs in participants ≥15 months to <5 years of age (Cohorts 1 and 2) and OPA GMFRS in participants ≥5 to <18 years of age (Cohorts 3 and 4) were generally similar in male and female participants and in each of the race subgroups.

Subgroup Analyses by Timing of Last Prior Dose of 13vPnC in Participants ≥15 to <24 Months of Age

Among participants ≥15 to <24 months of age, 24.9% (N = 52) received their last dose of 13vPnC as part of their routine health care prior to study enrollment at <1 year of age (ie, received 20vPnC in this study as a toddler dose following only infant doses of 13vPnC), and 75.1% (N = 157) received their last dose of 13vPnC at ≥1 year of age followed by 20vPnC in this study. The sample size was small in the subgroup with last prior 13vPnC dose at <1 year of age, but robust and comparable responses to the 13vPnC serotypes were observed after 20vPnC whether participants previously received infant doses of 13vPnC only, or infant and toddler doses of 13vPnC. The percentages of participants ≥15 to <24 months of age with predefined IgG concentrations for the 13vPnC serotypes 1 month after 20vPnC were generally similar in the 2 subgroups (Supplemental Table 14.18), with percentages in both subgroups >93% for 12 of the 13vPnC serotypes and 70.2% and 71.3% for serotype 3.

IgG GMCs for the 13vPnC serotypes before vaccination were higher in participants who received their last dose of 13vPnC at ⩾1 year of age, as expected in this group vaccinated with infant doses and a toddler dose of 13vPnC. At 1 month after 20vPnC, IgG GMCs were similar in the subgroups.

Phase 2 Trial in Infants (B7471003)

Study Design: Study B7471003 was a phase 2, multicenter, randomized, double-blind, active comparator-controlled trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine (20vPnC) in healthy infants and inform further clinical development of 20vPnC in the paediatric populations.

Treatment: Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (infant series, Doses 1 through 3) and 12 months of age (Dose 4). Pediarix (GSK), a vaccine containing diphtheria, tetanus, and acellular pertussis, polio, and hepatitis B antigens was provided by the sponsor for concomitant administration with Doses 1 to 3.

Study Participants: The study population consisted of healthy male or female infants born at >36 weeks of gestation and aged 2 months (≥42 to ≤98 days) at the time of consent. Study subjects did not receive previous vaccination with pneumococcal vaccines or had a history of microbiologically proven invasive disease caused by *S. pneumoniae*. Infants who received treatment with immunosuppressive therapy or with known/suspected immunodeficiency were also excluded from the study population.

A total of 460 participants were randomized across both vaccine groups. In the 20vPnC and 13vPnC groups, 83.2% and 82.5% of participants completed the visit 1 month after Dose 4, respectively.

Demographics and baseline characteristics, including age, gender and ethnicity were presented descriptively. The median age was 64.5 days, ranging from 44 to 95 days. The majority of participants (50.7% male; 49.3% female) were not Hispanic or Latino (81.0%). Demographic and baseline characteristics were generally comparable for vaccinated participants across intervention groups.

Objectives: The objectives of this study were (1) to describe the safety profile of 20-valent pneumococcal conjugate vaccine (20vPnC) in healthy infants, (2) to describe the immunogenicity of 20vPnC in healthy infants, (3) to further describe the immunogenicity of 20vPnC in healthy infants; to further describe the immunogenicity of 20vPnC in healthy infants.

Results:

Vaccination with 20vPnC elicited serotype-specific immune responses, as assessed by IgG GMCs at 1 month after dose 3 and dose 4, respectively for all 20 serotypes contained in the vaccine. For the 13 serotypes common to both 20vPnC and 13vPnC, the IgG GMCs were comparable but overall, numerically lower in the 20vPnC group compared to the 13vPnC group. For the 7 additional serotypes in 20vPnC, the IgG GMCs were higher in the 20vPnC group compared to the 13vPnC group.

Table 52.

Summary of Pneumococcal IgG GMCs – 1 Month After Dose 3 – 1 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	189	0.92	(0.81, 1.05)	187	1.16	(1.00, 1.33)
3	189	0.43	(0.38, 0.48)	187	0.56	(0.49, 0.64)
4	189	1.36	(1.16, 1.61)	187	1.64	(1.39, 1.93)
5	189	0.93	(0.79, 1.11)	187	1.13	(0.96, 1.34)
6A	189	2.28	(1.94, 2.67)	187	2.57	(2.16, 3.05)
6B	189	0.63	(0.49, 0.80)	187	0.99	(0.77, 1.27)
7F	189	2.15	(1.92, 2.40)	187	2.59	(2.28, 2.93)
9V	189	1.22	(1.05, 1.42)	187	1.45	(1.24, 1.70)
14	189	3.15	(2.69, 3.70)	187	3.60	(3.07, 4.21)
18C	189	1.59	(1.37, 1.84)	187	2.05	(1.76, 2.38)
19A	189	0.85	(0.74, 0.96)	187	1.02	(0.89, 1.17)
19F	189	1.98	(1.76, 2.22)	187	2.28	(1.99, 2.61)
23F	189	0.94	(0.78, 1.14)	187	1.26	(1.03, 1.55)
Additional						
8	189	2.09	(1.90, 2.30)	187	0.04	(0.03, 0.04)
10A	189	1.67	(1.35, 2.08)	187	0.03	(0.03, 0.03)
11A	189	1.94	(1.70, 2.21)	187	0.01	(0.01, 0.01)
12F	189	0.86	(0.72, 1.01)	187	0.02	(0.02, 0.02)
15B	189	5.86	(5.11, 6.72)	187	0.04	(0.04, 0.05)
22F	189	4.62	(3.99, 5.35)	187	0.01	(0.01, 0.01)
33F	189	2.21	(1.87, 2.61)	187	0.05	(0.04, 0.05)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.
b. GMCs and 2-sided CIs were calculated by back transforming the mean logarithm of the concentrations and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR/adva_s001_gmc_1md3_d3_eval Date of Generation: 06APR2020 (11:40)

Table 53

Summary of Pneumococcal IgG GMCs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	168	2.65	(2.33, 3.02)	166	3.63	(3.20, 4.11)
3	168	1.15	(0.97, 1.35)	166	1.49	(1.28, 1.74)
4	168	7.16	(6.22, 8.24)	166	9.45	(8.16, 10.95)
5	168	3.41	(2.95, 3.93)	166	4.95	(4.29, 5.71)
6A	168	13.77	(12.16, 15.59)	166	18.83	(16.39, 21.63)
6B	168	6.37	(5.42, 7.50)	166	9.73	(8.13, 11.65)
7F	168	6.14	(5.51, 6.83)	166	9.32	(8.26, 10.52)
9V	168	5.52	(4.82, 6.31)	166	7.78	(6.77, 8.95)
14	168	8.61	(7.32, 10.12)	166	11.04	(9.44, 12.90)
18C	168	5.58	(4.89, 6.36)	166	8.46	(7.25, 9.88)
19A	168	5.71	(4.91, 6.64)	166	7.05	(6.04, 8.24)
19F	168	7.79	(6.73, 9.01)	166	9.30	(7.99, 10.83)
23F	168	6.06	(5.16, 7.12)	166	9.81	(8.10, 11.88)
Additional						
8	168	3.12	(2.78, 3.49)	166	0.05	(0.04, 0.06)
10A	168	9.93	(8.58, 11.50)	166	0.03	(0.03, 0.04)
11A	168	5.70	(4.96, 6.54)	166	0.01	(0.01, 0.02)
12F	168	1.92	(1.68, 2.20)	166	0.02	(0.02, 0.03)
15B	168	18.45	(16.43, 20.72)	166	0.04	(0.04, 0.05)
22F	168	14.68	(12.62, 17.08)	166	0.01	(0.01, 0.01)
33F	168	4.70	(4.20, 5.27)	166	0.05	(0.04, 0.05)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.
b. GMCs and 2-sided CIs were calculated by back transforming the mean logarithm of the concentrations and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR/adva_s001_gmc_1md4_d4_eval Date of Generation: 06APR2020 (12:14)

OPA titres were determined on sera from a small number of randomly selected participants. For the 13 serotypes common to both 20vPnC and 13vPnC, the OPA geometric mean titres (GMTs) were usually numerically lower in the 20vPnC group compared to the 13vPnC group after dose 3 and dose 4, respectively. For the 7 additional serotypes in 20vPnC, OPA GMTs were higher in the 20vPnC group compared to the 13vPnC group.

Table 54

Summary of Pneumococcal OPA GMTs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	49	16.3	(12.8, 20.8)	56	31.3	(22.8, 43.0)
3	52	50.2	(39.0, 64.6)	57	61.8	(50.1, 76.2)
4	53	424.5	(296.2, 608.2)	54	390.3	(239.5, 636.0)
5	52	32.4	(25.1, 41.7)	56	45.2	(35.9, 57.0)
6A	51	817.0	(590.3, 1130.7)	57	866.8	(690.3, 1088.6)
6B	51	432.6	(287.0, 652.2)	57	668.8	(474.8, 942.2)
7F	52	1480.4	(1155.5, 1896.6)	57	1390.7	(1040.6, 1858.4)
9V	50	522.4	(359.1, 759.8)	55	601.4	(400.6, 902.7)
14	49	606.9	(400.9, 918.7)	55	456.9	(310.0, 673.4)
18C	49	1218.6	(948.2, 1566.2)	53	1491.7	(1070.7, 2078.2)
19A	53	105.3	(73.2, 151.4)	57	157.2	(105.1, 235.3)
19F	52	90.9	(66.2, 124.8)	57	121.2	(91.3, 160.9)
23F	47	234.1	(158.0, 346.7)	53	268.2	(157.0, 458.3)
Additional						
8	56	475.5	(346.6, 652.2)	57	17.3	(15.2, 19.8)
10A	61	1846.7	(1347.6, 2530.5)	57	36.8	(31.6, 42.8)
11A	60	423.9	(287.0, 626.3)	52	19.9	(14.6, 27.2)
12F	59	6084.9	(4578.8, 8086.4)	58	26.5	(22.7, 30.9)
15B	60	1085.8	(702.9, 1677.4)	57	22.8	(17.4, 29.9)
22F	53	6304.0	(4430.3, 8970.1)	59	11.1	(8.6, 14.1)
33F	57	7266.5	(4855.4, 10875.1)	57	60.7	(39.5, 93.3)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: OPA titers were determined on serum from a randomly selected subset of subjects assuring equal representation of both vaccine series in each subset.
a. n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.
b. GMTs and 2-sided CIs were calculated by back transforming the mean logarithm of the titers and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR_OPA/adva_s001_gmt_1md3_d3_eval Date of Generation: 02JUN2020 (15:53)

Table 55

Summary of Pneumococcal OPA GMTs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC						
1	49	50.4	(35.4, 71.9)	49	92.9	(65.9, 131.1)
3	46	93.0	(73.1, 118.4)	51	109.3	(92.4, 129.2)
4	48	490.3	(310.6, 774.0)	50	662.5	(415.3, 1056.9)
5	42	78.7	(59.3, 104.5)	50	112.8	(85.6, 148.6)
6A	44	1671.4	(1181.4, 2364.5)	50	2155.8	(1716.2, 2708.1)
6B	45	1354.9	(987.1, 1859.8)	49	1808.1	(1269.4, 2575.4)
7F	48	2590.7	(2143.2, 3131.7)	51	3280.7	(2576.5, 4177.5)
9V	48	1280.2	(981.6, 1669.7)	51	2030.0	(1469.6, 2804.3)
14	46	933.8	(715.8, 1218.1)	51	1127.9	(831.5, 1530.0)
18C	48	2016.2	(1596.5, 2546.1)	49	2703.3	(1980.4, 3690.0)
19A	47	651.3	(519.9, 816.0)	48	874.8	(650.6, 1176.4)
19F	46	500.5	(337.2, 743.0)	50	751.0	(546.6, 1032.0)
23F	45	693.1	(519.9, 923.8)	49	1253.9	(894.6, 1757.6)
Additional						
8	58	1721.7	(1298.7, 2282.6)	50	35.2	(23.2, 53.3)
10A	59	2697.7	(2082.3, 3494.8)	49	63.1	(43.2, 92.3)
11A	58	5307.7	(4007.3, 7030.2)	37	76.7	(33.6, 175.2)
12F	56	8518.9	(6030.5, 12034.1)	48	27.8	(22.6, 34.1)
15B	58	3087.9	(2304.5, 4137.6)	50	28.2	(19.1, 41.7)
22F	59	9339.2	(6575.3, 13265.0)	50	16.5	(11.0, 24.9)
33F	56	8244.6	(5797.7, 11724.2)	44	135.6	(77.7, 236.5)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: OPA titers were determined on serum from a randomly selected subset of subjects assuring equal representation of both vaccine series in each subset.
a. n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.
b. GMTs and 2-sided CIs were calculated by back transforming the mean logarithm of the titers and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./ndal/B7471003_CSR_OPA/adva_s001_gmt_1md4_d4_eval Date of Generation: 02JUN2020 (15:54)

The concomitant vaccine responses were assessed on randomly selected serum subsets with sufficient sera volumes. Antibody concentrations to the diphtheria and pertussis vaccine antigens were determined for 20vPnC and 13vPnC groups on sera collected 1 month after Dose 3. Overall, diphtheria and pertussis GMCs were similar after vaccination with 13vPnC or 20vPnC at the investigated interval.

Table 56

Summary of Diphtheria and Pertussis GMs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Concomitant Vaccine Antigen	n[a]	GM[b]	(95% CI[b])	n[a]	GM[b]	(95% CI[b])
Diphtheria	83	0.63	(0.53, 0.75)	96	0.61	(0.51, 0.73)
Pertussis						
PT	83	70.64	(59.41, 83.99)	96	78.06	(66.55, 91.56)
FHA	83	109.28	(94.97, 125.74)	96	102.48	(90.49, 116.05)
Pertactin	83	84.52	(69.77, 102.38)	96	67.12	(56.42, 79.86)

Abbreviations: FHA = filamentous hemagglutinin; GM = geometric mean; LLOQ = lower limit of quantitation; PT = pertussis toxoid.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: Antibody concentrations to the diphtheria and pertussis vaccine antigens were determined on sera collected 1 month after Dose 3 from a randomly selected subset of subjects with sufficient sera volumes.
a. n = Number of subjects with valid and determinate assay results for the given antigen at the specified time point.
b. GMs and 2-sided CIs were calculated by back transforming the mean logarithm of the concentrations and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR/adva_s001_dtap_1md3_d3_eval Date of Generation: 20APR2020 (11:48)

Additional considerations

- No studies have been performed to support the transitioning from another PCV to 20vPnC
- There is an ongoing study (B7471027) which will evaluate 1 or 2 catch-up doses of 20vPnC in toddlers 12-24 months of age (who have received 2 prior infant doses of Prevenar 13) and will also include a Prevenar 13 control arm.
- No studies have been performed to support catch up vaccination of unvaccinated children aged 7 months to 5 years of age

2.4.2. Discussion on immunogenicity

This application is based on the inference of 20vPnC effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of non-inferior immune responses to the 13 shared serotypes included in 13vPnC. The immunobridging approach is in accordance with EMA guidance (EMEA/CHMP/VWP/164653/2005) and has already been used for the approval of other pneumococcal conjugated vaccines.

A surrogate of protection, IgG of 0.35 µg/mL, has been established for invasive pneumococcal disease (IPD) in children, which can be used to infer protection against IPD. However, for pneumonia and acute otitis media (AOM), no correlate or surrogate of protection exists. 13vPnC has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed. However, no exact vaccine efficacy estimate was determined, nor the immune response required to achieve protection. Therefore,

the strategy of NI testing for 20vPnC to 13vPnC introduces the possibility that, since the observed immune response with 20vPnC was lower than with 13vPnC, 20vPnC might not be effective against pneumonia and AOM. The clinical significance of NI evaluations for pneumonia and AOM remains unknown. In addition, it is currently unknown whether the threshold of ≥0.35 µg/mL can also be considered protective for the new serotypes included in this vaccine for any indication.

Clinical study programme of Prevenar 20 in paediatric population comprised 5 clinical studies. Immunogenicity (alongside safety) was investigated in 4 clinical studies of which three are phase 3 studies (B7471012, B7471011 and B7471014) and one is a phase 2 study (B7471003). Studies B7471012 and B7471011 are considered pivotal as they provide the main evidence for immunogenicity and safety in the target population. An additional phase 3, randomised, double-blind trial in infants, using a 4-dose schedule study (B7471013) has been presented by the applicant. This was primarily a safety study, immunogenicity was not assessed, hence this study is not further discussed in this section.

Design and conduct of clinical studies

Both pivotal trials were phase 3, randomised, active-controlled, double-blind, multicentre, to evaluate the safety, tolerability, and immunogenicity of 20vPnC in healthy infants when administered as a series of 2 infant doses and 1 toddler dose (B7471012), or as a series of 3 infant doses and 1 toddler dose (B7471011). The former regimen is the most used regimen across the EU countries, while the latter represents an alternative regimen recommended in some EU countries or in specific cased e.g., in pre-term children. Both pivotal trials were designed to provide non-inferiority (NI) comparisons of the 20vPnC immune responses with those of 13vPnC. The choice of 13vPnC as comparator is acceptable, as 13vPnC is the only currently available conjugated pneumococcal vaccine for which effectiveness has been demonstrated in post-authorisation effectiveness studies. In addition, 20vPnC and 13vPnC were administered concomitantly with vaccines recommended in the frame of routine child vaccination programmes as offered in some European countries. Studies were conducted globally. Given different distribution of serotypes across the world, it is important to note that EU sites were also included in B7471012.

In both pivotal trials, last immunogenicity evaluations were performed approximately 1-month post-toddler dose; no measurements are available for later time points. This precludes assessment of the duration of the immune response and associated assumed long-term efficacy. In B7471012 safety follow-up was conducted for only one month after the last dose. However, this can be accepted since the safety data from the B7471011 study, for which the safety follow-up was 6 months, is reassuring (see safety).

Subjects were randomised in a 1:1 ratio to receive either 20vPnC or 13vPnC. In the 3-dose schedule vaccines were administered at roughly 2-3, 4-5, and 11-12 months of age, while in the 4-dose schedule vaccines were administered at roughly 2, 4, 6, and 12 to 15 months of age.

In B7471012 (3-dose series), the primary NI immunogenicity comparisons were based on 1) percentages of participants achieving predefined serotype-specific IgG concentrations at 1 month after the last infant dose (Dose 2); 2) serotype-specific IgG GMCs at 1 month after the last infant dose (Dose 2); and 3) IgG GMCs at 1 month after the toddler dose (Dose 3).

In B7471011 (4-dose series), the primary NI immunogenicity comparisons were based on 1) percentage of participants with predefined pneumococcal serotype-specific IgG concentration 1 month after the last infant dose (Dose 3); and 2) pneumococcal serotype-specific IgG concentration 1 month after the toddler dose (Dose 4). Pneumococcal serotype-specific IgG GMCs 1 month after last infant dose (Dose 3) has

been included as key secondary pneumococcal immunogenicity objective. Hypotheses were tested for primary and key secondary immunogenicity endpoints.

In general, the comparison of immune responses after the last infant dose is the most sensitive time point for detecting potential differences between vaccines. In addition, this time point is important to understand whether 20vPnC can provide a similar level of protection as 13vPnC for the 13 shared serotypes in the period between the last infant dose and the toddler dose.

The immunobridging approach based on non-inferiority is generally acceptable. However, it should be noted that, while the NI margin of -10% for the difference (20vPnC minus 13vPnC) in percentage of participants achieving the predefined IgG antibody concentration) and NI margin of 0.5 for the pneumococcal IgG GMR (20vPnC/13vPnC) have been previously used in clinical studies of authorised pneumococcal vaccines, they have not been justified from a clinical perspective. Therefore, meeting or not meeting these NI criteria is of unknown clinical relevance. The assessment and interpretation of analysis outcome contained in the assessment documents is thoroughly based on the margins that had been implemented.

The statistical methodology planned and applied per each of the numerous NI tests is considered adequate. However, there is poor correspondence between planning documents and the clinical study report (CSR) as regard the definition of the set of individual primary immunogenicity NI evaluations (hypothesis tests). The requirement to conclude NI in all primary tests was no longer pursued. The consequence thereof is in principle inadequate control of type-1-error. Also, further considerations in relation to multiplicity are hampered as 15/60 statistical tests did not reveal sufficient evidence to conclude on NI.

Furthermore, the approach for NI comparisons of the 7 additional serotypes against the lowest observed response among the vaccine serotypes in the 13vPnC group (excluding serotype 3) is considered rather uninformative and might even be potentially misleading. From the methodological perspective, this way of choosing the comparator threshold disregards the fact that IgG concentrations (/increases) for different serotypes follow different distributions (i.e., can be expected to differ in mean and variability). Consequently, the estimated values for the 20vPnC/13vPnC-ratios for GMC and percentage above predefined IgG-levels can get unreasonably high. Furthermore, given the tendency that lower mean response is associated with smaller variability in the raw concentration data, the width of the 95% CIs computed for the NI evaluation (for ratios) could become arbitrarily small. Consequently, NI testing setup for the 7 additional serotypes is not considered sufficiently informative, neither for the evaluation of IgG-response, nor for the potential implication for disease protection. Location and widths of the CIs as displayed in the corresponding figures of the CSR have a strong potential to mislead the interpretation of the actual response data for the 7 additional serotypes, with a clear systematic tendency for overestimation of the 20vPnC benefit. This is further aggravated using different assays for the 13 shared and the 7 additional serotypes, respectively, and the inadequacy to quantitatively compare titres. Consequently, the current approach hampers the interpretation of titres for the 7 additional serotypes in comparison to that of the 13 shared serotypes. Due to the above-mentioned shortcomings, additional immunogenicity response variables for which corresponding comparative analyses do not rely on so many arbitrary assumptions [e.g., GMFR and Proportions of Participants with ≥ 4 fold rise (IgG, OPA)] have also taken into consideration during assessment.

B7471014 was a single-arm trial which evaluated immunogenicity of a single dose of 20vPnC administered to participants ≥15 months to <5 years of age previously immunised with 13vPnC and participants ≥5 years to <18 years of age (regardless of previous vaccination with 7vPnC or 13vPnC) with respect to the 7 additional serotypes. The single-arm design of this study has already been questioned

during two scientific advice procedures. In addition, it appears that based on the results of this study, the MAH claims a broader indication. The information in the SmPC should reflect data available for Prevenar 20, with a reference which recommendations are based on experience with Prevenar 13.

Results and additional analyses

In both pivotal studies, the inclusion criterion was that infants are born at >36 weeks of gestation. No immunogenicity data is available for preterm infants.

In B7471012 (3-dose series), there were 3 primary pneumococcal immunogenicity endpoints: 1) Percentages of participants with predefined IgG concentrations after Dose 2, 2) Pneumococcal serotype-specific IgG GMCs after Dose 2 and 3) pneumococcal serotype-specific IgG GMCs after Dose 3. In B7471011 (4-dose series), there were two primary pneumococcal immunogenicity objectives: Percentages of participants with predefined IgG concentrations after Dose 3 (last infant dose), and Pneumococcal serotype-specific IgG GMCs after Dose 4 (toddler dose).

Both pivotal trials failed to meet their primary objectives as non-inferiority was not met for each of the 20 serotypes, for all co-primary endpoints (as required per respective study protocols). In B7471012 15/60 statistical tests failed, while in B7471011 6/40 tests failed. Both pivotal trials are thus considered formally failed.

The comparison of immune responses after last infant dose is considered the most sensitive time point to detect differences between vaccines. Results after the last infant dose are therefore presented separately from the results after the toddler dose, using both response rate and IgG GMC as main parameters of interest.

It is noted that assessment of percentage of participants with pre-defined IgG concentrations is based on thresholds initially provided by the Applicant, not endorsed by the CHMP and thus additional analyses were requested. Although the point estimates and the corresponding confidence intervals differed from the initially submitted analyses, the overall results were not substantially different, and the conclusions are maintained.

Immune response after last infant dose

B7471012 (3-dose series)

In B7471012, in total 11/20 serotypes missed the NI criterion for response rate, and 4/20 serotypes missed the NI criterion for IgG GMC 1 month after last infant dose in the 3-dose series (Dose 2).

Immune response was numerically lower in the 20vPnC group compared to 13vPnC group for all 13 shared serotypes, including those for which the NI criteria were met, as measured by both response rate and IgG GMC. Regarding response rates, the point estimates for majority of shared serotypes lay below the NI margin of -10%, and for serotypes 3, 6B and 23F, respective 95% CI lay entirely below the NI margin of -10%. Regarding IgG GMCs, the point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.51 (serotype 6B) to 0.82 (serotype 14). Importantly, for most shared serotypes in 20vPnC group, the IgG GMCs were very close to or even below the pre-defined cut-offs. In the 13vPnC group, IgG GMCs were generally higher and above the pre-defined cut-offs for most serotypes. Additional parameters after Dose 2 (RCDC, OPA GMTs) were overall consistent with primary endpoints i.e., numerically lower values were observed with 20vPnC compared to 13vPnC for majority of shared serotypes.

Two of the 7 additional serotypes (10A and 12F) failed the NI criterion for the response rate, whereas all met the NI criterion for the IgG GMC. The comparison of IgG GMC for the 7 additional serotypes was made for serotype 6B in 13vPnC group was strikingly similar to IgG GMC measured for serotype 15B in 13vPnC group (0.06 vs. 0.04 µg/mL), although the latter is not included in 13vPnC. Of note, for 3 additional serotypes (10A, 12F and 33F), the point estimates for IgG GMC were below the cut-off of 0.35 µg/mL. The NI testing setup for the 7 additional serotypes is not considered sufficiently informative and has a strong potential to mislead the interpretation of the actual response data for the 7 additional serotypes, with a clear systematic tendency for overestimation of the 20vPnC benefit. Hence, the position and width of the 95% CIs for additional serotypes in the forest plots must be interpreted with caution due to the potential of overestimation. For this reason, failure to meet NI criteria is particularly concerning. Furthermore, taking into consideration additional uncertainties with assays for the 7 additional serotypes discussed in the pharmacology section, as well as the dubious applicability of the IgG concentration of ≥0.35 µg/mL as a surrogate of protection for the additional serotypes, the immune response to the 7 additional serotypes is difficult to assess by means of parameters of primary interest (i.e., response rate and IgG GMC). IgG fold-rises are considered more reliable parameters; however, these were not presented from before Dose 2 to after Dose 2. Of note, IgG GMC before Dose 2 was measured only in a subset of participants. IgG GMCs and OPA titres for all 7 additional serotypes were higher than the IgG GMCs and OPA titres for the corresponding serotypes in the 13vPnC group (including OPA titres for serotypes 10A and 12F), which shows that 7 additional serotype elicit serotype-specific immune responses and offers mild reassurance as regards the potential benefit of these additional 7 serotypes.

B7471011 (4-dose series)

In B7471011, in total 6/20 serotypes missed the NI criterion for response rate; NI criterion was met for all serotypes for IgG GMC after last infant dose in the 4-dose series (Dose 3).

Like the 3-dose series, immune response in the 4-dose series was numerically lower in the 20vPnC group compared to 13vPnC group for all 13 shared serotypes, including those for which the NI criteria were met, as measured by both response rate and IgG GMC. The difference between vaccines in the 4-dose regimen was less pronounced than after the last infant dose in 3-dose regimen. The point estimates for majority of shared serotypes lay above the NI margin of -10%; only for serotype 3 the 95% CI lay entirely below the NI margin of -10%, suggesting potential benefit of an additional dose in the primary series. In contrast, the point estimates for IgG GMR (20vPnC/13vPnC) ranged from 0.60 (serotype 6B) to 0.79 (serotypes 14, 19A and 19F), which is in a similar range as with the 3-dose regimen. Nonetheless, for most serotypes (except serotype 3), the IgG GMCs were well above the pre-defined cut-offs in contrast to 3-dose regimen where majority of serotypes were below the predefined cut-offs.

As regards the 7 additional serotypes, same uncertainties as described above apply here. Serotype 12F missed the NI criterion for the response rate, and the entire 95% CI lay below the NI margin of -10%. No fold-rises from before Dose 3 to after Dose 3 were presented. IgG GMCs all 7 additional serotypes were much higher than the IgG GMCs and OPA titres for the corresponding serotypes in the 13vPnC group (including OPA titres for serotypes 10A and 12F), which shows that 7 additional serotype elicit serotype-specific immune responses and offers some reassurance as regards the benefit of the additional 7 serotypes. This difference was also more pronounced than in the 3-dose series.

Immune response after toddler dose

B7471012 (3-dose series)

After administration of toddler dose, differences between 20vPnC and 13vPnC generally decreased.

Only serotype 6B missed the NI criterion for IgG GMC, other shared serotypes met the NI criterion for IgG GMC. Non-inferiority was not formally tested for the response rate after Dose3. For the 13 matched serotypes, the observed differences (20vPnC–13vPnC) in response rate ranged from -10.6% (2-sided 95% CI: -14.7%, -6.7%) for serotype 3 to 1.0% (2-sided 95% CI: -0.5%, 2.7%) for serotype 18C). No substantial differences were seen between vaccines for the response rate except for the serotype 3, which had a lower bound <-10% at this time point. In contrast, numerically lower IgG GMCs were observed for majority of shared serotypes with 20vPnC compared to 13vPnC, despite meeting the NI criterion. The surrogate of protection was achieved by majority of participants for the shared serotypes. Further clarification was provided regarding the bridging between the assays used for the 13 shared serotypes in 20vPnC studies compared to the WHO ELISA. OPA GMTs are overall consistent with the results observed for IgG GMC i.e., numerically lower titres were measured with 20vPnC. Based on IgG GMFRs, two vaccines showed similar pattern at different time points and similar boosting potential. The boosting effect based on OPA GMFR was somewhat higher for 13vPnC compared to 20vPnC for all serotypes.

NI was shown for all additional 7 serotypes as assessed by the IgG GMC. The observed response rate ranged from 96.6% (serotype 12F) to 99.4% (serotype 15B). However, these results have to be interpreted with reservations. IgG (and OPA) GMFRs are considered more reliable variables. IgG GMFR for additional serotypes from before Dose 3 to after Dose 3 ranged from 12.7 (serotype 8) to 16.5 (serotype 12F) in the 20vPnC group and were broadly comparable with GMFRs of the 13 serotypes. The percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 83.5% (serotype 15B) to 95.5% (serotype 12F) in the 20vPnC group. The percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 3 ranged from 47.0% (serotype 33F) to 92.2% (serotype 22F) in the 20vPnC group. Very few participants had ≥4-fold- rises in IgG GMC or OPA titres for the 7 additional serotypes in the 13vPnC group, as expected.

The antibody concentration declined from 1 month after Dose 2 to before Dose 3, which ranged similarly in both groups and increased again after administration of toddler dose to levels higher than post Dose 2. This indicated that immune memory is induced.

B7471011 (4-dose series)

Consistent with observations for the 3-dose series, after administration of toddler dose, differences between 20vPnC and 13vPnC generally decreased. The NI criterion for IgG GMRs after Dose 4 was met for all shared and all additional serotypes. Results for the response rate were presented only descriptively. Although NI was not formally tested for this endpoint, for serotype 3 the point estimate for the difference in response rate was below -10% (-12.1%, 95% CI -16.2, -8.1%). The percentage of participants who achieved the pre-defined cut-off for the serotype 3 was 73.6% in the 20vPnC group compared to 85.8% in the 13vPnC group. For majority of shared serotypes in both groups, the IgG GMCs were well above the pre-defined cut-offs.

IgG GMFRs for additional serotypes from before Dose 4 to after Dose 4 ranged from 8.1 (serotypes 10A and 15B) to 10.0 (serotype 12F) in the 20vPnC group and were broadly comparable with GMFRs of the 13 serotypes. The percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 4 ranged from 77.6% (serotype 15B) to 90.6% (serotype 12F) in the 20vPnC group. Interestingly, these proportions were lower compared to those after toddler dose in the 3-dose regimen. Very few participants had ≥4-fold- rises for the 7 additional serotypes in the 13vPnC group, as expected. For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in OPA titres from before to 1 month after Dose 4 of 20vPnC ranged from 57.8% (serotype 33F) to 86.8% (serotype 22F).

In conclusion, following administration of toddler dose, IgG GMCs and the response rates increased compared to measurements after last infant dose in both vaccine groups. Whilst the immune response to 20vPnC was still lower compared to 13vPnC, differences between vaccines were less pronounced.

In both pivotal studies, antibody responses to concomitant vaccination with common infant vaccines were assessed. These analyses indicate that the immunogenicity of concomitant vaccination is similar when administered with 20vPnC or the authorised 13vPnC.

Overall immunogenicity data on 3-dose and 4-dose regimen

Significant differences between vaccines were observed after the last infant dose in the 3-dose regimen, demonstrated by multiple (15/40) failed NI tests for both primary endpoints (response rate and IgG GMC). Differences between vaccines were also observed after the last infant dose in the 4-dose regimen, albeit to a lesser extent. Given that the highest burden of invasive pneumococcal disease in paediatric population is in infants <1 year of age (ECDC Invasive pneumococcal disease - Annual Epidemiological Report for 2017, 2018), it is crucial that vaccines offer sufficient protection in the window between the last infant and the toddler dose (between 4-5 and 11-12 months of age).

Furthermore, a substantial disease burden at this age is also due to pneumonia and acute otitis media (AOM). As there is only a surrogate of protection available for IPD but not for pneumonia or AOM it is difficult to interpret the clinical impact of these lower titres on the protection against pneumonia and AOM. Moreover, higher antibody responses are thought to be necessary for the protection against pneumonia and AOM compared to IPD, as the protection should take place at the mucosal level or the ear instead of blood.

Considering the above-mentioned, the adequacy of the 2+1 regimen to achieve and maintain protection, especially in the window between the last infant and the toddler dose raises major concerns. The cross-study comparison, with direct comparisons between 20vPnC and 13vPnc within each study, indicate that the 3+1 regimen is more likely to achieve and maintain antibody levels above the threshold value for IgG between the last infant and the toddler dose. The available OPA data paint a similar picture. The MAH was asked to provide a thorough justification that, despite multiple failed NI tests and many serotypes being below the predefined cut-off for a protective level, the 3-dose regimen of 20vPnC offers sufficient protection against invasive pneumococcal disease in infants between the last infant and the toddler dose, particularly against severe courses of the disease. In addition, the MAH was asked to provide an elaborate justification for the 3-dose regimen, given overall better immune responses elicited after the last infant dose with 4-dose regimen.

In the response, the Applicant disputed the suitability of the IgG concentration threshold of 0.35 µg/mL for the purpose of inferring protection after 2 infant doses, given that this threshold was defined based on IgG concentrations after 3 infant doses; and argues that no IgG concentration threshold is established after 2 infant doses. Considering these limitations, the Applicant emphasised the importance of totality of data. It should be noted that CHMP considered the totality of data during assessment. It is stressed however, that the primary analysis should be based on IgG concentrations 4 weeks after completion of the primary infant immunization series; whereas analyses after the toddler dose are intended to detect whether an immune memory response has been induced during the infant immunisation series.

The Applicant further argued that the use of the 3-dose regimen substantially relies on the benefits of indirect protection elicited via high uptake of the toddler dose. As most of the European countries have high PCV uptake, the 13vPnC vaccine-type transmission levels are low, subsequently leading to indirect protection of unvaccinated persons of all age as well as incompletely vaccinated infants <1 year. Thus, the Applicant considers that despite the numerically lower immunogenicity with 20vPnC, infants

vaccinated with 3-dose regimen would not have a greater risk of 13vPnC vaccine-type IPD than infants vaccinated with 4-dose regimen as because they would be rarely exposed to vaccine serotypes. As the Applicant points out, currently in European countries 13vPnC-type IPD incidence is extremely low, suggesting low levels of 13vPnC transmission. However, the low IPD incidence and low levels of transmission are the result of effective vaccines on the market. As it is expected that 20vPnC would replace 13vPnC, given many uncertainties with the effectiveness of 20vPnC, it is unknown if the same level of herd immunity will be maintained.

Furthermore, the Applicant also put emphasis on previous experience with Prevenar 13, which, despite lower immunogenicity compared to 7vPnC observed during Prevenar13 registration studies, demonstrated to be effective in the post-marketing setting. However, the same does not necessarily applies to 20vPnC and cannot be used as argument, providing benefit of the doubt to Prevenar 20. These uncertainties are not restricted to one or two serotypes but pertain to all serotypes included in the vaccine. Furthermore, it remains unclear if a further reduction of antibody titres is still effective in prevention of disease.

The Applicant put focus on the non-inferiority analyses and the potential benefit of the 7 additional serotypes. It should be reiterated that substantial parts of the concern of the markedly lower immunogenicity compared to Prevenar-13 results from the poor immune response data for the 13 shared serotypes. The key requirement for a MAA is the successful bridging for the 13 shared serotypes in accordance with the immunobridging approach. The *potential benefit* of the 7 additional serotypes is not sufficient to offset the uncertainties related to the lower immunogenicity for the shared serotypes. Additionally, several limitations associated with the interpretation of the data for the 7 additional serotypes further contribute to the uncertainties regarding the *actual benefit* of the additional serotypes.

Given that the basis for this procedure is immunobridging to Prevenar-13, the additional trade-off analyses are not considered relevant. Even if such analyses might be considered, several assumptions and the methodology used in these trade-off analyses are not acceptable. Similarly, additional indirect comparisons to PCV-10 are not deemed relevant or suitable to counterbalance uncertainties arising from a direct comparison with Prevenar-13 within the current application.

In a nutshell, additional arguments did not alter the initial conclusion that the Benefit/Risk for the 3-dose regimen is considered negative. In contrast, given the overall better immunogenicity, the 4-dose regimen is more likely to achieve protection; this would however need to be confirmed in the post-marketing. This pertains to all serotypes contained in 20vPnC in general, and particularly to the 7 additional serotypes for which the interpretation of immunogenicity data was severely limited.
The Applicant proposed a multicountry IPD surveillance study to evaluate the effectiveness of 20vPnC against IPD. Following a feasibility assessment, the applicant determined that the indirect cohort method would be the preferred approach for evaluating direct vaccine effectiveness. An important limitation for the planned commitment is that the evaluation of 20vPnC effectiveness post-authorisation is contingent on the recommendation of 20vPnC for children according to the authorised posology and that the vaccine is used for several years. In addition, the Applicant confirmed that a respective study in the US is planned. Overall, the presented plans for confirming VE appear acceptable, however some specific aspects such as VE against 7 additional serotypes and the basis for the sample size calculations are missing. A detailed protocol proposal for CHMP approval should be provided before commencing the post-authorisation studies (REC). The final study results should be provided in the respective post-authorisation procedure (type II variation). The Applicant committed to submitting the requested information.

Supportive studies

Study B7471014

Study B7471014 provides some evidence on immunogenicity of 7 additional serotypes elicited by 20vPnC when administered as a single dose to infants previously vaccinated with at least 3 doses of 13vPnC and when administered as a single dose to children 5 to less than 18 years of age regardless of prior pneumococcal conjugate vaccination. However, it is unclear whether a single (priming) dose of 20vPnC is sufficient to achieve protection against the 7 extra serotypes and induces robust immunological memory. The incidence of paediatric pneumococcal disease declines with age, particularly in children >5 years of age. Though IPD is infrequent in this age group, the proportion of reported cases due to 20vPnC serotypes in some European countries is not considered irrelevant. A single dose of 20vPnC elicited immune response in all age subgroups. Whether the elicited immune response is sufficient to provide protection against pneumococcal disease due to additional 7 serotypes and how long this protection lasts is not determined. Nonetheless, a single dose of 20vPnC has a potential to offer some level of additional protection which could be important for subjects at high risk of pneumococcal disease. Therefore, a single dose of Prevenar 20 may be considered on an individual basis. As regards the potential protection against otitis media and pneumonia, no conclusions can be made based on provided data, since no correlate of protection for these indications and antibody concentrations that prevent otitis media are likely to be higher than those needed to protect against IPD. It should be noted that no safety data is available for paediatric population at higher risk of pneumococcal disease for Prevenar 20. However, based on experience with Prevenar13, it is not expected to be considerably worse compared to the healthy population.

Concomitant vaccinations

Antibody responses to concomitant vaccines were similar after vaccination with 13vPnC or 20vPnC across all studies. For instance, NI of 20vPnC compared to 13vPnC was demonstrated by the percentages of participants with pre-specified antibody levels to diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens at 1 month after dose 3 as well as the GMRs of antibody levels to MMR and varicella vaccine antigens at 1 month after dose 4 (B7471011). Hence, data provided indicate that the immunogenicity of concomitant vaccination with the specified vaccines is similar between 20vPnC and the approved 13vPnC. Since all participants received the respective concomitant vaccines, no conclusions can be drawn regarding potential differences between separate and concomitant vaccinations.

Additional expert consultation

The CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the immunogenicity results for the 2+1 regimen, discuss the following questions:

1. How do you evaluate the potential benefit of the seven added serotypes in the context of the EU epidemiological situation?

The experts noted the position of the MAH that most of the remaining paediatric invasive pneumococcal disease (IPD) burden is due to serotypes not included in 13-valent or 15-valent PCV. With PCV20 one could potentially address this residual disease burden by expanding protection to additional prevalent and medically important serotypes in Europe. As per data presented by the MAH for 2019, PCV20 covered 33-35% more paediatric IPD than PCV13 and 24-25% more than PCV15 in the EU (ECDC, 2019).

Experts concurred that there are reasons to believe that there is a potential benefit with the new vaccine, acknowledging the opportunity for prevention regarding the additional serotypes. However, it is difficult

to estimate the magnitude of this effect in the post-pandemic (COVID-19) period. It was noted that there are issues regarding the stated epidemiological figures because these are based on data from 2019 and do not reflect the recent evolution in epidemiology, representing the post-pandemic reality; hence the overall benefit of the seven added serotypes remains to be elucidated; e.g., from data in infants recently obtained in Spain, serotype 10A prevalence is recorded as relatively high and serotype 3, already included in PCV13, has been also seen in severe cases and vaccine-breakthrough infections. National IPD surveillance data (2022) from Spain (with PCV-13 coverage > 98 % in paediatric immunisation scheme) found that 11.5% of IPD in children <2 years of age was due to the serotype 3 (similar to figure for serotype 10A). For this serotype, immune response has been shown to be much lower in the 2+1 vaccination regimens than in 3+1 schemes. Since for serotype 10A also an obviously lower IgG response is shown after two infant doses of Prevenar 20, this observation remains a concern for adequate protection of the 6-11 months aged, and moreover in respect to the high-risk groups, including e.g., immunosuppressed, and premature born for whom adequate data on immunogenicity remains lacking.

The experts also acknowledged the argumentation that booster effect with toddler dose could reduce carriage of vaccine type *S. pneumoniae* and thus ultimately may indirectly protect infants and the overall population. They however asserted that the magnitude of such benefit remains difficult to estimate since the impact on carriage is still unknown, and the ultimate benefit may be short lived due to potential serotype replacement phenomenon.

2. To what extent do the immunogenicity results for the 2+1 regimen cause concerns of lower protection against the serotypes already included in Prevenar 13?

The MAH argued that although the serotypes missing non-inferiority (NI) for at least one primary objective post-infant series may create some uncertainty, data may not be judged in isolation. IgG responses from post-toddler dose and additional immunogenicity parameters after dose 2 and dose 3 (OPA, boosting of IgG and OPA, comparability of IgG distribution for PCV13 and PCV20 recipients) for all shared serotypes, provide reassurance of overall expected impact of PCV20. It was highlighted that the implementation challenges for a PCV20 3+1 as the only regimen in the EU could potentially be detrimental as a barrier, –acknowledging that the majority of EU countries presently use a 2+1 schedule for PCV-, denying protection against vaccine preventable serotypes in some EU countries.

The experts assessed if based on the main immunogenicity parameters, the 2 infant dose regimen (2+1) for PCV20 is adequate to achieve memory and potentially reduce carriage and in this way maintain indirect protection, especially in the window between the last infant and the toddler dose: 9/13 shared serotypes failed NI for the response rate, 4/13 shared serotypes failed NI for IgG GMC. The clinical implications of these findings are difficult to judge in absence of a known threshold for protection and carriage reduction. Experts also stressed that data need judging in relation to the entire pneumococcal disease spectrum, thus including non-invasive disease, which constitutes most of the disease burden and depends on prevention of acquisition and carriage of vaccine-serotypes.

In conclusion, in terms of immunogenicity data, experts judged that there seems a clear benefit for the 3+1 dosage regimen versus 2+1 schedule, although the larger loss of immunogenicity with the 2+1 regimen is difficult to discern in terms of consequences for effectiveness regarding IPD as well as non-invasive disease and indirect protection through carriage reduction. It was noted that potentially a higher level of antibodies would be warranted to protect against acute otitis media and pneumonia. Overall, the

above constitute important uncertainties whether the 2+1 schedule with PCV20 may provide optimal protection against the spectrum of pneumococcal disease.

2.4.3. Conclusions on immunogenicity

Both pivotal trials failed to meet their primary objectives as non-inferiority was not met for each of the 20 serotypes for all co-primary endpoints. In B7471012 15/60 statistical tests failed, while in B7471011 6/40 tests failed. Both pivotal trials are thus considered formally failed.

Overall, 20vPnC was immunogenic in all studies and induced a serotype-specific immune response to all 20 serotypes included in the vaccine. Nonetheless, the immune response for the 13 shared serotypes was consistently lower in the 20vPnC group compared to 13vPnC group for all serotypes in both 3-dose and 4-dose regimen. Significant differences between vaccines were observed after the last infant dose in the 3-dose regimen, demonstrated by multiple (15/40) failed NI tests for both primary parameters, response rate and IgG GMC. Differences between vaccines were also observed after last infant dose in 4-dose regimen, as well as after toddler dose in both 3-dose and 4-dose regimen, albeit to a lesser extent.

The CHMP concurs with the (WHO) statement “that missing the statistical NI criteria for individual serotypes for one or both sets of criteria do not necessarily predict lack of vaccine efficacy” and may not be completely unexpected due to the sheer number of NI comparisons made. However, from the assessment perspective, it is important that this uncertainty in prediction would also not rule out a clinically relevant lack of vaccine efficacy, because of failed NI in IgG response. The key issue in this context remains the fact that – in absence of a reliable correlate of protection – the whole setup of the immunology NI evaluation relies on many pre-specifications and assumptions (e.g. IgG-concentration threshold for binary response description, width of NI-margins, etc), such that actual NI conclusions (positive or negative) need to be *per se* considered rather uninformative as regards disease protective potential (vaccine efficacy).

Furthermore, the approach for NI comparisons of the 7 additional serotypes against the lowest observed response among the vaccine serotypes in the 13vPnC group (excluding serotype 3) is considered rather uninformative and might even be potentially misleading, with a systematic tendency for overestimation of the 20vPnC benefit. Although, the assessment of secondary parameters such as IgG and OPA GMFRs clearly shows that 7 additional parameters induce serotype-specific immune response, it remains unclear whether elicited titres are indeed effective against disease.

Finally, due to the overall lower IgG GMCs with 20vPnC, it can be expected that the (assumed) protective effect wanes earlier compared to 13vPnC.

Given that the highest burden of invasive pneumococcal disease in paediatric population is in infants <1 year of age (ECDC Invasive pneumococcal disease - Annual Epidemiological Report for 2017, 2018), it is crucial that vaccines offer sufficient protection in the window between the last infant and the toddler dose (between 4-5 and 11-12 months of age). Furthermore, a substantial disease burden at this age is also due to pneumonia and acute otitis media. As there is only a surrogate of protection available for IPD but not for pneumonia or AOM it is difficult to interpret the clinical impact of these lower titres on the protection against pneumonia and AOM. Moreover, higher antibody responses are thought to be necessary for the protection against pneumonia and AOM compared to IPD, as the protection should take place at the mucosal level or the ear instead of blood. Considering the above-mentioned, the adequacy of the 2+1 regimen to achieve and maintain protection, especially in the window between the last infant and the toddler dose raises major concerns.

The cross-study comparison, with direct comparisons between 20vPnC and 13vPnc within each study, indicate that the 3 infant + 1 toddler schedule (3+1) is likely to achieve and maintain antibody levels above the threshold value for IgG between the last infant and the toddler dose. The Applicant had to justify that, despite multiple failed NI tests and majority of serotypes being below the predefined cut-off for a protective level, the 3-dose regimen of 20vPnC offers sufficient protection against invasive pneumococcal disease in infants between the last infant and the toddler dose, particularly against severe courses of the disease. Also, the Applicant was requested to provide an elaborate justification for the 3-dose regimen, given overall better immune responses elicited after the last infant dose with 4-dose regimen. The additional arguments provided by the Applicant did not dissipate major concerns regarding the efficacy of the 2+1 regimen. These uncertainties are not restricted to one or two serotypes but pertain to all serotypes included in the vaccine.

In contrast, given the overall better immunogenicity, the 4-dose regimen is more likely to achieve protection; this would however need to be confirmed in the post-marketing. The Applicant confirmed that a global study to evaluate 20vPnC effectiveness against vaccine-type IPD administered according to the vaccine schedule(s) that will be licensed in the EU is feasible and ensured that substantial progress was made in establishing an IPD surveillance network for this purpose. In addition, the Applicant confirmed that a respective study in the US is planned.

As regards other claimed indications, it should be noted that a surrogate of protection, IgG of 0.35 µg/mL after 3 infant doses, has been established in children for IPD only and applies to the 13 shared serotypes. No correlate or surrogate of protection exists for pneumonia and AOM. Therefore, the strategy of NI testing for 20vPnC to 13vPnC, especially when a lower immune response is observed with 20vPnC compared to 13vPnC introduces the possibility that 20vPnC might not be effective in these indications. Further, it is currently unknown whether the threshold of 0.35 µg/mL can also be considered protective for the new serotypes included in this vaccine for any indication.

Overall conclusion: The immunogenicity data of the 3-dose regimen are considered insufficient to recommend approval of this dose regimen for paediatric patients. While post-approval effectiveness evaluation can be used to address some uncertainties present at the time of the assessment, pre-approval immunogenicity data should be sufficiently convincing. However, in case of the 3-dose regimen immunogenicity data raise substantial concerns that preclude the recommendation of this regimen.

Given the overall better immunogenicity results, the 4-dose regimen is more likely to provide protection against the pneumococcal disease. The VE of the 4-dose regimen needs to be confirmed in the post-marketing, including the VE of the 7 additional serotypes, as the interpretation of data from pivotal studies regarding these serotypes was severely limited. The Applicant agreed to conduct a Phase 4 observational, real-world study of the 20-valent Pneumococcal Conjugate Vaccine. This study will use surveillance data to evaluate the effectiveness of 20vPnC used in a 3+1 schedule against invasive pneumococcal disease in children. Detailed protocol proposals for EMA agreement should be provided before commencing the studies. The final study results should be reflected via the respective post-authorisation procedure (type II variation).

Recommendation [REC]

The Applicant will provide detailed protocol proposals for EMA approval before commencing the studies (REC). The final study results should be provided in the respective post-authorisation procedure (type II variation).

Study	Description	Protocol submission date
Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Paediatric Vaccine-Type Invasive Pneumococcal Disease in children	This study will use surveillance data to evaluate the effectiveness of 20vPnC used in a 3+1 schedule against invasive pneumococcal disease in children.	30 June 2025

2.5. Clinical safety

Introduction

Overview of 20vPnC paediatric clinical trials:

The 20vPnC paediatric clinical development program was designed to characterize the safety, tolerability, and immunogenicity of 20vPnC in infants and children <18 years of age.

- Infants were evaluated in one Phase 3 trial (B7471012) conducted using a 3-dose schedule and two Phase 3 trials (B7471011 and B7471013) and one Phase 2 trial (B7471003) conducted using a 4-dose schedule.
- Another Phase 3 trial (B7471014) studied a single dose of 20vPnC administered to children ≥15 months to <5 years of age previously immunized with at least 3 doses of 13vPnC and children ≥5 to <18 years of years of age regardless of previous pneumococcal conjugate vaccination.

Five clinical trials support this submission regarding safety and tolerability of 20vPnC:

- Four Phase 3 trials:
    - B7471012 – Pivotal double-blind, active-controlled Phase 3 trial of safety and immunogenicity in infants randomized 1:1 to receive a 3-dose series of either 20vPnC or 13vPnC at approximately 2 to 3, 4 to 5, and 11 to 12 months of age, conducted in Europe and Australia
    - B7471011 – Double-blind, active-controlled Phase 3 trial of safety and immunogenicity in infants randomized 1:1 to receive a 4-dose series of either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age, conducted in the USA and the US territory of Puerto Rico
    - B7471013 – Double-blind, Phase 3 trial of tolerability and safety in infants randomized, 2:1 to receive a 4-dose series of either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age, conducted in multiple countries
    - B7471014 – Single-arm, Phase 3 trial of safety and immunogenicity of a single dose of 20vPnC in children from ≥15 months to <18 years of age, conducted in the USA; children ≥15 months to <5 years of age in this trial had documentation of at least 3 doses of 13vPnC prior to enrolment
- One Phase 2 trial:

- B7471003 – Double-blind, active-controlled Phase 2 trial of safety and immunogenicity in infants randomized 1:1 to receive a 4-dose series of either 20vPnC or 13vPnC at 2, 4, 6, and 12 months of age, conducted in the USA

Routine concomitant paediatric vaccines were also administered in these studies.

Data Pooling:

For an integrated analysis of safety, AE data were pooled from the Phase 2 (B7471003) and the Phase 3 infant trials (B7471012, B7471011, and B7471013) as these trials collect similar safety data and have similar study populations and designs (randomized, double-blinded, with the same active control of [13vPnC], and same safety follow-up time frame [6 months after last dose, except for B7471012 which was 1 month after last dose]).

For local reactions and systemic events, B7471012 (3-dose series) data are summarized separately from the combined data for the other 3 trials (4-dose series) conducted in infants due to the different administration schedules. Additionally, where applicable, data were pooled across the infant trials and B7471014 conducted in children ≥15 months to <18 years of age to summarize specific safety parameters to provide a complete overview of events across all paediatric ages studied.

The pooling strategy is as follows:

Pooling Strategy	Parameters
B7471012 displayed side-by-side with B7471003, B7471011, and B7471013 pooled (by vaccine group)[a]	Local reactions and systemic events
B7471003, B7471011, B7471012, and B7471013 pooled (by vaccine group)	AEs, related AEs, and severe AEs from Dose 1 to 1 month after the last infant dose; SAEs (entire study duration and from Dose 1 to 1 month after the last infant dose and from the toddler dose to 1 month after the toddler dose); and seizure or seizure-like events after Dose 1 (for specific dose intervals)
B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1[b] pooled (by vaccine group)	AEs, related AEs, and severe AEs from the study-specified toddler dose to 1 month after the toddler dose; immediate AEs after each dose; SAEs (entire study duration)
B7471003, B7471011, B7471012, B7471013, and B7471014 (all cohorts) pooled (by vaccine group)	SAEs, related AEs, AEs resulting in withdrawal from study vaccination, deaths, seizure or seizure-like events after Dose 1 (entire study duration)

a. B7471012 (3-dose schedule) data are summarized separately from the combined data from B7471003, B7471011, and B7471013 (4-dose schedule) due to the different administration schedules.
b. B7471014 Cohort 1 included children ≥15 to <24 months of age who had previously received at least 3 doses of 13vPnC. These children received a single dose of 20vPnC in trial.

Local reaction, systemic event, and AE data from children ≥2 years to <18 years of age from B7471014 are described separately.

Safety Parameters:

The methods and the timeframes for safety data collection and analysis were similar in all trials. Safety was evaluated based on the following parameters:

- Specific events occurring within 7 days after vaccination were prompted for and collected by the participants' parents/legal guardians in an e-diary, device, or application. These events included:
    - local reactions (redness, swelling, and pain at the injection site)

- systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability in infants and toddlers ≥6 weeks to <24 months of age; and fever, fatigue, headache, muscle pain, and joint pain in children ≥2 to <18 years of age)

- Immediate AEs occurring within the first 30 minutes after each vaccination
- AEs reported from Dose 1 to 1 month after Dose 2 or Dose 3 (the last study-specified infant dose) and from the study-specified toddler dose (Dose 3 or Dose 4) to 1 month after the toddler dose (the toddler dose summary also includes the single dose of 20vPnC in toddlers ≥15 to <24 months of age with at least 3 prior doses of 13vPnC from B7471014 [Cohort 1]); and within 1 month after the single 20vPnC dose for children ≥2 to <18 years of age
- SAEs reported from Dose 1 to 1 month after Dose 3/last dose for B7471012, and from Dose 1 through 6 months after Dose 4/last dose in B7471003, B7471011, B7471013, and the single 20vPnC dose in B7471014

Safety Data Analyses:

Descriptive summary statistics were provided for each vaccine group for most safety parameters.

A 3-tier approach was used to summarize the integrated AEs across trials. Between-group differences (20vPnC – 13vPnC) in percentages of local reactions, systemic events, and Tier 2 AEs were also assessed (without including participants from B7471014, which has no control group). For the summary of between group difference in percentages across multiple studies, the study-adjusted between-group difference and the corresponding 95% CI for the difference were calculated using the stratified Miettinen and Nurminen method with inverse-variance stratum weights for individual studies.

Participants were included in the vaccine group corresponding to the vaccine that was actually administered. For summarization, AEs were categorized according to the MedDRA, by SOC and PT.

Patient exposure

Across all 5 trials, 5987 participants received at least 1 dose of study vaccine: 3664 received 20vPnC and 2323 received control 13vPnC.

One participant in B7471013 who was randomized to 13vPnC but received 20vPnC at Dose 1 and was excluded from the integrated summary of safety results.

In the 4 infant trials (B7471003, B7471011, B7471012, and B7471013), 5156 participants (not counting the participant in B7471013 who was randomized to 13vPnC but received 20vPnC at Dose 1) received at least 1 dose of study vaccine: 2833 received 20vPnC and 2323 received 13vPnC.

Overall, approximately 90% of participants in each group received all doses through the study-specified toddler dose.

The numbers of vaccinated participants in the 5 paediatric trials are shown by pooled dataset, vaccine group, and dose administered in the following table. Three participants in B7471011 who were randomized to 13vPnC but received 20vPnC after Dose 1 (2 at Dose 2 and 1 at Dose 4) were excluded from the integrated summary starting from the first analysis period the incorrect vaccine occurred.

In study B7471014, 831 participants received a single dose of 20vPnC:

- 209 participants ≥15 months to <2 years of age;

- 216 participants ≥2 to <5 years of age;
- 201 participants ≥5 to <10 years of age; and
- 205 participants ≥10 to <18 years of age

Table 57. Number (%) of Participants Who Received the Specified Dose(s) – All Vaccinated Participants

Studies Dose	Vaccine Group (as Administered) 20vPnC n[a] (%)	 13vPnC n[a] (%)	 Total n[a] (%)
B7471003, B7471011, B7471012 and B7471013			
Total exposure[b]	N=2833	N=2323	N=5156
Dose 1 (infant)	2833 (100.0)	2323 (100.0)	5156 (100.0)
Dose 2 (infant)	2752 (97.1)	2249 (96.8)	5001 (97.0)
Dose 3 (infant)	2108 (74.4)	1612 (69.4)	3720 (72.1)
Dose 4/Dose 3 (toddler)	2561 (90.4)	2090 (90.0)	4651 (90.2)
B7471003, B7471011, B7471012, B7471013 and B7471014 Cohort 1			
Total exposure[c]	N=3042	N=2323	N=5365
Dose 4/Dose 3 (toddler)/vaccination (toddler)	2770 (91.1)	2090 (90.0)	4860 (90.6)
B7471003, B7471011, B7471012, B7471013 and B7471014 all cohorts			
Total exposure[d]	N=3664	N=2323	N=5987

Note: Dose 3 (infant) is Dose 3 from the B7471003, B7471011, and B7471013 trials combined. Dose 4/Dose 3 (toddler) comprises Dose 4 in B7471003, B7471011 and B7471013 and Dose 3 in B7471012. Dose 4/Dose 3 (toddler)/vaccination (toddler) comprises Dose 4 in B7471003, B7471011 and B7471013, Dose 3 in B7471012, and the single dose of 20vPnC in B7471014 Cohort 1 (children 15 to <24 months of age with at least 3 prior infant doses of 13vPnC).

Note: Participants counted for a specified dose have also received all preceding doses per individual study protocols.

Note: One participant in B7471013 was randomized to 13vPnC but received 20vPnC at Dose 1 and is completely excluded from this table. Three other participants were randomized to 13vPnC but received 20vPnC at the later doses (Dose 2: 2 in B7471011; Dose 4: 1 in B7471011) and are included in the total exposure rows but excluded from the exposure rows for the dose with incorrect study vaccine administration and the subsequent doses. Local reactions and systemic events collected from participants after the incorrect study vaccine administration are excluded from the summary tables and figures for that and all subsequent doses. Adverse events from participants who received any incorrect study vaccination in a specified reporting time period are excluded from the summary tables and figures for that and all subsequent reporting periods. All data are included in listings.

a. n = Number of participants with the specified characteristic.

b. N = number of participants receiving any dose in the specified group. This value is the denominator for the percentage calculations for B7471003, B7471011, B7471012, and B7471013.

c. N = number of participants receiving any dose in the specified group. This value is the denominator for the percentage calculations for B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1.

d. N = number of participants receiving any dose in the specified group.

Across the trials, the percentage of participants who withdrew from the trials ranged from 2.4% (B7471014) to 18.7% (B7471011). Withdrawals were more common in the infant trials where the length of the schedule and duration of follow-up for a given participant was more than 15 months. The most frequent reasons for withdrawal of participants were lost to follow-up and withdrawal by parent/guardian.

Table 58. Subjects withdrawn from studies

	B7471011		B7471012		B7471013		B7471003		B7471014
	20vPnC	13vPnC	20vPnC	13vPnC	20vPnC	13vPnC	20vPnC	13vPnC	20vPnC
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	1004	993	603	604	1006	505	232	228	839
Total withdrawn	183 (18.2)	191 (19.2)	20 (3.3)	14 (2.3)	96 (9.5)	54 (10.7)	25 (10.8)	24 (10.5)	20 (2.4)
Reason for withdrawal									
Lost to follow-up	48 (4.8)	63 (6.3)	5 (0.8)	4 (0.7)	31 (3.1)	21 (4.2)	8 (3.4)	5 (2.2)	9 (1.1)
Withdrawal by parent/guardian	50 (5.0)	56 (5.6)	7 (1.2)	5 (0.8)	36 (3.6)	15 (3.0)	12 (5.2)	14 (6.1)	7 (0.8)
No longer meets eligibility criteria	51 (5.1)	44 (4.4)	3 (0.5)	3 (0.5)	14 (1.4)	11 (2.2)	3 (1.3)	1 (0.4)	3 (0.4)
Protocol deviation	29 (2.9)	23 (2.3)	2 (0.3)	1 (0.2)	11 (1.1)	6 (1.2)	1 (0.4)	2 (0.9)	
Adverse event	2 (0.2)	4 (0.4)	3 (0.5)	0	2 (0.2)	0			
Physician decision	0	1 (0.1)			2 (0.2)	1 (0.2)	0	2 (0.9)	
Other	3 (0.3)	0	0	1 (0.2)			1 (0.4)	0	1 (0.1)

Across all 5 trials, 12 (0.2%) participants withdrew from the trials due to AEs: 9 (0.3%) infants who received 20vPnC and 3 (0.1%) infants who received 13vPnC.

The types of AEs most frequently resulting in withdrawal of these infants were seizures/seizure-associated conditions (three 20vPnC [0.1%] recipients and one 13vPnC recipient [<0.1%]) and failure to thrive (two 20vPnC [0.1%] recipients and one 13vPnC recipient [<0.1%]). In general, participants with seizures/seizure-associated conditions were often withdrawn due to questions of continued eligibility.

Demographic Characteristics

Participant demographic characteristics (sex, race, ethnicity, country, age at Dose 1 and at the study-specified Dose 3/Dose 4 (toddler vaccination), for the pooled datasets are summarized in Table 57.

Within each pooled population, demographic characteristics were generally comparable between participants who received 20vPnC and those who received 13vPnC.

Across all 5 trials, there were similar percentages of male and female participants among the 20vPnC recipients and the 13vPnC recipients. Overall, 83.5% of 20vPnC recipients were White, 7.9% Black, 1.6% Asian, and 24.0% Hispanic, with similar distribution among 13vPnC recipients.

Within B7471014, there was a higher percentage of a male participants than female participants ≥15 months to <24 months of age (Cohort 1) and ≥10 to <18 years of age (Cohort 4) (~56% vs ~44%). Participants were predominantly White (80.1%–86.8%), with nearly all the other participants being Black or African American (8.3%–12.4%); 15.4% to 21.0% were Hispanic.

Table 59. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)					
	B7471003, B7471011, B7471012, and B7471013		B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1		B7471003, B7471011, B7471012, B7471013, and B7471014 All Cohorts	
	20vPnC (N[a]=2833) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)	20vPnC (N[a]=3042) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)	20vPnC (N[a]=3664) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)
Sex						
Male	1453 (51.3)	1172 (50.5)	1570 (51.6)	1172 (50.5)	1899 (51.8)	1172 (50.5)
Female	1380 (48.7)	1148 (49.5)	1472 (48.4)	1148 (49.5)	1765 (48.2)	1148 (49.5)
Race						
White	2367 (83.6)	1950 (84.1)	2535 (83.3)	1950 (84.1)	3060 (83.5)	1950 (84.1)
Black or African American	200 (7.1)	153 (6.6)	226 (7.4)	153 (6.6)	291 (7.9)	153 (6.6)
Asian	54 (1.9)	35 (1.5)	57 (1.9)	35 (1.5)	57 (1.6)	35 (1.5)
American Indian or Alaska Native	12 (0.4)	7 (0.3)	12 (0.4)	7 (0.3)	13 (0.4)	7 (0.3)
Native Hawaiian or Other Pacific Islander	5 (0.2)	7 (0.3)	5 (0.2)	7 (0.3)	6 (0.2)	7 (0.3)
Multiracial	126 (4.4)	109 (4.7)	136 (4.5)	109 (4.7)	163 (4.4)	109 (4.7)
Not reported	69 (2.4)	59 (2.5)	71 (2.3)	59 (2.5)	74 (2.0)	59 (2.5)
Ethnicity						
Hispanic or Latino	724 (25.6)	527 (22.7)	759 (25.0)	527 (22.7)	878 (24.0)	527 (22.7)
Not Hispanic or Latino	2049 (72.3)	1735 (74.8)	2221 (73.0)	1735 (74.8)	2721 (74.3)	1735 (74.8)
Not reported	60 (2.1)	58 (2.5)	62 (2.0)	58 (2.5)	65 (1.8)	58 (2.5)
Country[c]						
Argentina	51 (1.8)	28 (1.2)	51 (1.7)	28 (1.2)	51 (1.4)	28 (1.2)
Australia	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Belgium	7 (0.2)	8 (0.3)	7 (0.2)	8 (0.3)	7 (0.2)	8 (0.3)
Canada	127 (4.5)	62 (2.7)	127 (4.2)	62 (2.7)	127 (3.5)	62 (2.7)

	Vaccine Group (as Administered)					
	B7471003, B7471011, B7471012, and B7471013		B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1		B7471003, B7471011, B7471012, B7471013, and B7471014 All Cohorts	
	20vPnC (N[a]=2833) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)	20vPnC (N[a]=3042) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)	20vPnC (N[a]=3664) n[b] (%)	13vPnC (N[a]=2320) n[b] (%)
Chile	20 (0.7)	10 (0.4)	20 (0.7)	10 (0.4)	20 (0.5)	10 (0.4)
Czech Republic	56 (2.0)	45 (1.9)	56 (1.8)	45 (1.9)	56 (1.5)	45 (1.9)
Germany	32 (1.1)	17 (0.7)	32 (1.1)	17 (0.7)	32 (0.9)	17 (0.7)
Denmark	1 (0.0)	2 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)	2 (0.1)
Spain	212 (7.5)	108 (4.7)	212 (7.0)	108 (4.7)	212 (5.8)	108 (4.7)
Estonia	38 (1.3)	40 (1.7)	38 (1.2)	40 (1.7)	38 (1.0)	40 (1.7)
Finland	188 (6.6)	183 (7.9)	188 (6.2)	183 (7.9)	188 (5.1)	183 (7.9)
Greece	20 (0.7)	11 (0.5)	20 (0.7)	11 (0.5)	20 (0.5)	11 (0.5)
Hungary	172 (6.1)	90 (3.9)	172 (5.7)	90 (3.9)	172 (4.7)	90 (3.9)
Italy	36 (1.3)	36 (1.6)	36 (1.2)	36 (1.6)	36 (1.0)	36 (1.6)
Netherlands	7 (0.2)	7 (0.3)	7 (0.2)	7 (0.3)	7 (0.2)	7 (0.3)
Norway	7 (0.2)	7 (0.3)	7 (0.2)	7 (0.3)	7 (0.2)	7 (0.3)
Poland	274 (9.7)	272 (11.7)	274 (9.0)	272 (11.7)	274 (7.5)	272 (11.7)
Puerto Rico	120 (4.2)	113 (4.9)	120 (3.9)	113 (4.9)	120 (3.3)	113 (4.9)
Slovakia	17 (0.6)	17 (0.7)	17 (0.6)	17 (0.7)	17 (0.5)	17 (0.7)
USA	1447 (51.1)	1263 (54.4)	1656 (54.4)	1263 (54.4)	2278 (62.2)	1263 (54.4)
Age at Dose 1 (infant) (days)						
Mean (SD)	66.0 (11.09)	66.5 (11.58)				
Median	64.0	64.0				
Min, max	(42, 112)	(43, 112)				
Age at Dose 4/Dose 3 (toddler)/vaccination (toddler) (days)						
Mean (SD)	376.7 (16.16)	376.2 (16.16)	390.4 (54.95)	376.2 (16.16)		
Median	372.0	372.0	373.0	372.0		

Min, max	(335, 460)	(335, 468)	(335, 731)	(335, 468)

Note: Dose 4/Dose 3 (toddler)/vaccination (toddler) comprises Dose 4 in B7471003, B7471011, and B7471013, Dose 3 in B7471012, and the single dose of 20vPnC in B7471014 Cohort 1 (children 15 to <24 months of age with at least 3 prior infant doses of 13vPnC).

a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations. Participants who received any incorrect study vaccination during the study are excluded.

b. n = Number of participants with the specified characteristic.

c. B7471011 was conducted in the USA and Puerto Rico; B7471012 was conducted in Australia, Belgium, Czech Republic, Denmark, Estonia, Finland, Italy, Netherlands, Norway, Poland, and Slovakia; B7471013 was conducted in Argentina, Canada, Chile, Czech Republic, Finland, Germany, Greece, Hungary, Puerto Rico, Spain, and USA; and B7471014 was conducted in the USA.

PFIZER CONFIDENTIAL Source Data: adsl Output File: ./b747 pediatric sec/B747 PED MAA/adsl demo saf Date of Generation: 28SEP2022 (11:46)

Adverse events

Immediate Adverse Events occurring within the first 30 minutes after each vaccination

In B7471012 (3-dose series), immediate AEs were reported infrequently (for ≤0.7% of participants after each dose in both vaccine groups). There were no immediate AEs reported after Dose 3 in the 13vPnC group. None of the immediate AEs represented serious allergic reactions to 20vPnC.

The percentages of pooled participants enrolled at <2 years of age with immediate AEs (within 30 minutes) after each dose (0.1%–0.2%) were similar for 20vPnC and 13vPnC recipients in B7471003, B7471011, B7471012, B7471013 and B7471014 Cohort 1. Most of the events were in the General disorders and administration site conditions System Organ Class. There were no cases of immediate allergic reactions associated with bronchospasm, facial oedema, or generalized urticaria within 30 minutes of vaccination. Events representing potential allergic reactions were infrequent (1 participant in the 20vPnC group had injection site hypersensitivity within 30 minutes after both Dose 2 and Dose 3). One case of stridor of mild severity was reported after Dose 2 of 20vPnC on the day of vaccination but had a duration of 50 days, which makes it unlikely for the event to represent an allergic reaction. There was no trend to increasing rates of immediate AEs with subsequent doses of vaccine. None of the immediate AEs resulted in withdrawal of the participants from the trial.

There were no immediate AEs (within 30 minutes of vaccination) in participants ≥2 to <18 years of age.

Table 60. Immediate Adverse Events Reported After Each Dose, by System Organ Class and Preferred Term – B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1

Dose	System Organ Class	Vaccine Group (as Administered)			
	Preferred Term	20vPnC		13vPnC	
		n[a] (%)	(95% CI[b])	n[a] (%)	(95% CI[b])
Dose 1 (infant)[c]		N=2833		N=2323	
	Any adverse event	*3 (0.1)*	*(0.0, 0.3)*	*5 (0.2)*	*(0.1, 0.5)*
	Gastrointestinal disorders	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
	Abdominal pain	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
	General disorders and administration site conditions	2 (0.1)	(0.0, 0.3)	4 (0.2)	(0.0, 0.4)
	Injection site erythema	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
	Vaccination site pain	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
	Injection site pain	0	(0.0, 0.1)	2 (0.1)	(0.0, 0.3)
	Vaccination site erythema	0	(0.0, 0.1)	2 (0.1)	(0.0, 0.3)
	Skin and subcutaneous tissue disorders	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
	Dermatitis contact	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
Dose 2 (infant)[c]		N=2752		N=2249	
	Any adverse event	*5 (0.2)*	*(0.1, 0.4)*	*4 (0.2)*	*(0.0, 0.5)*
	General disorders and administration site conditions	4 (0.1)	(0.0, 0.4)	3 (0.1)	(0.0, 0.4)
	Injection site erythema	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
	Injection site hypersensitivity	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
	Pyrexia	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)

		Vaccination site erythema	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
		Vaccination site pain	0	(0.0, 0.1)	2 (0.1)	(0.0, 0.3)
	Respiratory, thoracic and mediastinal disorders		1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
		Stridor	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
	Skin and subcutaneous tissue disorders		0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
		Erythema	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Dose 3 (infant)[c]			N=2108		N=1612	
	Any adverse event		*3 (0.1)*	*(0.0, 0.4)*	*2 (0.1)*	*(0.0, 0.4)*
	General disorders and administration site conditions		3 (0.1)	(0.0, 0.4)	1 (0.1)	(0.0, 0.3)
		Injection site erythema	1 (0.0)	(0.0, 0.3)	1 (0.1)	(0.0, 0.3)
		Injection site hypersensitivity	1 (0.0)	(0.0, 0.3)	0	(0.0, 0.2)
		Vaccination site erythema	1 (0.0)	(0.0, 0.3)	0	(0.0, 0.2)
	Psychiatric disorders		0	(0.0, 0.2)	1 (0.1)	(0.0, 0.3)
		Breath holding	0	(0.0, 0.2)	1 (0.1)	(0.0, 0.3)
Dose 4/Dose 3 (toddler)/vaccination (toddler)[c]			N=2770		N=2090	
	Any adverse event		*3 (0.1)*	*(0.0, 0.3)*	*2 (0.1)*	*(0.0, 0.3)*
	General disorders and administration site conditions		1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.3)
		Vaccination site swelling	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
		Injection site erythema	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.3)
	Infections and infestations		1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
		Nasopharyngitis	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
	Injury, poisoning and procedural complications		0	(0.0, 0.1)	1 (0.0)	(0.0, 0.3)
		Scratch	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.3)
	Psychiatric disorders		1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
		Irritability	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)

Note: MedDRA (v25.0) coding dictionary applied.

Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.

Note: One AE that began 33 minutes after Dose 1 and another AE that began 31 minutes after Dose 3 were included in this summary. Both AEs were from B7471012.

Note: Dose 3 (infant) is Dose 3 in B7471003, B7471011, and B7471013 trials combined. Dose 4/Dose 3 (toddler)/vaccination (toddler) comprises Dose 4 vaccination in B7471003, B7471011, and B7471013, and the single dose of 20vPnC in B7471014 Cohort 1 (children 15 to <24 months of age with at least 3 prior infant doses of 13vPnC).

a. n = Number of participants reporting at least 1 occurrence of the specified event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any specified event.

b. Exact 2-sided CI, based on the Clopper and Pearson method.

c. N = number of participants who received the specified dose. This value is the denominator for the percentage calculations.

Specific events occurring within 7 days after vaccination

Specific events including local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability in infants and toddlers ≥6 weeks to <24 months of age; and fever, fatigue, headache, muscle pain, and joint pain in children ≥2 to <18 years of age) were collected by the participants' parents/legal guardians in an e-diary, device, or application.

Local Reactions in Infants and Toddlers

In B7471012 (3-dose series), the percentages of participants with *local reactions* (redness, swelling, or pain at the injection site) within 7 days after each of the 3 doses were generally similar after either 20vPnC or 13vPnC, with no clinically important differences between the vaccine groups. Between-group differences (20vPnC – 13vPnC) ranged from -3.2% to 5.3%.

Percentages of participants with local reactions were also generally similar after either 20vPnC or 13vPnC in the pooled infant population administered a 4-dose series (from B7471003, B7471011, and B7471013). Between-group differences (20vPnC – 13vPnC) ranged from -3.1% to 1.5%.

With both schedules, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently (0–0.5%). There were no strong trends in severity of local reactions with subsequent doses.

With a 3-dose series, the *most frequently reported local reaction* was pain at the injection site (22.8%–42.4% in the 20vPnC group; 24.6%–39.9% in the 13vPnC group), followed by redness (25.3%–36.9% in the 20vPnC; 27.5%–33.8% in the 13vPnC) and swelling (21.4%-29.8% in the 20vPnC group; 20.2%–24.6% in the 13vPnC group).

Similarly, in the pooled population given a 4-dose series, the most frequently reported local reaction was pain at the injection site (32.8%–45.5% in the 20vPnC group, 34.6%–45.4% in the 13vPnC group), followed by redness (22.6%–24.5% in the 20vPnC group, 23.2%–25.7% in the 13vPnC group) and swelling (15.1%–17.6% in the 20vPnC group, 16.0%–18.0% in the 13vPnC group).

In B7471012 (3-dose series), the percentages of participants with any local reaction, particularly pain at the injection site and redness, were higher *after the toddler dose than after the 2 infant doses*. In the pooled infant population (4-dose series), percentages of participants with pain at the injection site generally decreased slightly after subsequent infant doses (from Doses 1–3).

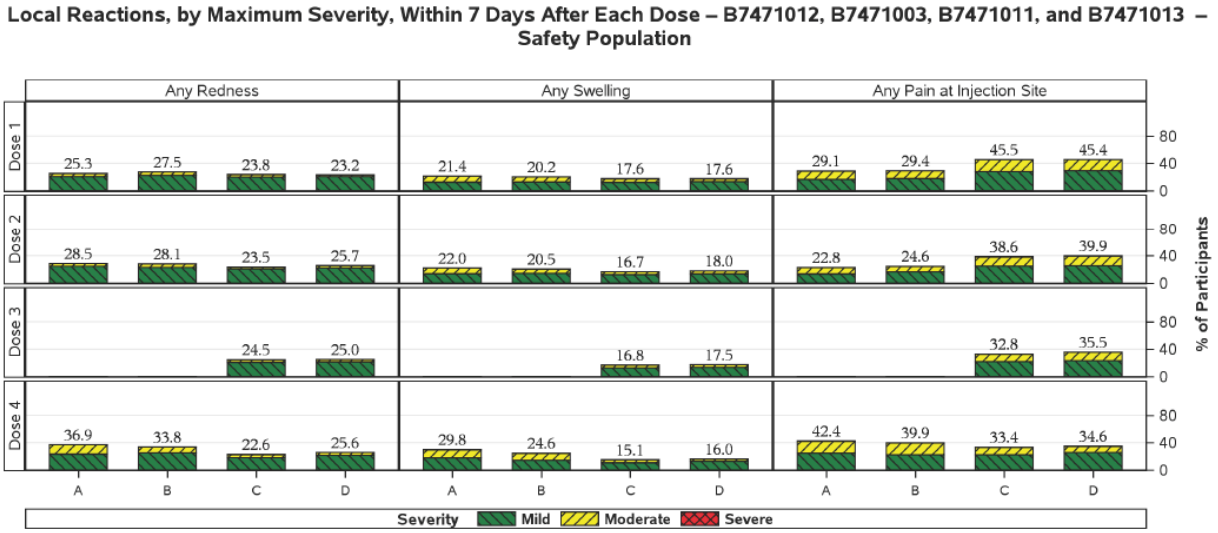
The frequencies obtained for local reactions with each of the dosing schedules were similar, except for pain at the injection site, which was reported less frequently after any infant dose of the 3-dose series (22.8% [Dose 2]–29.4% [Dose 1]) than after any infant dose of the 4-dose schedule (32.8% [infant Dose 3]–45.5% [Dose 1]). After the toddler dose, the percentages of participants in B7471012 (3-dose series) with any local reaction (59.8% and 57.0% in the 20vPnC and 13vPnC groups, respectively) were higher than in the pooled trials using a 4-dose schedule (43.2% and 45.0% in the 20vPnC and 13vPnC groups, respectively).

These are between-population comparisons and should be interpreted with caution.

For participants ≥15 to <24 months of age enrolled in B7471014 Cohort 1, most local reactions were mild or moderate in severity after the single dose of 20vPnC. Pain at the injection site, redness, and swelling were reported in 52.5%, 37.7% and 22.1% of participants, respectively. The frequencies of local reactions after 20vPnC in this toddler population were similar to those after the toddler dose in B7471012 (3-dose series) and slightly higher than after (toddler) Dose 4 in the pooled 4-dose trials. These are between-population comparisons and should be interpreted with caution.

Across all doses, the median onset day for local reactions in participants after 20vPnC was Day 1 or Day 2 (Day 1 was the day of vaccination), and reactions resolved with a median duration of 1 to 3 days.

Table 61. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – B7471012, B7471003, B7471011, and B7471013 – Safety Population



Note: A=B7471012 - 20vPnC, B=B7471012 - 13vPnC, C=B7471003, B7471011, and B7471013 - 20vPnC, D=B7471003, B7471011, and B7471013 - 13vPnC.
Note: Dose 3 is Dose 3 (infant) from B7471003, B7471011, and B7471013; Dose 4 is Dose 3 (toddler) from B7471012, and Dose 4 (toddler) from B7471003, B7471011, and B7471013.
PFIZER CONFIDENTIAL Source Data: adfacevd Output File: ./b747_pediatric_sec/B747_PED_MAA/adce_f001_lr_saf Date of Generation: 27SEP2022 (13:42)

Local Reactions in Children ≥2 to <18 Years of Age

The percentages of participants in B7471014 with any local reaction (redness, swelling, and pain at the injection site) were 70.2%, 86.4%, and 83.9% in children ≥2 to <5 years, ≥5 to <10 years, and ≥10 to <18 years of age (Cohorts 2, 3, and 4), respectively. Most local reactions were mild or moderate. Severe local reactions were reported infrequently at ≤2% for all local reactions.

Across all age groups, the most commonly reported local reaction was pain at the injection site (66.0%–82.9% of participants), followed by redness (15.1%–39.1%), and swelling (15.6%–27.1%). The rate of pain at the injection site generally increased with age, while rates of redness and swelling were lowest in the oldest age cohort.

Local reactions had a median onset day of Day 1 or Day 2 (Day 1 was the day of vaccination) and a median duration of 1 or 2 days in children ≥2 to <18 years of age.

Systemic Events in Infants and Toddlers

For all doses, the median onset day for systemic events in infants and toddlers was Day 1 or Day 2, and events generally resolved with a median duration of 1 to 3 days.

With both schedules, most systemic events were mild or moderate in severity. Severe events were reported infrequently: 0.0% to 2.2% for all events, except for severe irritability, which was reported at slightly higher frequencies (2.1%–8.6%) that generally decreased with subsequent doses.

In B7471012 (3-dose schedule), the percentages of participants with systemic events (fever, decreased appetite, drowsiness, and irritability) within 7 days after each of the 3 doses of 20vPnC were generally similar to those after the corresponding dose of 13vPnC, with no clinically important differences between the vaccine groups. Between-group (20vPnC – 13vPnC) differences ranged from -2.6% to 5.3%.

Percentages of participants with systemic events were also generally similar after either 20vPnC or 13vPnC in the pooled infant population administered a 4-dose series. Between group differences (20vPnC – 13vPnC) ranged from -1.7% to 2.2%.

With a 3-dose series, the most frequently reported systemic events were irritability (71.0%-71.9% in the 20vPnC group; 68.4%–72.5% in the 13vPnC group) and drowsiness (50.9%–61.2% in the 20vPnC group; 48.6%–63.7% in the 13vPnC group). Decreased appetite was reported at lower frequencies (24.7%–39.3% in the 20vPnC group; 19.4%-36.5% in the 13vPnC group). Fever of ≥38.0°C (i.e,"any" fever) occurred in 8.9% to 24.3% of participants after 20vPnC; and 8.5% to 23.7% after 13vPnC after each dose; frequencies were lowest after Dose 1. Fever of >40.0°C was reported for 2 (0.3%) participants after the toddler dose only.

Similarly, in the pooled population (4-dose series), the most frequently reported systemic events were irritability (58.5%–70.6% in the 20vPnC group; 59.4%–71.5% in the 13vPnC group) and drowsiness (37.7%–66.2% in the 20vPnC group; 38.1%–65.6% in the 13vPnC group). Decreased appetite was reported at lower frequencies (23.0%–26.4% in the 20vPnC group; 22.3%–25.9% in the 13vPnC group). Fever of ≥38.0°C (ie, "any" fever) occurred in dose. Fever of >40.0°C was reported for 0 to 3 (0.2%) participants after any dose.

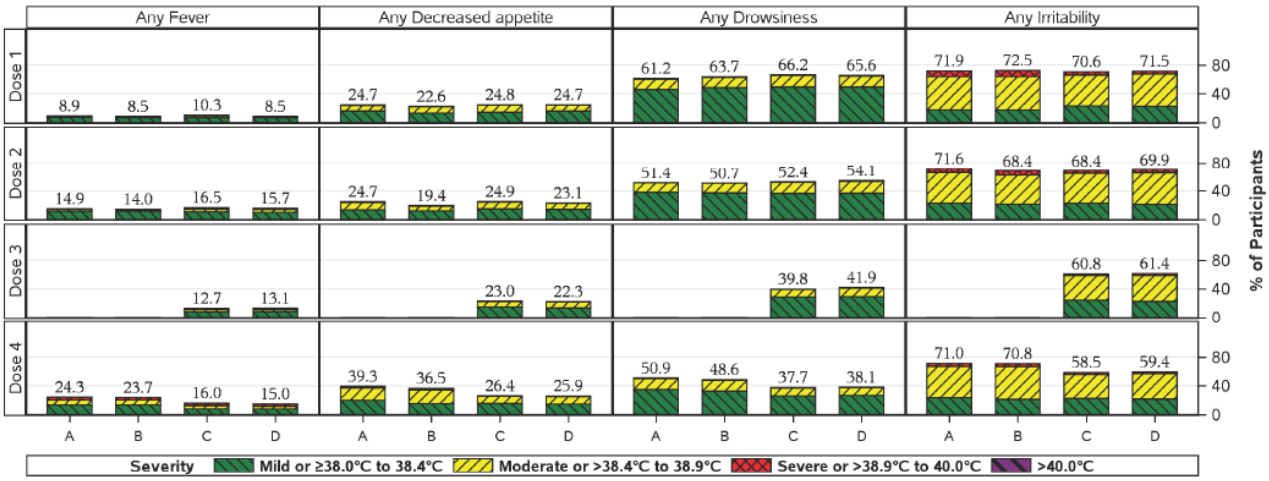
In B7471012 (3-dose series), the frequencies for fever of ≥38.0°C and decreased appetite were higher after the toddler dose than after the 2 infant doses. Drowsiness was more frequently reported after Dose 1. In the pooled infant population (4-dose series), the frequencies of irritability and drowsiness decreased slightly after subsequent doses.

Upon examining the frequencies obtained for each dosing schedule, the percentages of participants in B7471012 (3-dose series) with any systemic event after the toddler dose (83.1% and 81.4% in the 20vPnC and 13vPnC groups, respectively) were higher than in the pooled population (4-dose schedule) (68.5% and 70.5% in the 20vPnC and 13vPnC groups, respectively). Use of antipyretic or pain medication was more frequent after the toddler dose among the B7471012 participants (3-dose series) compared with after the toddler dose of the 4-dose series and more frequent after the infant doses among the pooled population (4-dose series) compared with after the infant doses of the 3-dose series. These are between-population comparisons and should be interpreted with caution.

For participants ≥15 to <24 months of age with 3 prior doses of 13vPnC enrolled in B7471014 Cohort 1, the most frequently reported systemic event was irritability (61.8%), followed by drowsiness/increased sleep (41.7%), and decreased appetite (25.0%). Fever was reported in 11.8% of participants, and fever >38.9°C was uncommon (2.9%) with no reported fever >40°C. The frequencies of systemic events after 20vPnC in this toddler population were lower than those after the toddler dose in B7471012 (3-dose series) and similar to those after (toddler) Dose 4 in the pooled 4-dose trials. These are between-population comparisons and should be interpreted with caution.

Table 62. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – B7471012, B7471003, B7471011, and B7471013 – Safety Population

Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – B7471012, B7471003, B7471011, and B7471013 – Safety Population



Note: A=B7471012 - 20vPnC, B=B7471012 - 13vPnC, C=B7471003, B7471011, and B7471013 - 20vPnC, D=B7471003, B7471011, and B7471013 - 13vPnC.
Note: Dose 3 is Dose 3 (infant) from B7471003, B7471011, and B7471013; Dose 4 is Dose 3 (toddler) from B7471012, and Dose 4 (toddler) from B7471003, B7471011, and B7471013.
PFIZER CONFIDENTIAL Source Data: adfacevd Output File: ./b747_pediatric_sec/B747_PED_MAA/adce_f001_se_saf Date of Generation: 27SEP2022 (13:42)

Systemic Events in Children ≥2 to <18 Years of Age

The percentages of participants in B7471014 with any systemic event (fever, fatigue, headache, muscle pain, or joint pain in participants ≥2 to <18 years of age (Cohorts 2–4) were 50.2%, 58.3%, and 68.3% in children ≥2 to <5 years, ≥5 to <10 years, and ≥10 to <18 years of age (Cohorts 2, 3, and 4), respectively. Most systemic events were mild or moderate. Severe systemic events were reported infrequently at ≤1.5% for all systemic events.

For participants ≥2 to <18 years of age (Cohorts 2–4), muscle pain (26.5%–48.3%) and fatigue (27.8%–37.2%) were most frequently reported, followed by headache (5.6%–29.3%) and joint pain (3.7%–8.3%) (Module 5.3.5.2 B7471014 Report Body Table 15). The reported rates of headache and muscle pain increased with age, while fatigue was somewhat more common in children ≥2 to <5 years. Fever was uncommon in children 2 to <18 years of age, with 3.3% of children ≥2 to <5 years reporting any fever, and 1 participant >5 years of age reporting fever.

The median onset day for systemic events in children ≥2 to <18 years of age was Day 1 or Day 2, and events resolved with a median duration of 1 or 2 days.

Adverse Events – other timepoints

In this section, Adverse Events are listed that were reported:

- from Dose 1 to 1 month after Dose 2 or Dose 3 (the last study-specified infant dose) and
- from the study-specified toddler dose (Dose 3 or Dose 4) to 1 month after the toddler dose (the toddler dose summary also includes the single dose of 20vPnC in toddlers ≥15 to <24 months of age with at least 3 prior doses of 13vPnC from B7471014 [Cohort 1]);
- and within 1 month after the single 20vPnC dose for children ≥2 to <18 years of age

Adverse Events in Infants and Toddlers

The AEs reported in B7471012 (3-dose series) generally reflected diseases and conditions often observed in the infant population. The percentages of participants with any AEs were similar among 20vPnC and 13vPnC recipients from Dose 1 to 1 month after Dose 2 (13.8% in the 20vPnC group and 14.4% in the 13vPnC group) and from the toddler dose to 1 month after the toddler dose (15.5% in the 20vPnC group and 16.5% in the 13vPnC group).

The AEs reported in the larger pools of infant and toddler participants also generally reflected diseases and conditions often observed in the infant and toddler population. From Dose 1 to 1 month after the last study-specified infant dose (for the pool of infants from B7471003, B7471011, B7471012, and B7471013), AEs were reported in 31.3% of participants in the 20vPnC group and 32.1% in the 13vPnC group.

From the study-specified toddler dose to 1 month after the toddler dose (for the pool of participants enrolled at <2 years of age from B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1), AEs were reported in 16.1% of participants in the 20vPnC group and 16.7% in the 13vPnC group.

AEs with a pooled event rate of ≥1% in at least 1 (pooled) vaccine group (Tier 2 AEs) were comparable between 20vPnC and 13vPnC recipients. Between-group differences in the percentages of participants reporting Tier 2 AEs from Dose 1 to 1 month after the last study specified infant dose were low (-0.2% to 0.5%).

The between-group differences from the study-specified toddler dose to 1 month after the toddler dose were also low (-0.9% to 0.7%). The most frequently reported Tier 2 AEs were common paediatric infections or conditions: upper respiratory tract infection and nasopharyngitis in both groups.

Tier 2 AEs during the whole study duration: Tier 2 AEs (AE preferred terms reported by ≥1% of participants in at least one vaccine group) and between-group differences are provided for the 3-dose regimen trial in Table 2 and the pooled 4-dose regimen trials in Table 3. The percentages of participants with Tier-2 AEs were low and comparable in the 20vPnC and 13vPnC groups, both in the 3-dose regimen trial and in the pooled 4-dose regimen trials, with between-group differences (20vPnC – 13vPnC) between 2.4% and 1.5% in the 3-dose regimen trial and between -0.5% and 0.7% in the pooled 4-dose regimen trials. All 95% CIs for the percentage differences of Tier 2 events crossed 0% except for 2 events (out of 35 Tier 2 events by preferred term): conjunctivitis in the 3-dose regimen trial (lower 95% CI of 0.1) and fall in the 4-dose regimen trials (lower 95% CI of 0.0). Based on the number of comparisons, the minor difference, and nature of the events (conjunctivitis and fall, which don't have a plausible pathophysiologic link to vaccination), the differences are considered to be due to chance.

Adverse Events in Children ≥2 to <18 Years of Age

The AEs reported in children ≥2 to <18 years of age generally reflected diseases and conditions often observed in the paediatric population. The percentages of participants with AEs within 1 month of 20vPnC in B7471014 decreased with increasing age: 7.9% of participants ≥2 to <5 years (Cohort 2), 6.5% of participants ≥5 to <10 years (Cohort 3), and 4.4% of participants ≥10 to <18 years of age (Cohort 4).

Table 63. Adverse events limited to AEs occurring **≥0.5%** in any group (Adverse Events Reported From Dose 1 to 1 Month After the Last Study-Specified Infant Dose, and Reported From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose) (Table compiled by Rapporteur based on ISS Table 1 and 2)

System Organ Class		From Dose 1 to 1 Month After the Last Study-Specified Infant Dose B7471003, B7471011, B7471012 and B7471013						From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose B7471003, B7471011, B7471012, B7471013 and B7471014					
		Vaccine Group (as Administered)											
	Preferred Term	20vPnC (N[a]=2833)			13vPnC (N[a]=2321)			20vPnC (N[a]=2770)			13vPnC (N[a]=2090)		
		n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any Event		887	31.3	(29.6, 33.1)	746	32.1	(30.2, 34.1)	446	16.1	(14.8, 17.5)	348	16.7	(15.1, 18.3)
Congenital, familial and genetic disorders		46	1.6	(1.2, 2.2)	29	1.2	(0.8, 1.8)	1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
	Plagiocephaly	14	0.5	(0.3, 0.8)	12	0.5	(0.3, 0.9)						
Ear and labyrinth disorders		15	0.5	(0.3, 0.9)	13	0.6	(0.3, 1.0)	4	0.1	(0.0, 0.4)	1	0.0	(0.0, 0.3)
Eye disorders		25	0.9	(0.6, 1.3)	7	0.3	(0.1, 0.6)	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
Gastrointestinal disorders		163	5.8	(4.9, 6.7)	151	6.5	(5.5, 7.6)	26	0.9	(0.6, 1.4)	27	1.3	(0.9, 1.9)
	Constipation	36	1.3	(0.9, 1.8)	27	1.2	(0.8, 1.7)	5	0.2	(0.1, 0.4)	4	0.2	(0.1, 0.5)
	Diarrhoea	29	1.0	(0.7, 1.5)	25	1.1	(0.7, 1.6)	7	0.3	(0.1, 0.5)	9	0.4	(0.2, 0.8)
	Gastrooesophageal reflux disease	51	1.8	(1.3, 2.4)	36	1.6	(1.1, 2.1)	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.3)
	Teething	9	0.3	(0.1, 0.6)	15	0.6	(0.4, 1.1)	2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Vomiting	25	0.9	(0.6, 1.3)	23	1.0	(0.6, 1.5)	8	0.3	(0.1, 0.6)	8	0.4	(0.2, 0.8)
General disorders and administration site conditions		54	1.9	(1.4, 2.5)	47	2.0	(1.5, 2.7)	32	1.2	(0.8, 1.6)	33	1.6	(1.1, 2.2)
	Pyrexia	42	1.5	(1.1, 2.0)	34	1.5	(1.0, 2.0)	25	0.9	(0.6, 1.3)	24	1.1	(0.7, 1.7)
Immune system disorders		23	0.8	(0.5, 1.2)	19	0.8	(0.5, 1.3)	1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
	Food allergy	13	0.5	(0.2, 0.8)	7	0.3	(0.1, 0.6)	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.3)
Infections and infestations		571	20.2	(18.7, 21.7)	463	19.9	(18.3, 21.6)	345	12.5	(11.2, 13.7)	261	12.5	(11.1, 14.0)
	Bronchiolitis	48	1.7	(1.3, 2.2)	37	1.6	(1.1, 2.2)	12	0.4	(0.2, 0.8)	12	0.6	(0.3, 1.0)
	Bronchitis	13	0.5	(0.2, 0.8)	9	0.4	(0.2, 0.7)	13	0.5	(0.3, 0.8)	9	0.4	(0.2, 0.8)
	COVID-19	20	0.7	(0.4, 1.1)	18	0.8	(0.5, 1.2)	21	0.8	(0.5, 1.2)	13	0.6	(0.3, 1.1)
	Candida infection	6	0.2	(0.1, 0.5)	13	0.6	(0.3, 1.0)	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.3)
	Conjunctivitis	32	1.1	(0.8, 1.6)	23	1.0	(0.6, 1.5)	14	0.5	(0.3, 0.8)	11	0.5	(0.3, 0.9)
	Croup infectious	17	0.6	(0.3, 1.0)	16	0.7	(0.4, 1.1)	7	0.3	(0.1, 0.5)	4	0.2	(0.1, 0.5)
	Gastroenteritis	18	0.6	(0.4, 1.0)	21	0.9	(0.6, 1.4)	19	0.7	(0.4, 1.1)	12	0.6	(0.3, 1.0)
	Gastroenteritis viral	15	0.5	(0.3, 0.9)	8	0.3	(0.1, 0.7)	9	0.3	(0.1, 0.6)	8	0.4	(0.2, 0.8)

	Hand-foot-and-mouth disease	2	0.1	(0.0, 0.3)	5	0.2	(0.1, 0.5)	11	0.4	(0.2, 0.7)	13	0.6	(0.3, 1.1)
	Nasopharyngitis	68	2.4	(1.9, 3.0)	61	2.6	(2.0, 3.4)	46	1.7	(1.2, 2.2)	20	1.0	(0.6, 1.5)
	Oral candidiasis	20	0.7	(0.4, 1.1)	20	0.9	(0.5, 1.3)						
	Otitis media	63	2.2	(1.7, 2.8)	53	2.3	(1.7, 3.0)	48	1.7	(1.3, 2.3)	39	1.9	(1.3, 2.5)
	Otitis media acute	41	1.4	(1.0, 2.0)	43	1.9	(1.3, 2.5)	30	1.1	(0.7, 1.5)	17	0.8	(0.5, 1.3)
	Respiratory syncytial virus infection	14	0.5	(0.3, 0.8)	7	0.3	(0.1, 0.6)	6	0.2	(0.1, 0.5)	3	0.1	(0.0, 0.4)
	Respiratory tract infection viral	18	0.6	(0.4, 1.0)	10	0.4	(0.2, 0.8)	8	0.3	(0.1, 0.6)	5	0.2	(0.1, 0.6)
	Upper respiratory tract infection	181	6.4	(5.5, 7.4)	167	7.2	(6.2, 8.3)	66	2.4	(1.8, 3.0)	70	3.3	(2.6, 4.2)
	Urinary tract infection	13	0.5	(0.2, 0.8)	10	0.4	(0.2, 0.8)	1	0.0	(0.0, 0.2)	4	0.2	(0.1, 0.5)
	Viral infection	30	1.1	(0.7, 1.5)	21	0.9	(0.6, 1.4)	9	0.3	(0.1, 0.6)	11	0.5	(0.3, 0.9)
	Viral upper respiratory tract infection	52	1.8	(1.4, 2.4)	36	1.6	(1.1, 2.1)	15	0.5	(0.3, 0.9)	5	0.2	(0.1, 0.6)
Injury, poisoning and procedural complications		29	1.0	(0.7, 1.5)	25	1.1	(0.7, 1.6)	20	0.7	(0.4, 1.1)	11	0.5	(0.3, 0.9)
	Fall	21	0.7	(0.5, 1.1)	9	0.4	(0.2, 0.7)	13	0.5	(0.3, 0.8)	3	0.1	(0.0, 0.4)
Investigations		32	1.1	(0.8, 1.6)	30	1.3	(0.9, 1.8)	24	0.9	(0.6, 1.3)	15	0.7	(0.4, 1.2)
	SARS-CoV-2 test positive	21	0.7	(0.5, 1.1)	19	0.8	(0.5, 1.3)	18	0.6	(0.4, 1.0)	10	0.5	(0.2, 0.9)
Metabolism and nutrition disorders		41	1.4	(1.0, 2.0)	36	1.6	(1.1, 2.1)	0	0	(0.0, 0.1)	6	0.3	(0.1, 0.6)
Musculoskeletal and connective tissue disorders		27	1.0	(0.6, 1.4)	21	0.9	(0.6, 1.4)	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.3)
	Acquired plagiocephaly	12	0.4	(0.2, 0.7)	14	0.6	(0.3, 1.0)						
Nervous system disorders		22	0.8	(0.5, 1.2)	22	0.9	(0.6, 1.4)	6	0.2	(0.1, 0.5)	3	0.1	(0.0, 0.4)
Reproductive system and breast disorders		14	0.5	(0.3, 0.8)	19	0.8	(0.5, 1.3)	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.3)
Respiratory, thoracic and mediastinal disorders		117	4.1	(3.4, 4.9)	82	3.5	(2.8, 4.4)	30	1.1	(0.7, 1.5)	27	1.3	(0.9, 1.9)
	Cough	38	1.3	(1.0, 1.8)	27	1.2	(0.8, 1.7)	7	0.3	(0.1, 0.5)	8	0.4	(0.2, 0.8)
	Nasal congestion	46	1.6	(1.2, 2.2)	28	1.2	(0.8, 1.7)	5	0.2	(0.1, 0.4)	5	0.2	(0.1, 0.6)
	Rhinitis allergic	16	0.6	(0.3, 0.9)	9	0.4	(0.2, 0.7)	4	0.1	(0.0, 0.4)	2	0.1	(0.0, 0.3)
	Rhinorrhoea	9	0.3	(0.1, 0.6)	12	0.5	(0.3, 0.9)	3	0.1	(0.0, 0.3)	5	0.2	(0.1, 0.6)
Skin and subcutaneous tissue disorders		219	7.7	(6.8, 8.8)	176	7.6	(6.5, 8.7)	38	1.4	(1.0, 1.9)	37	1.8	(1.2, 2.4)
	Dermatitis	15	0.5	(0.3, 0.9)	7	0.3	(0.1, 0.6)	2	0.1	(0.0, 0.3)	0 0		(0.0, 0.2)
	Dermatitis atopic	62	2.2	(1.7, 2.8)	42	1.8	(1.3, 2.4)	2	0.1	(0.0, 0.3)	4	0.2	(0.1, 0.5)

	Dermatitis diaper	25	0.9	(0.6, 1.3)	15	0.6	(0.4, 1.1)	4	0.1	(0.0, 0.4)	10	0.5	(0.2, 0.9)
	Eczema	45	1.6	(1.2, 2.1)	40	1.7	(1.2, 2.3)	6	0.2	(0.1, 0.5)	2	0.1	(0.0, 0.3)
	Rash	13	0.5	(0.2, 0.8)	14	0.6	(0.3, 1.0)	12	0.4	(0.2, 0.8)	10	0.5	(0.2, 0.9)
	Seborrhoeic dermatitis	23	0.8	(0.5, 1.2)	28	1.2	(0.8, 1.7)						

Table 64. Tier 2 Adverse Events (Weighted Event Rate ≥1.0% in Any Vaccine Group) Reported Either From Dose 1 to 1 Month After the Last Study-Specified Infant Dose Or From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose

From Dose 1 to 1 Month After the Last Study-Specified Infant Dose								
	Vaccine Group (as Administered)							
System Organ Class	20vPnC (N[a]=2833)			13vPnC (N[a]=2321)			20vPnC – 13vPnC	
Preferred Term	n[b] (%)	(95% CI[c])	Weighted[d] (%)	n[b] (%)	(95% CI[c])	Weighted[d] (%)	Difference[d] (%)	(95% CI[d])
Gastrointestinal disorders								
Gastrooesophageal reflux disease	51 (1.8)	(1.3, 2.4)	1.2	36 (1.6)	(1.1, 2.1)	0.8	0.4	(-0.3, 1.0)
General disorders and administration site conditions								
Pyrexia	42 (1.5)	(1.1, 2.0)	1.2	34 (1.5)	(1.0, 2.0)	1.3	-0.2	(-0.9, 0.5)
Infections and infestations								
Conjunctivitis	32 (1.1)	(0.8, 1.6)	1.1	23 (1.0)	(0.6, 1.5)	0.6	0.5	(-0.0, 1.1)
Nasopharyngitis	68 (2.4)	(1.9, 3.0)	2.1	61 (2.6)	(2.0, 3.4)	2.2	-0.1	(-1.0, 0.7)
Upper respiratory tract infection	181 (6.4)	(5.5, 7.4)	4.0	167 (7.2)	(6.2, 8.3)	4.1	-0.2	(-1.3, 0.9)
Skin and subcutaneous tissue disorders								
Dermatitis atopic	62 (2.2)	(1.7, 2.8)	2.1	42 (1.8)	(1.3, 2.4)	1.7	0.4	(-0.4, 1.2)
Eczema	45 (1.6)	(1.2, 2.1)	1.0	40 (1.7)	(1.2, 2.3)	1.1	-0.2	(-0.8, 0.4)
From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose								
	Vaccine Group (as Administered)							
System Organ Class	20vPnC (N[a]=2561)			13vPnC (N[a]=2090)			20vPnC – 13vPnC	
Preferred Term	n[b] (%)	(95% CI[c])	Weighted[d] (%)	n[b] (%)	(95% CI[c])	Weighted[d] (%)	Difference[d] (%)	(95% CI[d])
Infections and infestations								
Nasopharyngitis	44 (1.7)	(1.3, 2.3)	1.4	20 (1.0)	(0.6, 1.5)	0.8	0.7	(-0.0, 1.3)
Otitis media	42 (1.6)	(1.2, 2.2)	1.2	39 (1.9)	(1.3, 2.5)	1.1	0.1	(-0.6, 0.7)
Upper respiratory tract infection	62 (2.4)	(1.9, 3.1)	2.5	70 (3.3)	(2.6, 4.2)	3.3	-0.9	(-1.9, 0.1)

Note: MedDRA (v25.0) coding dictionary applied.
Note: The last study-specified infant dose is Dose 2 from B7471012 and Dose 3 from B7471003, B7471011, and B7471013.
Note: The study-specified toddler dose is Dose 3 from B7471012 and Dose 4 from B7471003, B7471011, and B7471013.

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of an adverse event for the specified analysis interval.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Weighted percentage, percentage difference, and 2-sided CI are based on the weighted Miettinen and Nurminen method for the difference in proportions, expressed as a percentage, with inverse-variance weights for individual studies. CIs are not adjusted for multiplicity and should be used for screening purposes to identify potentially important adverse events only.

Table 65. Adverse Events Reported From Vaccination to 1 Month After Vaccination (Subjects **≥**15 months to <18 Years of Age, 20vPnC, in **≥1%** of subjects in any group) (Table limited to ≥1% by Rapporteur)

System Organ Class		⩾15 to <24 Months (N[a]=209)		⩾2 to <5 Years (N[a]=216)		⩾5 to <10 Years (N[a]=201)		⩾10 to <18 Years (N[a]=205)	
	Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event		*50 (23.9)*	*(18.3, 30.3)*	*17 (7.9)*	*(4.7, 12.3)*	*13 (6.5)*	*(3.5, 10.8)*	*9 (4.4)*	*(2.0, 8.2)*
Gastrointestinal disorders		4 (1.9)	(0.5, 4.8)	3 (1.4)	(0.3, 4.0)	1 (0.5)	(0.0, 2.7)	1 (0.5)	(0.0, 2.7)
	Diarrhoea	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Vomiting	3 (1.4)	(0.3, 4.1)	2 (0.9)	(0.1, 3.3)	0	(0.0, 1.8)	0	(0.0, 1.8)
General disorders and administration site conditions		2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Pyrexia	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
Infections and infestations		36 (17.2)	(12.4, 23.0)	7 (3.2)	(1.3, 6.6)	8 (4.0)	(1.7, 7.7)	5 (2.4)	(0.8, 5.6)
	Acute sinusitis	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Bronchiolitis	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Bronchitis	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	COVID-19	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	2 (1.0)	(0.1, 3.5)	2 (1.0)	(0.1, 3.5)
	Croup infectious	3 (1.4)	(0.3, 4.1)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Gastroenteritis viral	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	1 (0.5)	(0.0, 2.7)
	Nasopharyngitis	2 (1.0)	(0.1, 3.4)	1 (0.5)	(0.0, 2.6)	0	(0.0, 1.8)	1 (0.5)	(0.0, 2.7)
	Otitis media	6 (2.9)	(1.1, 6.1)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Otitis media acute	4 (1.9)	(0.5, 4.8)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Pharyngitis	0	(0.0, 1.7)	0	(0.0, 1.7)	2 (1.0)	(0.1, 3.5)	1 (0.5)	(0.0, 2.7)
	Respiratory syncytial virus infection	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Suspected COVID-19	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Upper respiratory tract infection	4 (1.9)	(0.5, 4.8)	1 (0.5)	(0.0, 2.6)	1 (0.5)	(0.0, 2.7)	0	(0.0, 1.8)
	Viral upper respiratory tract infection	4 (1.9)	(0.5, 4.8)	1 (0.5)	(0.0, 2.6)	0	(0.0, 1.8)	0	(0.0, 1.8)
Injury, poisoning and procedural complications		5 (2.4)	(0.8, 5.5)	1 (0.5)	(0.0, 2.6)	2 (1.0)	(0.1, 3.5)	2 (1.0)	(0.1, 3.5)
	Fall	3 (1.4)	(0.3, 4.1)	0	(0.0, 1.7)	0	(0.0, 1.8)	0	(0.0, 1.8)
	Skin laceration	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	1 (0.5)	(0.0, 2.7)	1 (0.5)	(0.0, 2.7)
	Investigations	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	2 (1.0)	(0.1, 3.5)	2 (1.0)	(0.1, 3.5)
	SARS-CoV-2 test positive	2 (1.0)	(0.1, 3.4)	0	(0.0, 1.7)	2 (1.0)	(0.1, 3.5)	2 (1.0)	(0.1, 3.5)
Respiratory, thoracic and mediastinal disorders		5 (2.4)	(0.8, 5.5)	3 (1.4)	(0.3, 4.0)	0	(0.0, 1.8)	0	(0.0, 1.8)
Skin and subcutaneous tissue disorders		6 (2.9)	(1.1, 6.1)	2 (0.9)	(0.1, 3.3)	1 (0.5)	(0.0, 2.7)	1 (0.5)	(0.0, 2.7)
	Rash	2 (1.0)	(0.1, 3.4)	1 (0.5)	(0.0, 2.6)	0	(0.0, 1.8)	0	(0.0, 1.8)

Note: MedDRA (v24.1) coding dictionary applied.

a. N = number of participants in the specified age cohort. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

AEs during the whole study duration

The AEs reported during the entire study duration for the 3-dose regimen and the 4-dose regimen trials were provided with the responses. The AEs reported were generally consistent with diseases and conditions commonly observed in infants. The percentage of participants with AEs in the 3-dose regimen trial was similar in the 20vPnC (27.6%) and 13vPnC (28.5%) groups. For the pooled analysis across the 4-dose regimen trials, the percentage of participants with AEs was also similar in the 20vPnC (42.5%) and 13vPnC (44.8%) groups. The most frequently reported AEs belonged to the system organ class (SOC) of infections and infestations and were similar in the 20vPnC (20.3% and 30.2%) and 13vPnC (21.2% and 30.6%) groups in the 3-dose regimen trial and the 4-dose regimen trials, respectively. AEs belonging to the SOC of skin and subcutaneous tissue disorders and the SOC of gastrointestinal disorders were also reported. The relative frequency of the events among the SOCs were similar between the regimens.

Related Adverse events

In B7471012 (3-dose series), the number and percentages of participants with AEs from Dose 1 to 1 month after Dose 2 that were assessed by the investigator as related to study intervention were generally similar for 20vPnC and 13vPnC recipients (2 [0.3%] and 4 [0.7%], respectively) (Module 5.3.5.1 B7471012 Report Body Table 21). From Dose 3 to 1 month after Dose 3, 1 related AE was reported in each vaccine group: dermatitis allergic (20vPnC) and injection site nodule (13vPnC) (Module 5.3.5.1 B7471012 Report Body Table 22). One SAE, inflammation in B7471012, considered by the investigator to be potentially related to study vaccine (or concomitant vaccine), is described in Section 2.7.4.2.4.

The percentages of pooled participants with AEs that were assessed by the investigator as related to study intervention were also similar among 20vPnC and 13vPnC recipients from Dose 1 to 1 month after the last study-specified infant dose in B7471003, B7471011, B7471012, and B7471013 (0.6% and 0.8%, respectively) and from the study-specified toddler dose to 1 month after the toddler dose in B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1 (0.2% and 0.3%).

The most frequently reported related AEs were injection site erythema (four 20vPnC and three 13vPnC) and diarrhoea (three 20vPnC and two 13vPnC) reported from Dose 1 to 1 month after the last study-specified infant dose. The other less frequently reported AEs (1-2 events/term) were considered related as they are reported as ADRs following Prevenar 13 administration, or in other cases based on temporal association alone, with limited physiologic plausibility.

In older subjects, only 1 participant had a related AE within 1 month after 20vPnC: 1 participant ≥5 to <10 years of age (0.5%; Cohort 3). The AE was for upper abdominal pain of mild severity that began on Day 12, lasted for 12 days, and was considered related based on temporal association.

Table 66. Related Adverse Events (Reported From Dose 1 to 1 Month After the Last Study-Specified Infant Dose and Reported From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose)

System Organ Class		Vaccine Group (as Administered)					
	Preferred Term	20vPnC (N[a]=2833)			13vPnC (N[a]=2321)		
		n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
From Dose 1 to 1 Month After the Last Study-Specified Infant Dose							
Any event		18	0.6	(0.4, 1.0)	19	0.8	(0.5, 1.3)
Gastrointestinal disorders		4	0.1	(0.0, 0.4)	5	0.2	(0.1, 0.5)

	Diarrhoea	3	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Dyschezia	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Gastrooesophageal reflux disease	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Salivary hypersecretion	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Vomiting	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
General disorders and administration site conditions		9	0.3	(0.1, 0.6)	10	0.4	(0.2, 0.8)
	Inflammation	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Injection site erythema	4	0.1	(0.0, 0.4)	3	0.1	(0.0, 0.4)
	Injection site hypersensitivity	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Injection site pain	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
	Pyrexia	2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Vaccination site erythema	1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
	Vaccination site pain	1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
Infections and infestations		0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Gastroenteritis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
Psychiatric disorders		2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Irritability	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
Skin and subcutaneous tissue disorders		3	0.1	(0.0, 0.3)	3	0.1	(0.0, 0.4)
	Dermatitis atopic	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Dermatitis contact	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Erythema	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Urticaria	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose							
		20vPnC (N[a]=2770)			13vPnC (N[a]=2090)		
Any event		5	0.2	(0.1, 0.4)	6	0.3	(0.1, 0.6)
Gastrointestinal disorders		1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
	Diarrhoea	1	0.0	(0.0, 0.2)	2	0.1	(0.0, 0.3)
	Vomiting	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.3)
General disorders and administration site conditions		1	0.0	(0.0, 0.2)	3	0.1	(0.0, 0.4)
	Injection site erythema	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.3)
	Injection site hypersensitivity	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.3)
	Injection site nodule	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.3)
	Injection site pain	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Injection site swelling	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Nervous system disorders		1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Somnolence	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Psychiatric disorders		2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.3)
	Irritability	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.3)
Skin and subcutaneous tissue disorders		1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Dermatitis allergic	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)

Note: MedDRA (v25.0) coding dictionary applied.

Note: The study-specified toddler dose is Dose 3 from B7471012; Dose 4 from B7471003, B7471011, and B7471013; and the single dose of 20vPnC from B7471014 Cohort 1 (children 15 to <24 months of age with at least 3 prior infant doses of 13vPnC).

a. N = number of participants who received a toddler dose in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.

c. Exact 2-sided CI, based on the Clopper and Pearson method.

AEs during the whole study duration

The percentages of participants with related AEs were low and similar between the 20vPnC and 13vPnC groups. Related AEs were reported in 0.5% and 0.9% (20vPnC) and 0.8% and 1.2% (13vPnC) of participants in the 3-dose regimen trial and the pooled 4-dose regimen trials, respectively. The most frequently reported related AEs were injection site reactions in the SOC of general disorders and

administration site conditions. These generally reflected adverse reactions already listed for 13vPnC or isolated events.

Severe Adverse Events

In B7471012, severe AEs were reported infrequently from Dose 1 to 1 month after Dose 2 (for ≤0.7% of participants) and from Dose 3 to 1 month after Dose 3 (for ≤0.9% of participants) (Module 5.3.5.1 B7471012 Supplemental Tables 14.43 and 14.44, respectively), and the percentages were similar in the 20vPnC and 13vPnC groups.

The percentages of pooled participants with severe AEs were also similar for 20vPnC and 13vPnC recipients from Dose 1 to 1 month after the last study-specified infant dose in B7471003, B7471011, B7471012, and B7471013 (0.8% and 0.7%, respectively; Module 5.3.5.3 ISS Table 8) and from the study-specified toddler dose to 1 month after the toddler dose in B7471003, B7471011, B7471012, B7471013, and B7471014 Cohort 1 (0.6% and 0.5%, respectively; Module 5.3.5.3 ISS Table 9). Most severe AEs were in the Infections and infestations SOC.

One participant ≥5 to <10 years of age (Cohort 3) had a severe AE of urticaria on Day 12 after 20vPnC which lasted for 13 days and was assessed by the investigator as not related to study intervention.

Table 67. Severe Adverse Events occurring in at least 2 subjects (Reported From Dose 1 to 1 Month After the Last Study-Specified Infant Dose and From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose) (ISS Table 8 and 9 combined by Rapporteur)

System Organ Class		Vaccine Group (as Administered)					
		20vPnC (N[a]=2833)			13vPnC (N[a]=2321)		
	Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
From Dose 1 to 1 Month After the Last Study-Specified Infant Dose							
Any event		23	0.8	(0.5, 1.2)	17	0.7	(0.4, 1.2)
Gastrointestinal disorders		5	0.2	(0.1, 0.4)	1	0.0	(0.0, 0.2)
	Gastroesophageal reflux disease	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
General disorders and administration site conditions		2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
Infections and infestations		11	0.4	(0.2, 0.7)	8	0.3	(0.1, 0.7)
	Bronchiolitis	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Urinary tract infection	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
Nervous system disorders		2	0.1	(0.0, 0.3)	5	0.2	(0.1, 0.5)
	Seizure like phenomena	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
Psychiatric disorders		0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
From the Study-Specified Toddler Dose to 1 Month After the Toddler Dose							
		20vPnC (N[a]=2770)			13vPnC (N[a]=2090)		
Any event		16	0.6	(0.3, 0.9)	10	0.5	(0.2, 0.9)
Infections and infestations		12	0.4	(0.2, 0.8)	8	0.4	(0.2, 0.8)
	Bronchiolitis	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Respiratory syncytial virus infection	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Upper respiratory tract infection	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
Nervous system disorders		2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Febrile convulsion	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
Respiratory, thoracic and mediastinal disorders		2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Bronchial hyperreactivity	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)

Note: MedDRA (v25.0) coding dictionary applied.

Note: The last study-specified infant dose is Dose 2 from B7471012 and Dose 3 from B7471003, B7471011, and B7471013.

Note: The study-specified toddler dose is Dose 3 from B7471012; Dose 4 from B7471003, B7471011, and B7471013; and the single dose of 20vPnC from B7471014 Cohort 1 (children 15 to <24 months of age with at least 3 prior infant doses of 13vPnC).

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.

c. Exact 2-sided CI, based on the Clopper and Pearson method.

AEs during the whole study duration

The percentages of participants with severe AEs were low and similar and reported in 2.5% and 2.0% of participants in the 20vPnC groups and 1.3% and 1.7% in the 13vPnC groups in the 3 dose regimen trial and the pooled 4-dose regimen trials, respectively. These were generally single events, and most frequently reported in the SOC of infections and infestations.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths in any of the trials.

Serious Adverse Events

The percentages of participants with SAEs in B7471012 were similar in the 20vPnC and 13vPnC control groups (5.7% and 6.6%, respectively).

The percentages of participants across all paediatric trials with SAEs from Dose 1 to the end of the trials were low (3.8% for 20vPnC recipients and 4.5% for 13vPnC recipients); ≤0.4% experienced a specific SAE.

Over the whole study duration, SAEs were reported at a rate of 5.7% and 3.4% in the 20vPnC groups, and 6.6% and 3.0% in the 13vPnC groups in the 3-dose regimen trial and the 4-dose regimen trials, respectively. As with the severe AEs, the most frequently reported SAEs were in the SOC of infections and infestations.

SAEs from Dose 1 to 1 month after the last study-specified infant dose and from the study-specified toddler dose to 1 month after the toddler dose were low and similar for 20vPnC (1.4% and 0.6%, respectively) and 13vPnC (1.5 % and 0.7%, respectively) recipients. SAEs included infections requiring hospitalization that may be expected to occur at a low background level in infants. During the 2-year study period for B7471011 and B7471013, rates of respiratory infections, particularly bronchiolitis occurred at a relatively high frequency and that is reflected in the SAEs. Participants with SAEs of failure to thrive (2 20vPnC recipients and 1 13vPnC recipient), cerebral haemorrhage (2 20vPnC recipients), and infantile spasm (1 20vPnC recipient) withdrew from their respective trials.

There was one SAE in B7471012 considered potentially related to study vaccine (or concomitant vaccine) by the investigator. A participant in the 20vPnC group was reported to have an SAE of inflammation with an onset date 7 days after Dose 1 and duration of 10 days. This participant was hospitalized with fever and laboratory tests revealed elevated inflammatory markers (CRP and procalcitonin). There was an area of painful swelling in the right groin, and a right inguinal hernia was diagnosed. A blood culture was negative, and no specific disease diagnosis was made. The participant received antibiotics in the hospital, and the event resolved. The investigator considered the event potentially related to study vaccine or Infanrix hexa. Pfizer did not concur as the inflammation was more likely related to the concomitant vaccine, Infanrix hexa, which was given in the right leg, the same side as the painful swelling. The concurrent inguinal hernia complicated by inflammation/infection was also considered to be a possible contributing factor. This participant was not withdrawn from the study and received Dose 2 and Dose 3 of

20vPnC with no repeat of the event, which also made the relationship to study intervention less likely. Besides this event, there were no other SAEs assessed as related to vaccine in any other trial.

In B7471011 there was 1 participant in the 20vPnC group with an SAE of immune thrombocytopenia on Day 141 after Dose 3, which lasted for 36 days. Another participant in the 20vPnC group had an SAE of Kawasaki's disease on Day 103 after Dose 3; the event was recovering/resolving when the participant was withdrawn from the trial due to receipt of immunoglobins which was prohibited by the protocol.

In B7471013 there were 2 participants in the 20vPnC group with SAEs of anaphylaxis and urticaria that warrant additional description; 1 participant had an anaphylactic reaction from food allergy 40 days after Dose 4 that resolved in 5 days, and the other participant developed urticaria 10 days after Dose 4 that resolved in 5 days. Neither were considered by the investigator to be related to study intervention.

The numbers and percentages of participants ≥15 months of age with SAEs were low: (2 participants [1.0%] ≥15 to <24 months of age [Cohort 1] and 3 participants [1.5%] ≥10 to <18 years of age [Cohort 4]). All SAEs were reported in the interval 1 to 6 months after vaccination, except a near drowning SAE in Cohort 1, that was reported within 1 month after vaccination.

Table 68. Serious Adverse Events Reported After Dose 1, by System Organ Class and Preferred Term – B7471003, B7471011, B7471012, B7471013

		Vaccine Group (as Administered)					
System Organ Class		20vPnC (N[a]=2833)			13vPnC (N[a]=2320)		
	Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event		135	4.8	(4.0, 5.6)	104	4.5	(3.7, 5.4)
Blood and lymphatic system disorders		5	0.2	(0.1, 0.4)	5	0.2	(0.1, 0.5)
	Anaemia	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Immune thrombocytopenia	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Lymphadenitis	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Lymphadenopathy	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Microcytic anaemia	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Neutropenia	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Thymus enlargement	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
Congenital, familial and genetic disorders		2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Aorticopulmonary septal defect	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Bronchogenic cyst	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Gastrointestinal disorders		3	0.1	(0.0, 0.3)	4	0.2	(0.0, 0.4)
	Allergic colitis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Colitis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Enteritis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Intestinal haemorrhage	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Intussusception	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
	Vomiting	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
General disorders and administration site conditions		4	0.1	(0.0, 0.4)	3	0.1	(0.0, 0.4)
	Adverse food reaction	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Inflammation	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Pyrexia	1	0.0	(0.0, 0.2)	3	0.1	(0.0, 0.4)
	Systemic inflammatory response syndrome	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Immune system disorders		1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Anaphylactic reaction	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
Infections and infestations		88	3.1	(2.5, 3.8)	72	3.1	(2.4, 3.9)
	Abscess	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Adenovirus infection	3	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Arthritis bacterial	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Bacterial infection	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)

	Bronchiolitis	12	0.4	(0.2, 0.7)	11	0.5	(0.2, 0.8)
	Bronchitis	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Bronchitis viral	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Bullous impetigo	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	COVID-19	1	0.0	(0.0, 0.2)	3	0.1	(0.0, 0.4)
	Cellulitis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Coronavirus infection	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Croup infectious	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Dengue fever	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Erythema infectiosum	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Escherichia urinary tract infection	1	0.0	(0.0, 0.2)	5	0.2	(0.1, 0.5)
	Gastroenteritis	8	0.3	(0.1, 0.6)	13	0.6	(0.3, 1.0)
	Gastroenteritis norovirus	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Gastroenteritis rotavirus	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Gastroenteritis salmonella	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Gastroenteritis viral	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Gastrointestinal infection	2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Gastrointestinal viral infection	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Groin abscess	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Hand-foot-and-mouth disease	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Herpangina	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Laryngitis	2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Lower respiratory tract infection viral	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Meningitis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Meningitis enteroviral	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Meningitis viral	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Metapneumovirus bronchiolitis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Oral candidiasis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Otitis media	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Otitis media acute	2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Parainfluenzae virus infection	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Pharyngotonsillitis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Pneumonia	5	0.2	(0.0, 0.4)	5	0.2	(0.1, 0.5)
	Pneumonia necrotising	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Pneumonia respiratory syncytial viral	2	0.1	(0.0, 0.2)	0	0	(0.0, 0.2)
	Pyelonephritis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Pyelonephritis acute	3	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Respiratory syncytial virus bronchiolitis	11	0.4	(0.1, 0.7)	4	0.2	(0.0, 0.4)
	Respiratory syncytial virus bronchitis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Respiratory syncytial virus infection	7	0.2	(0.1, 0.5)	3	0.1	(0.0, 0.4)
	Respiratory tract infection viral	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Sepsis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Skin infection	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Urinary tract infection	7	0.2	(0.1, 0.5)	6	0.3	(0.1, 0.6)
	Urinary tract infection bacterial	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Urinary tract infection pseudomonal	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Viraemia	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Viral infection	4	0.1	(0.0, 0.4)	3	0.1	(0.0, 0.4)
	Viral upper respiratory tract infection	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Injury, poisoning and procedural complications		10	0.4	(0.2, 0.6)	4	0.2	(0.0, 0.4)
	Accidental exposure to product	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Accidental poisoning	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)

	Concussion	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Extradural haematoma	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Fall	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Foreign body aspiration	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Humerus fracture	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Skull fracture	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Subdural haematoma	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Thermal burn	2	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
Metabolism and nutrition disorders		8	0.3	(0.1, 0.6)	6	0.3	(0.1, 0.6)
	Dehydration	3	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Failure to thrive	3	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Feeding disorder	0	0	(0.0, 0.1)	3	0.1	(0.0, 0.4)
	Malnutrition	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Poor feeding infant	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Type 1 diabetes mellitus	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Underweight	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1	0.1	(0.0, 0.2)	0	0	(0.0, 0.2)
	Benign salivary gland neoplasm	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Nervous system disorders		9	0.3	(0.1, 0.6)	10	0.4	(0.2, 0.8)
	Cerebral haemorrhage	2	0.1	(0.0, 0.3)	0	0	(0.0, 0.2)
	Febrile convulsion	4	0.1	(0.0, 0.4)	3	0.1	(0.0, 0.4)
	Hypoglycaemic seizure	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Hypotonia	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Infantile spasms	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Intracranial pressure increased	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Partial seizures	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Seizure	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
	Seizure like phenomena	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Status epilepticus	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
Psychiatric disorders		1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Breath holding	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Renal and urinary disorders		3	0.1	(0.0, 0.3)	1	0.0	(0.0, 0.2)
	Nephritis	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Oliguria	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Tubulointerstitial nephritis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Vesicoureteric reflux	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Respiratory, thoracic and mediastinal disorders		3	0.1	(0.0, 0.3)	4	0.2	(0.0, 0.4)
	Acute respiratory failure	0	0	(0.0, 0.1)	2	0.1	(0.0, 0.3)
	Asthma	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Bronchial hyperreactivity	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Bronchospasm	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
	Respiratory distress	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
Skin and subcutaneous tissue disorders		2	0.1	(0.0, 0.3)	2	0.1	(0.0, 0.3)
	Dermatitis atopic	0	0	(0.0, 0.1)	1	0.0	(0.0, 0.2)
	Hypersensitivity vasculitis	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Urticaria	1	0.0	(0.0, 0.2)	1	0.0	(0.0, 0.2)
Vascular disorders		1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)
	Kawasaki's disease	1	0.0	(0.0, 0.2)	0	0	(0.0, 0.2)

Note: MedDRA (v25.0) coding dictionary applied.

Note: SAEs were followed through 1 month after the last dose in B7471012 and 6 months after the last dose in B7471003, B7471011, B7471013, and B7471014.

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.

c. Exact 2-sided CI, based on the Clopper and Pearson method.

Other Significant Adverse Events

Seizures

Seizures or possible seizures were identified during the trials and then extracted from the database using MedDRA PTs (higher-level, lower-level, and dictionary terms), including, but not limited to convulsions, partial seizures, and epilepsy, etc. The percentages of participants across all paediatric trials who experienced seizures were low (14 [0.4%] for 20vPnC recipients and 11 [0.5%] for 13vPnC recipients). No seizures were considered by the investigator to be related to study vaccine.

Eight (0.2%) 20vPnC recipients and 3 (0.1%) 13vPnC recipients experienced a febrile convulsion. One infant participant in the 20vPnC group of B7471011 had a febrile convulsion on Day 7 after Dose 4, which was due to COVID-19 infection and unrelated to study intervention. The other febrile convulsions occurred between Days 14 and 252 after vaccination, including 1 febrile convulsion reported for a participant ≥15 to <24 months of age in B7471014.

Some atypical events such as partial seizure and seizure-like phenomena were experienced by participants in the infant trials. No event occurred within 4 days after vaccination. A listing of participants who experienced seizures during the trials was provided. No seizure was reported for any participant ≥2 years of age.

Seizures reported for infants by timeframe (Dose 1 to 1 month after Dose 3, 1 month after Dose 3 to before Dose 4, Dose 4 to 1 month after Dose 4, and 1 6 months after Dose 4) for B7471003, B7471011, B7471012 and B7471013 are presented in Table 62. Based on these analyses, seizures were reported at similar frequencies in the 20vPnC and 13vPnC groups in any study period. There was no trend in frequency of seizure occurrences based on trial phase.

Table 69. Number (%) of Participants Reporting Seizure or Seizure-Like Events – B7471003, B7471011, B7471012, B7471013, and B7471014 All Cohorts – Safety Population

	Vaccine Group (as Administered)			
	20vPnC (N[a]=3664)		13vPnC (N[a]=2320)	
Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	14 (0.4)	(0.2, 0.6)	11 (0.5)	(0.2, 0.8)
Epilepsy	0	(0.0, 0.1)	2 (0.1)	(0.0, 0.3)
Febrile convulsion	8 (0.2)	(0.1, 0.4)	3 (0.1)	(0.0, 0.4)
Gaze palsy	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
Hypoglycaemic seizure	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Infantile spasms	1 (0.0)	(0.0, 0.2)	0	(0.0, 0.2)
Partial seizures	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
Seizure	3 (0.1)	(0.0, 0.2)	2 (0.1)	(0.0, 0.3)
Seizure like phenomena	0	(0.0, 0.1)	2 (0.1)	(0.0, 0.3)
Status epilepticus	0	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

Table 70. Number (%) of Participants Reporting Seizure or Seizure-Like Events for Each Analysis Interval – B7471003, B7471011, B7471012, and B7471013 – Safety Population

	Vaccine Group (as Administered)							
	Dose 1 to 1 Month After the Last Study-Specified Infant Dose		1 Month After the Last Study-Specified Infant Dose to the Toddler Dose		Study-Specified Toddler Dose to 1 Month After the Toddler Dose		1 Month After the Study-Specified Toddler Dose to 6 Months After the Toddler Dose	
	20vPnC (N[a]=2833)	13vPnC (N[a]=2321)	20vPnC (N[a]=2833)	13vPnC (N[a]=2321)	20vPnC (N[a]=2561)	13vPnC (N[a]=2090)	20vPnC (N[a]=2561)	13vPnC (N[a]=2090)
Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any event	4 (0.1)	7 (0.3)	6 (0.2)	2 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)	2 (0.1)
Epilepsy	0	1 (0.0)	0	1 (0.0)	0	0	0	0
Febrile convulsion	1 (0.0)	0	3 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)
Gaze palsy	0	0	1 (0.0)	0	0	0	0	0
Hypoglycaemic seizure	0	0	0	0	0	0	0	1 (0.0)
Infantile spasms	1 (0.0)	0	0	0	0	0	0	0
Partial seizures	0	1 (0.0)	1 (0.0)	0	0	0	0	0
Seizure	2 (0.1)	2 (0.1)	1 (0.0)	0	0	0	0	0
Seizure like phenomena	0	2 (0.1)	0	0	0	0	0	0
Status epilepticus	0	1 (0.0)	0	0	0	0	0	0

Note: MedDRA (v25.0) coding dictionary applied.
Note: The last study-specified infant dose is Dose 2 from B7471012 and Dose 3 from B7471003, B7471011, and B7471013. The study-specified toddler dose is Dose 3 from B7471012; Dose 4 from B7471003, B7471011, and B7471013.
Note: Study B7471012 is not included in the 1-month after the study-specified toddler dose to 6 months after the toddler dose for either dose group.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./b747_pediatric_sec/B747_PED_MAA/adae_s150_5_7_2 Date of Generation: 28SEP2022 (11:53)

Seizures were evaluated as other significant event. Respective events were summarized with acceptable methods. Overall, less than 0.5% of participants reported seizure or seizure-like events in all studies. This is comparable over all studies and between groups that received 20vPnC or 13vPnC. No concerns are raised. Seizures are appropriately reflected in the SmPC.

Laboratory findings

Clinical laboratory evaluations were not performed systematically in any of the trials. Any clinical laboratory values of concern that came to the attention of the investigator were to be reported as AEs.

Body temperature was measured at clinic visits before vaccination in order to ensure that the infant did not have a fever, which would have required the vaccination to be postponed. These data were not summarized.

No other safety evaluations were performed systematically. Any signs or symptoms of concern related to vital signs, physical examinations, or other evaluations that came to the attention of the investigator were to be reported as AEs, SAEs, or NDCMCs if they occurred within the protocol-specified time frames for collection of safety information.

Safety in special populations

Pregnancies

There were no pregnancies reported in B7471014, the only trial that enrolled females of childbearing potential.

Late Preterm Infants (B7471013)

The safety and tolerability of 20vPnC administered with a 4-dose schedule at 2, 4, 6, and 12 to 15 months of age to late preterm infants (infants born at ≥34 to <37 weeks gestational age [late preterm] in B7471013) were similar to those in term infants administered 20vPnC and 13vPnC with the same schedule.

The local reactions and systemic events after Dose 1 to Dose 4 of 20vPnC and 13vPnC observed in late preterm infants were similar to those in term. The frequency of any reported local reaction (31.7% to 55.3% in the Prevenar 20 group and 37.9% to 47.1% in the Prevenar 13 group) and systemic event (65.0% to 85.5% in the Prevenar 20 group and 59.4% to 77.4% in the Prevenar 13 group).

The frequency of AEs reported from Dose 1 to 1 month after Dose 3 (31.2% after 20vPnC and 23.5% after 13vPnC) or from Dose 4 to 1 month after Dose 4 (14.3% after 20vPnC and 17.2% after 13vPnC) in late preterm infants was similar to that in term infants in B7471013.

Others

Subgroup analyses for local reactions, systemic events, and AEs were performed by sex in B7471012; by sex and race in B7471011 and B7471014; and by sex, race, and geographic region in B7471013. The results of these analyses are presented within the individual reports.

Safety related to drug-drug interactions and other interactions

In the infant trials, 20vPnC and 13vPnC were co-administered with the following vaccine antigens: diphtheria, tetanus, acellular pertussis, Hib, inactivated poliovirus vaccine, hepatitis B, MMR, and varicella.

Additionally, ≥55% of participants in B7471012 and ≥85% of participants in B7471003, B7471013, and B7471011, respectively, received concomitant rotavirus vaccine together with Dose 1 or Dose 2 of 20vPnC. Approximately 21% and 0.5%, 6% and 15%, and 12% and 10% of participants in the 20vPnC group received concomitant influenza vaccine with either Dose 3 or Dose 4, in the 3 trials, B7471003, B7471013, and B7471011, respectively. Approximately 44% (B7471013) and 5.5% (B7471011) of participants received hepatitis A vaccine with Dose 4 of 20vPnC.

In each age cohort of B7471014, between 0.5% (≥5 to <10 years; Cohort 3) and 13% (≥15 to <24 months; Cohort 1) of participants received a specific non-study vaccine on the same day they received 20vPnC. These non-study vaccines included Pentacel (DTaP, Hib, and inactivated poliovirus vaccine; Cohort 1 only); hepatitis A vaccines; influenza vaccines; DTaP (Cohort 1 only); and PedvaxHIB (Hib; Cohort 1 only).

In B7471011, local reactions, systemic events, and AEs were analyzed for participants with and without influenza vaccination. The safety profile was generally similar between participants vaccinated with 20vPnC and 13vPnC with and without influenza vaccination.

Rates of antipyretics/pain medication given to treat symptoms in study participants during the 7 days after study vaccination were generally similar between 20vPnC and 13vPnC control groups and therefore no disproportionate influence was expected to be exerted on the results in one group. The protocol provided instructions that prophylactic antipyretics/pain medication (ie, in the absence of symptoms) was to be discouraged.

Post marketing experience

20vPnC has not been marketed for infants or children in any country. Therefore, no relevant paediatric post-marketing data are available.

2.5.1. Discussion on clinical safety

Safety database

The safety of Prevenar 20 in the paediatric population is investigated in a total of 5 studies. The presented studies applied different dosing regimen and were performed in different age groups, however mainly focussing on infants, the main target group. In this age group a 2- or a 3-dose primary series followed by a toddler dose (also referred to as 3-dose or 4-dose regimen) were evaluated (3-dose regimen: B7471012; 4-dose regimen: B7471011, B7471013, B7471003). Based on the similarity on study design, population and dosing regimen the results for the 4-dose regimen are presented as pooled analysis. In general, the applied methods for data collection and analysis are considered appropriate. In older subjects (15 months – 18 years, who previously received at least 3 doses of 13vPnC) only one single dose was applied (study B7471014). In all infant trials 13vPnC was used as comparator vaccine, which is acceptable and in line with the immuno-bridging approach. Further, routine concomitant paediatric vaccines were additionally administered in all infant studies, which is considered informative. No post-marketing data is available for 20vPnC since it has not been marketed for infants or children in any country.

The presented safety population is considered representative for the main target population (healthy infants approximately 2 months of age). The demographic characteristics are comparable between infant trials and between vaccination groups.

In total, 3664 participants were exposed to Prevenar 20 and 2323 received the control vaccine 13vPnC. In the infant studies, 2833 subjects received at least one dose of 20vPnC. In addition, supportive data for 831 subjects (15 months to 18 years) receiving only one dose of Prevenar 20 are available. This supportive dataset is considered rather limited hampering conclusions for more specific age groups in this broad age range from 15 months to 18 years. Nevertheless, the size of the safety database is considered sufficient for the assessment of the safety profile of Prevenar 20 but it is not considered sufficient to evaluate less common adverse events.

Discontinuations

Overall, the percentage of subjects that withdrew due to adverse events of physician decision is low but some discrepancies in the reporting have been identified. The Applicant reported in total 12 subjects (9 infants who received 20vPnC and 3 infants who received 13vPnC) but the numbers in the individual study reports differ (7 for 20vPnV and 4 for 13vPnC). The Applicant clarified upon request that this is due to different time points for reporting for the pooled dataset and the reporting dates in the study reports. The Applicant provided a detailed explanation which subjects were discontinued and how the discrepancy occurred, and the issue was resolved. Taking either report into consideration, it seems that slightly more subjects discontinued due to AEs in the 20vPnV group compared to 13vPnC. Nevertheless, the numbers are generally low, and no concerns are raised in this regard. Most of the reported AEs were seizure-like events. According to the Applicant, participants with seizures/seizure-associated conditions were often withdrawn due to questions of continued eligibility, therewith underestimating the withdrawal due to AEs. The Applicant provided more detailed listing of seizure(-like) events and discontinuations related to such events and related conditions. Since the number of discontinuations of subjects with respective conditions

are similar between arms and the provided reasoning for discontinuation seems acceptable, the risk of underestimation of a general risk of seizure (-like) events is considered low.

Reporting of Adverse events

Immediate reaction occurring in the first 30 minutes, local reactions and systemic events occurring in the first seven days are presented separately, which is considered appropriate.

Overall, AEs were reported until one month after the last dose. However, reporting of SAEs and newly diagnosed chronic medical condition differed between studies. While in study B7471011 subjects were followed up 6 months after the last vaccination, the follow up in the 3-dose regimen study B7471012 was only 1 month. Since this is the only study evaluating the 3-dose regimen, the shorter follow up required justification. Although it was agreed in a Scientific Advice procedure, it was also stated that this would only be acceptable if the safety data from study B7471011 was reassuring. Upon request the Applicant provided an overview of AEs that were reported after 1 month after the last dose in the 4-dose regimen studies. No safety concerns were identified, consequently the shorter follow up time is acceptable.

Laboratory findings

Clinical laboratory evaluations were not performed systematically in any of the trials, which is acceptable. Fever was reported separately under systemic events.

Results

Immediate adverse events

Overall, immediate adverse events occurred infrequent (less than 1% of participants) with no apparent difference between doses. A slight difference between studies has been observed. The percentage of subjects with immediate events is slightly higher in the study evaluating the 3-dose regimen (~ 0.7%) compared to the pooled population (~0.2%). This slight difference could however also be due to the different group sizes. No concerns are raised in this respect.

In general, the percentage of participants with immediate AEs was comparable between 20vPnC and 13vPnC in all studies and the pooled analysis set.

The most common immediate adverse events were administration site conditions, e.g., injection site swelling, erythema pain and hypersensitivity.

Local reactions and systemic events occurring within 7 days after vaccination

The Applicant presented an analysis of local reactions and systemic events that occurred within the first 7 days after each vaccination including their severity. These AEs include redness, swelling and pain at the injection site as local reactions and fever, decreased appetite, drowsiness and irritability as systemic events.

Local reactions were observed in 15-45% of subjects (for details please refer to the effects table). Fever was reported in 8-24% of subjects. The other systemic events were more frequent: Irritability (~60-70%), Drowsiness (~40-66%) and decreased appetite (~20-40%).

In general, the reported events are mainly mild to moderate and resolved within 1-3 days.

The frequencies and severities are comparable between subjects that received 20vPnC and 13vPnC. Further, frequencies are rather constant for each dose throughout the regimen. Some differences were, however, noted between dosing regimen, especially regarding the toddler dose.

While the frequencies are constant for the 4-dose regimen, the frequencies reported for the toddler dose with the 3-dose regimen are higher compared to the infant doses. Overall, higher frequencies (difference 8-14%) with the 3-dose regimen were observed compared to the 4-dose regimen for all categories for the toddler dose. While for the other doses slightly higher frequencies were observed for some categories (e.g. redness and swelling events), the differences are not as pronounced as for the toddler dose.

The same pattern was also observed in the 13vPnC group and no concerns are raised regarding the reported events in general. Nevertheless, the differences between regimen regarding the toddler dose required further discussion. While some differences might be attributed to differences in group sizes (study B7471012 vs pooled data), the obvious trend requires further discussion. The Applicant claims that the observed differences between studies might be due to several factors introducing variability including concomitant vaccination and region/country specific perception of the reported AEs. Further, the Applicant claims that the observed difference regarding the toddler dose might be due to the concomitant vaccination with Infanrix hexa (DTaP combination vaccine), with the toddler dose of 20vPnC or 13vPnC in this study. While the later argument can be followed, the assumed differences in study population would have potentially also affected one of the other 3+1 regimen studies. Given the presented data and the Applicants arguments, it cannot be excluded that a slight difference exists between both vaccination regimen. The Applicant further argued that in the respective studies similar rates have been observed between 20vPnC and 13vPnC. While it is reassuring that this is not a 20vPnC specific effect, the observed difference between regimen is still maintained as uncertainty for this procedure.

Local reactions and systemic events were also evaluated in older children (>2 years). No comparator vaccine was applied in this study, therefore no comparisons to other vaccines can be made.

The reported rates for redness and swelling are comparable to the infant studies. Pain at the injection site was however reported by a much higher percentage compared to the infant studies (52-80% vs 22-42%). This may be explained by the age of the subjects as children can more directly communicate pain at the injections site than infants. Severity, onset of events and severity is comparable to the infant studies.

For children (2-18 years) evaluated systemic events included: fever, headache, fatigue and muscle or joint pain. The most frequently reported events are muscle pain (26.5%–48.3%) and fatigue (27.8%–37.2%), followed by headache (5.6%–29.3%) and joint pain (3.7%–8.3%) Fever occurred mainly in younger children (3.3%) and only one report in the older cohorts. While the reported rates for fatigue and joint pain seem to rather constant with age. The rates for headache and muscle pain increase with age.

Other Adverse events

The most common AEs are Infections and infestations (Conjunctivitis, Nasopharyngitis, Upper respiratory tract infection, Otitis media), pyrexia, Skin and subcutaneous tissue disorders (Dermatitis atopic, Eczema) and Gastroesophageal reflux disease. This is in line with common conditions and diseases in the studied age group. Overall, the reported AEs are similar between groups that received 20vPnc or 13vPnC. No concerns are raised based on the currently presented data, however some additional analyses were requested.

In the presented reports the analysis of AEs is split between primary vaccination series and toddler dose. While this presentation is in principle appreciated to assess potential differences between primary series and toddler dose, but the chosen presentation does not allow for a valid comparison between doses as all data from all 2 or 3 infant doses are combined. This does not allow for a quantitative comparison between infant doses and toddler dose. However, no qualitative differences were observed, and no concerns are raised regarding potential differences of AEs between infant and toddler doses.

The Applicant further presented so called Tier 2 AEs, which are defined as AEs with a pooled event rate of ≥1% in at least 1 (pooled) vaccine group, together with the estimated difference between vaccination groups (20vPnC and 13vPnC). Although this analysis is appreciated, the analyses are again performed for the infant series and the toddler dose data separately. No analysis for the pooled dataset for any is presented.

For the general representation of AEs and a suitable calculation of incidences regarding the vaccine a pooled analysis of all subjects in the multiple dose studies for all doses/the whole study duration was requested together with an updated representation of tier 2 events, related and severe events, which was provided by the Applicant as requested. The provided data are overall in line with the previously presented data and no new concerns arose.

Study B7471014 evaluated a single dose in children starting from 15 months of age up to <18 years of age. The safety data is presented in four age groups (≥15 to <24 Months; ≥2 to <5 Years; ≥5 to <10 Years; ≥10 to <18 Years). Overall reported AEs seem to decrease with age. While in the youngest age group 24% of subjects report AEs, only 4.4-7.9% report AEs in the older three subgroups. In general, the reported AEs are in line with conditions and diseases expected for these age groups. No concerns are raised.

It is noted that in the SmPC AEs are listed by age group, which is in principle appreciated but the presented age groups are: “6 weeks to less than 5 year of age” and “5 to less than 18 years of age”. No analysis for these age groups had been initially provided. The Applicant specified that for the age group “6 weeks to <5 years of age” data from B7471012 trial, the combined 4-dose trials, participants 15 to <24 months of age and 2 to <5 years of age from the B7471014 trial were examined and the highest frequency category was chosen to be presented in the SmPC. For the “5 to <18 years of age“ group data from study B74741014 for subjects 5 to <10 years of age and 10 to <18 years of age were considered. Further the rates for each frequency category in the SmPC have been presented. This approach is acceptable.

Related Adverse events

Vaccine-related AEs, that were not reported as immediate events or events occurring in 7 days after each dose were reported in less than 1% of subjects in both vaccine arms and for all doses. The most common related AEs were injection site related events and diarrhoea. The results are generally similar for both vaccines.

Related events have been appropriately included in the SmPC.

Severe Adverse Events

Severe adverse events were generally observed in less than 1% of subjects and most reported preferred terms for severe events occurred only in one subject. Most severe events were Infections and infestations.

Serious adverse event/deaths/other significant events

No deaths were reported during the paediatric development programme.

SAE occurred in less 5% of all subjects in the infant trials. The results between 20vPnC and 13vPnC are comparable. No trends between doses, age groups have been observed. In study B7471012 evaluating the 3-dose regimen, a slightly higher percentage of subjects reported SAEs (5.8%) but this was also comparable to the 13vPnC group in the study (6.6%). No concerns are raised.

The most common SAEs are related to infections (Bronchiolitis, Gastroenteritis, Urinary tract infection, Pneumonia, Respiratory syncytial virus bronchiolitis and Respiratory syncytial virus infection) and seizures (Febrile convulsion). The latter are further discussed below as other significant adverse event.

Only 1 SAE was considered related to study vaccine (inflammation requiring hospitalization). The Applicant detailed other events that were further investigated and considered not related. The presented respective reasoning can be followed for the presented cases. No concerns arose from the separately provided narratives.

In total 5 subjects withdraw due to SAEs in the 20vPnC vaccination groups (1 for 13vPnC). The Applicant reported that some instances of seizure-like events rendered the subject no longer eligible for the trial and they were excluded. The respective reason for withdrawal in consequently not listed as “due to AE”. The Applicant provided more detailed listing of seizure(-like) events and discontinuations related to such events and related conditions (for details please refer to the assessment of the responses). Since the number of discontinuations of subjects with respective conditions are similar between arms and the provided reasoning for discontinuation seems acceptable, the risk of underestimation of a general risk of seizure (-like) events is considered low.

Seizures were evaluated as other significant event included several seizure-like and related events. Overall, less than 0.5% of participants reported such events in all studies. This is comparable over all studies and between groups that received 20vPnC or 13vPnC. Such events are appropriately reflected in the SmPC.

Special populations

Only one study included pre-term infants. The results show no apparent differences in the safety profile compared to full term infants. However, only 110 subjects (76 20vPnC, 34 13vPnC) were included as pre-term infants. Whether these subjects could be regarded as representative for pre-term infant in general required further clarification, since the included infants were born with ⩾34 to <37 weeks gestational age and could therefore only be classified as late preterm infants. The Applicant reported the results of a previously performed study with 13vPnC, that has also been submitted for a Type II variation for Prevenar 13. The study showed that in general the safety profile in infants with lower gestational age was similar to later pre-term infants. The study concluded that after each dose of the infant series, infants born at an earlier GA (i.e., GA <29 weeks) generally experienced more tenderness, redness, and swelling at the injection site than did infants born at a later GA. But overall, the safety profile was comparable between gestational age subgroups. Based on the presented results it can be assumed that the data presented for preterm infants with 20vPnC are overall applicable to infants with lower GA. The Applicant will further discuss the use of 20vPnC in preterm infants in upcoming PSUSAs.

No data is available for immunocompromised paediatric patients or paediatric patients with other risk factors.

No differences have been observed in subgroup analyses of local reactions, systemic events and other AEs based on sex, race and geographic region.

Safety related to drug-drug interactions and other interactions

In the infant trials, all subjects received routine infant vaccinations concomitantly with 20vPnC and 13vPnC for the following: diphtheria, tetanus, acellular pertussis, Hib, inactivated poliovirus vaccine, hepatitis B, MMR, and varicella. Since no control group was included, no conclusions can be drawn regarding potential differences between concomitant and separate vaccinations. Nevertheless, the

observed safety profile between 20vPnC and 13vPnC groups are comparable and no safety signal was identified for any of these vaccinations.

Other vaccines have been administered in subgroups including rotavirus vaccine, influenza vaccine and hepatitis A vaccine. The Applicant initially proposed mention of rotavirus and influenza vaccines in the SmPC. While the safety profile of 20vPnC in the respective studies does not raise safety concerns in general, a statement to that effect is currently not supported by the provided data due to lack of respective analyses. Only in study B7471011 (4-dose regimen) separate analyses for local reactions, systemic events and AEs were presented for the co-administration with influenza vaccine. These analyses showed overall comparable safety reports. Only about 10% more participants reported fever in the concomitant vaccination group, which was also reported in the group receiving 13vPnC concomitantly with influenza vaccine. No information was provided in the other studies or for participants that received rotavirus or hepatitis A vaccines. The applicant was asked to provide safety analyses for the other studies, with regard to influenza, rotavirus and hepatitis A vaccines. It was clarified that in study B7471011, the rate of concomitant rotavirus administration with 20vPnC or Prevenar 13 were very high due to the rotavirus vaccination scheme recommended in the US (87.3% for Dose 1, 84.9% for Dose 2, and 65.8% for Dose 3 for 20vPnC). Consequently, no meaningful comparison between subjects with or without concomitant rotavirus vaccination can be drawn. But since most of the subjects received concomitant vaccinations with both vaccines, the safety profile established in study B7471011 can be regarded as representative for the concomitant vaccination and no major safety concerns were raised. Regarding study B7471012, since this was performed in several countries with different childhood vaccination recommendation, a comparison between concomitant and separate rotavirus vaccination was possible (47% received a concomitant rotavirus vaccine) and the data was presented. With respect to study B7471013, it was argued that no new information would result from such analyses. Overall, presented data for studies B7471011 and B7471012 and the overall safety data presented for study B7471013 do not indicate safety concerns.

Since reduced titres have been observed in the adult population when 20vPnC was administered concomitantly with influenza vaccine, co-administration might also influence the protective potential of 20vPnC in the paediatric population. The Applicant was therefore requested to present the immunogenicity data for the subgroups presented for the influenza vaccination in study B7471011. This was however not further pursued and hence, an SmPC statement for flu concomitant administration in the paediatric population is omitted.

As regard to immunogenicity data made for the subgroups formed for the safety analysis regarding the rotavirus vaccination for study B7471012, data for the 2+1 schedule after the second dose shows reduced titres for both Prevenar 20 and Prevenar 13. Concomitant vaccination is seen critical with a 2+1 schedule and in order to ensure protection, a third infant dose would be recommended.

In older paediatric subjects, non-study vaccines were concomitantly administered in small subgroups (Pentacel (DTaP, Hib, and inactivated poliovirus vaccine), hepatitis A vaccines; influenza vaccines, DTaP, and PedvaxHIB). The concomitantly vaccinated subgroups are however too small to draw valid conclusions.

Rates of antipyretics/pain medication given to treat symptoms in study participants during the 7 days after study vaccination were generally similar between 20vPnC and 13vPnC control groups. Prophylactic antipyretics/pain medication was allowed but should be discouraged.

2.5.2. Conclusions on clinical safety

20vPnC is overall well tolerated and the safety profile of 20vPnC is comparable to 13vPnC. Reactogenicity and other adverse events are mostly characterized as mild to moderate and the AE profile does not suggest any serious safety concerns.

However, higher rates of local and systemic events especially for the toddler dose have been observed for the 3-dose (2+1) regimen. Although this has also been observed with 13vPnC, this remains as uncertainty for the 2+1 regimen.

In the presented dossier, only limited safety datasets were presented for: Pre-term infants and children > 2 years of age. While no major concerns are raised regarding these populations based on the presented safety data, uncertainties regarding these populations remain due to the limited available data. However, the Applicant provided supportive data from 13vPnC on the claim that the provided pre-term data is also representative for infants with lower gestational age, mitigating some of the raised concerns. In addition, the Applicant commits to discuss the use of 20vPnC in preterm infants in upcoming PSUSAs.

As discussed in the sections regarding the assessment of immunogenicity, overall lower immune response to 20vPnC compared to 13vPnC has been observed for the 13 shared serotypes. The clinical relevance of this reduction is currently not known but might affect the duration of a protection effect. Further, it is not known whether the obtained titres for the 7 additional serotypes indeed elicit a protective effect. Consequently, a potential lack of efficacy can currently not be excluded, and the Applicant is requested to perform post marketing surveillance and potential studies to confirm effectiveness of the vaccine. Please also refer to the discussion in the immunogenicity/efficacy section for further detail.

Regarding co-administration, the following statement in the SmPC for Prevenar 20 when used as a four (3+1) dose schedule can be supported:

“In infants and children, 6 weeks to less than 5 years of age, Prevenar 20 can be administered concomitantly with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular pertussis, hepatitis B, *Haemophilus influenzae* type b, inactivated poliomyelitis, measles, mumps, rubella, and varicella vaccines. In clinical trials, rotavirus vaccines were permitted to be administered concomitantly with Prevenar 20 and no safety concerns were observed.”

Recommendation [REC]

The Applicant will discuss the use of 20vPnC in preterm infants in upcoming PSUSAs.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 3.0 with this application (at start of procedure). The variation proposes to extend the approved indication of 20vPnC to include infants, children, and adolescents from 6 weeks to less than 18 years of age for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae.*

The *main proposed RMP changes* were the following:

- Product overview: Updated to include proposed paediatric indication and dosage.
- Module SI. Epidemiology of the Indication(s) and Target Populations.
- Module SIII. Clinical Trial Exposure: Updated to include exposure tables from the paediatric studies.
- Module SIV. Populations Not Studied in Clinical Trials: Updated to add main exclusion criteria applied in the paediatric studies
- Module SV. Post-Authorisation Experience: Updated to include post-authorisation exposure as of the data-lock point of the 1st EU PSUR (07 June 2022).

There were *no major changes proposed in the identified and potential risks, in the pharmacovigilance plan or risk minimisation measures*.

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

The Applicant was requested to provide a consolidated version of the RMP, considering vs 2.2 as baseline. In addition, during the further course of the procedure, variation II/16, with associated RMP version 4.0 was authorised and further taken into account, as basis for consolidation.

The PRAC considered that the risk management plan version 4.1 (consolidated version) is acceptable.

Safety concern

The table below lists the safety concerns for 20vPnC at start of procedure. The item listed as missing information "*Concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine or COVID-19 mRNA vaccine* was removed post conclusion of the coadministration studies B7471004 and B7471026.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine or COVID-19 mRNA vaccine.[a]

a. In adults ⩾65 years of age.

Module SVIII: Summary of the Safety Concerns

There are no important identified/potential risks or missing information for 20vPnC.The Applicant is requested to discuss the use of 20vPnC in preterm infants within PSUSA.

Pharmacovigilance plan

There are no ongoing or planned pharmacovigilance activities for 20vPnC.

Plans for post-authorisation efficacy studies

Post-authorisation efficacy studies (PAES) which are conditions or specific obligations of the MAA in adults are presented in table below.

Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations[a]

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Study B7471015: A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20-valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically Confirmed Community-Acquired Pneumonia in Adults ≥65 Years of Age. Ongoing	Evaluate the long-term effectiveness of 20vPnC for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*	Vaccine efficacy (VE) against vaccine-type (VT) radiologically confirmed community acquired pneumonia (CAP) in adults ≥65 years of age	Submission of final study results by	31/12/2027
European specific analysis results of Study B7471015 (A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20 valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically Confirmed Community-Acquired Pneumonia in Adults ⩾65 Years of Age Planned	Evaluate the long-term effectiveness of 20vPnC for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*	VE against radiologically confirmed VT CAP in adults ≥65 years of age	Feasibility assessment by. Submission of statistical analysis plan (including the Europe specific analysisby Submission of final study results by	31/03/2024 31/03/2024 31/12/2030
Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Europe. Planned	Evaluate the long-term effectiveness of 20vPnC against vaccine-type invasive pneumococcal disease in adults in the EU.	VE against VT IPD and duration of protection	Feasibility assessment currently ongoing. Submission of study protocol by Submission of final study results by	31/03/2024 31/12/2030
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				

a. Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS).

Risk minimisation measures

Routine risk minimisation measures

Routine risk minimization actions include the use of the SmPC and the package leaflet (PL) to support safe use of the vaccine.

Additional risk minimisation measures

No additional risk minimisation measures are proposed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Prevenar 20 (pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for an extension of indication for Prevenar 20 (20vPnC). The indication applied for is “active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age.”

3.1.2. Available therapies and unmet medical need

Currently, three vaccines are licensed for this indication in children in the EU: Prevenar 13 (13vPnC), Vaxneuvance (15vPnC) and Synflorix (10vPnC, only for children up to 5 years of age). Prevenar 20 (20vPnC) contains 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in the licensed Prevenar13, plus 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F and 33F), not included in Prevenar13 or Synflorix, 2 of which are included in Vaxneuvance (22F and 33F).

In 2019, the 7 additional serotypes covered by PCV20 caused 35% and 33% of IPD among children aged <1 and 1-4 years in Europe, respectively, or a total of 424 IPD cases, based on surveillance data from 30 countries reporting to the ECDC. Five of these serotypes (serotypes 8, 10A, 11A, 12F and 15B) are not covered by any licensed PCV and caused 25% and 24% of remaining IPD in children age <1 and 1-4 years in Europe, respectively.

According to the ECDC, the most confirmed and reported cases of IPD in 2021 (the most recent data) was due to serotypes 3 (16.9%), 8 (14.4%) and 19A (10.6%). Serotypes 3 and 19A are contained in Prevenar 13 vaccine, while the serotype 8 is not.

According to the MAH, 20vPnC has been developed to replace 13vPnC. The Apexxnar trade name is replaced by Prevenar 20.

3.1.3. Main clinical studies

No efficacy studies have been performed with 20vPnC; efficacy is inferred based on immunogenicity. Studies B7471012 and B7471011 are considered pivotal as they provide the main evidence for immunogenicity and safety in the target population. Both pivotal trials were phase 3, randomised, active-controlled, double-blind, multicentre studies, to evaluate the safety, tolerability, and immunogenicity of 20vPnC in healthy infants when administered as a series of 2 infant doses and 1 toddler dose (B7471012) or as a series of 3 infant doses and 1 toddler dose (B7471011). Both pivotal trials were designed to provide non-inferiority (NI) comparisons of the 20vPnC immune responses with those of 13vPnC, for which effectiveness has been demonstrated.

In the 3-dose schedule vaccines were administered at roughly 2-3, 4-5, and 11-12 months of age, while in the 4-dose schedule vaccines were administered at roughly 2, 4, 6, and 12 to 15 months of age. Immunogenicity was evaluated 1 month after the last infant dose and 1 month after the toddler dose. In the main studies, participants also received routine childhood vaccinations. The chosen population is considered sensitive for the intended immuno-bridging exercise.

3.2. Favourable effects

20vPnC was immunogenic in all clinical studies in all subgroups.

B7471012 (3-dose series):

After the last infant dose (Dose 2), NI criterion for response rate was met for 4/13 shared serotypes and 5/7 additional serotypes; and NI criterion for IgG GMR was met for 9/13 shared serotypes and for all 7 additional serotypes.

After the toddler dose (Dose 3), difference between treatments decreased; the NI criterion for IgG GMR was met for 12/13 shared serotypes and for all 7 additional serotypes. After the toddler dose, for the majority of shared serotypes, the IgG GMCs were well above the pre-defined cut-offs. Pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in the 13vPnC group, demonstrating that Prevenar 20 elicits immune response to 7 additional serotypes. After the toddler dose NI was not formally tested for the response rate; however, the differences between vaccines were small for majority of shared serotypes.

B7471011 (4-dose series):

After the last infant dose (Dose 3), NI criterion for response rate was met for 8/13 shared serotypes and for 6/7 additional serotypes; and NI criterion for IgG GMR was met for all shared and all additional serotypes (the latter was a key secondary endpoint).

After the toddler dose (Dose 4), difference between treatments decreased; the NI criterion for IgG GMR was met for all shared and all additional serotypes. For most shared serotypes in both groups, the IgG GMCs were well above the pre-defined cut-offs. Same as in the 3-dose series, pneumococcal IgG GMCs for all 7 additional serotypes were much higher than the IgG GMCs from the corresponding serotypes in

the 13vPnC group. After toddler dose NI was not formally tested for the response rate; however, the differences between vaccines were small for the majority of shared serotypes.

Furthermore, 20vPnC was able to elicit functional antibodies as measured by the OPA titres to all 20 serotypes contained in the vaccine. 20vPnC was also able to induce immune memory.

The immune response to the concomitantly administered vaccines was comparable between 20vPnC and 13vPnC group, indicating that 20vPnC can be administered concomitantly with vaccines against diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib, commonly used in this age group, without having a negative impact on the protection against these diseases.

3.3. Uncertainties and limitations about favourable effects

Assays. Two different assays (13-plex dLIA and 7-plex dLIA) were used to obtain antibody titres for the 13 serotypes also contained in 13vPnC and the 7 additional serotypes, respectively. This design does not allow quantitative comparisons between the two sets of serotypes since the influence of specific serotype combinations on the dLIA measurement of serotype-specific IgG concentrations is unclear. Consequently, the current approach limits the interpretation of titres for the 7 additional serotypes in comparison to that of the 13 shared serotypes.

No efficacy/effectiveness data. No efficacy or effectiveness data is available for 20vPnC in infants and children. The application to extend the indication to infants and children is based on the inference of 20vPnC efficacy for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of non-inferior immune responses to 13vPnC, for which effectiveness has been demonstrated.

Failed pivotal trials. Both pivotal trials failed to meet their primary objectives as non-inferiority was not met for each of the 20 serotypes for all co-primary endpoints. In B7471012 after the last infant dose, the NI criterion for the response rate was missed for 9/13 shared and 2/7 additional serotypes; and the NI criterion for the IgG GMR was missed for 4/13 shared serotypes. After the toddler dose in B7471012, the NI criterion for the response rate was missed for 1/13 shared serotypes (serotype 6B). In total, 15/60 statistical tests failed in B7471012. In B7471011 after the last infant dose, the NI criterion was missed for 5/13 shared and 1/7 additional serotypes for the response rate. In total, 6/40 statistical tests failed in B7471011.

Unknown clinical relevance of NI margins (NIMs). The immunobridging approach based on non-inferiority is generally acceptable. However, it should be noted that, while the NI margin of -10% for the difference (20vPnC minus 13vPnC) in response rate (percentage of participants achieving the predefined IgG antibody concentration) and NIM of 0.5 for the pneumococcal IgG GMR (20vPnC/13vPnC) have been previously used in clinical studies of approved pneumococcal vaccines, they have not been justified from a clinical perspective. Therefore, meeting or not meeting these NI criteria is of unknown clinical relevance.

No correlate of protection. There is no established correlate of protection for the additional 7 serotypes. The clinical relevance of the obtained titres is currently unknown.

Further there is no correlate of protection known for pneumonia or AOM for any of the 20 serotypes. The indications of pneumonia and AOM were granted to 13vPnC based on non-inferiority of immune response to 7vPnC. 13vPnC has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed. However, no exact vaccine efficacy was determined, nor the immune response required to achieve protection. Therefore, the strategy of non-inferiority testing for 20vPnC to 13vPnC, especially when lower immune response is observed with 20vPnC compared to 13vPnC, introduces the possibility that 20vPnC might not be effective against pneumonia and AOM. In addition,

whether the correlate of protection also applies for the 7 new serotypes included in 20vPnC, is currently unknown.

NI comparison for additional serotypes. The approach for NI comparisons of the 7 additional serotypes against the lowest observed response among the vaccine serotypes in the 13vPnC group (excluding serotype 3) is considered rather uninformative and might even be potentially misleading. From the methodological perspective, this way of choosing the comparator threshold disregards the fact that IgG concentrations (/increases) for different serotypes follow different distributions (i.e., can be expected to differ in mean and variability). Consequently, the estimated values for the 20vPnC/13vPnC-ratios for GMC and percentage above predefined IgG-levels can get unreasonably high. Furthermore, given the tendency that lower mean response is associated with smaller variability in the raw concentration data, the width of the 95% CIs computed for the NI evaluation (for ratios) could become arbitrarily small. Consequently, NI testing setup for the 7 additional serotypes is not considered sufficiently informative, neither for the evaluation of IgG-response, nor for the potential implication for disease protection. Location and widths of the CIs as displayed in the corresponding figures of the CSR have a strong potential to mislead the interpretation of the actual response data for the 7 additional serotypes, with a clear systematic tendency for overestimation of the 20vPnC benefit.

Reduced immunogenicity response. Generally, the immune response to 20vPnC was numerically lower compared to 13vPnC as assessed by IgG GMC for all shared serotypes both after last infant dose and after toddler dose and by response rates for a majority of shared serotypes after last infant dose. Regarding IgG GMC, the ratio fell below 1 for all shared serotypes in both pivotal trials after last infant dose and after toddler dose.

Persistence of assumed protective effect. Since the last available immunogenicity measurements were 1 moth post toddler dose, no long-term data are available. The data indicate that IgG concentrations decline at a similar rate after vaccination with 20vPnC and 13vPnC and consequently also the response rates. Given that the initial concentrations were lower with 20vPnC, it could be expected that the assumed protective effect of 20vPnC might wane earlier compared to 13vPnC.

Immune response in pre-term infants. No immunogenicity data is available for pre-terms infants.

No data is available for infants and children at higher risk of pneumococcal disease. No studies have been conducted with 20vPnC in children who have underlying conditions predisposing them to invasive pneumococcal disease (such as sickle cell disease, HSCT or HIV infection).

A single dose of 20vPnC in infants fully immunised with lower-valency PCV. 20vPnC elicited immediate serotype-specific immune response to all 7 additional serotypes, however it is unclear whether a single (priming) dose of 20vPnC is sufficient to achieve protection against the 7 extra serotypes and to induce robust immunological memory.

Co-administration with other vaccines. No immunogenicity data has been provided for subjects that received concomitant vaccination of 20vPnC with influenza and hepatitis A vaccines. Data was presented for the pneumococcal vaccines with and without the concomitant vaccination with rotavirus vaccine. Reduced titres have been observed with the concomitant vaccination for 20vPnC and 13vPnc.

3.4. Unfavourable effects

Immediate adverse events occurring within 30 minutes after vaccination

Immediate adverse events occurred in less than 1% of participants with no apparent difference between doses: In the study evaluating the 3-dose regimen: ~ 0.7%; in the pooled population for the 4-dose

regimen ~0.2%. The results are comparable between 20vPnC and 13vPnC in all studies and the pooled analysis set. The most common immediate adverse events were administration site conditions, e.g., injection site swelling, erythema pain and hypersensitivity.

Local reactions and systemic events occurring within 7 days after vaccination

These AEs include redness, swelling and pain at the injection site as local reactions and fever, decreased appetite, drowsiness and irritability as systemic events.

Local reactions were observed in 15-45% of subjects (for details please refer to the effects table). Fever was reported in 8-24% of subjects. The other systemic events were more frequent: Irritability (~60-70%), Drowsiness (~40-66%) and decreased appetite (~20-40%).

For the toddler dose, higher frequencies (difference 8-14%) with the 3-dose regimen were observed compared to the 4-dose regimen for all presented categories. Otherwise, frequencies are comparable between doses throughout the regimen.

In general, the reported events are mild to moderate and resolved within 1-3 days. Overall, the frequencies and severities are comparable between subjects that received 20vPnC and 13vPnC.

In older children (2-18 years), the reported rates for redness and swelling are comparable to the infant studies. Pain at the injection site was reported by a higher percentage compared to the infant studies (52-80% vs 22-42%). Severity, onset of events and severity is comparable to the infant studies.

For children (2-18 years) evaluated systemic events included: fever, headache, fatigue and muscle or joint pain. The most frequently reported events are muscle pain (26.5%–48.3%) and fatigue (27.8%–37.2%), followed by headache (5.6%–29.3%) and joint pain (3.7%–8.3%). Fever occurred mainly in younger children (3.3%) and only 1 report in the older cohorts. While the reported rates for fatigue and joint pain are rather constant with age. The rates for headache and muscle pain increase with age.

Other Adverse events

The most common AEs are Infections and infestations (Conjunctivitis, Nasopharyngitis, Upper respiratory tract infection, Otitis media), pyrexia, skin and subcutaneous tissue disorders (Dermatitis atopic, Eczema) and gastro-oesophageal reflux disease. Overall, the reported AEs are similar between groups that received 20vPnc or 13vPnC.

Other Adverse events were reported by 15%-32% of participants in the different studies. Similar reporting rates are presented for subjects receiving 13vPnC.

Related other Adverse Events

Vaccine-related AEs that were not reported as immediate events or as local reactions and systemic events occurring within 7 days after vaccination were reported in less than 1% of subjects in both vaccine arms and for all doses. The most common related AEs were injection site related events and diarrhoea. The results are generally similar for both vaccines.

Severe other Adverse Events

Less than 1% of subjects reported severe adverse events. Most reported AEs occurred only in one subject. Most severe events were Infections and infestations.

Serious adverse event/deaths/other significant events

No deaths were reported during the paediatric development programme.

SAE occurred in less 5% of all subjects in the infant trials. The results between 20vPnC and 13vPnC are comparable. No trends between doses, age groups have been observed.

The most common SAEs are related to infections (Bronchiolitis, Gastroenteritis, Urinary tract infection, Pneumonia, Respiratory syncytial virus bronchiolitis and Respiratory syncytial virus infection) and seizures (Febrile convulsion).

One SAE was considered related to study vaccine: Inflammation requiring hospitalization occurring 7 days after dose 1. The event resolved after the participant received antibiotics.

In total 5 subjects withdraw due to SAEs in the 20vPnC vaccination groups (1 for 13vPnC). These events mainly include seizure-like events.

Seizures were evaluated as other significant event included several seizure-like and related events. Overall, less than 0.5% of participants reported such events in all studies. This is comparable over all studies and between groups that received 20vPnC or 13vPnC.

Special populations

One study included 110 late preterm infants (born with ≥34 to <37 weeks gestational age). The results are comparable to the safety profile of full-term infants.

Discontinuations

Overall, the number subjects that withdrew due to adverse events or physician decision is low (all studies: adverse events: 20vPnC: 7, 13vPnC 4; physician decision: 20vPnC: 2, 13vPnC 4).

Safety related to drug-drug interactions and other interactions

In the infant trials, all subjects received routine infant vaccinations concomitantly with 20vPnC and 13vPnV: diphtheria, tetanus, acellular pertussis, Hib, inactivated poliovirus vaccine, hepatitis B MMR, and varicella. The observed safety profile between 20vPnC and 13vPnC groups are comparable and no safety signal was identified for any of these vaccinations.

Other vaccines have been administered in subgroups including rotavirus vaccine, influenza vaccine and hepatitis A vaccine. In study B7471011 (4-dose regimen) separate safety analyses were presented for the co-administration with influenza vaccine. About 10% more participants reported fever in the group receiving influenza vaccine concomitantly with either 20vPnC or 13vPnC. All other parameters indicate overall comparable safety profiles.

3.5. Uncertainties and limitations about unfavourable effects

Children 2-18 years

Children (2-18 years) were only evaluated in one single dose study. Overall, the dataset is limited to 622 subjects and no comparator vaccine was applied.

Special populations

Only one study included preterm infants. The results show no apparent differences in the safety profile compared to full term infants. However, only 110 preterm infants (20vPnC: 76, 13vPnC: 34) were included. Whether these subjects could be regarded as representative for pre-term infant in general required further clarification, since the included infants were born with ≥34 to <37 weeks gestational age and could therefore only be classified as late preterm infants. Supportive data from 13vPnC was provided indicating that the obtained results in this population are also representative for pre-term infants with lower GA. However, no data for 20vPnC is available for preterm infants with a gestational age of <34 weeks.

No data is available for immunocompromised paediatric patients or paediatric patients with other risk factors.

Safety related to drug-drug interactions and other interactions

In the infant trials, no control group was included that did not receive the indicated paediatric vaccinations. Therefore, no conclusions can be drawn regarding potential differences between concomitant and separate vaccinations.

Rotavirus vaccine and influenza vaccine have been administered in subgroups. For study B7471011 separate safety analyses were presented for the co-administration with influenza vaccine and for study B7471012 separate safety analyses for rotavirus vaccine.

In older paediatric subjects, non-study vaccines were concomitantly administered in small subgroups (Pentacel (DTaP, Hib, and inactivated poliovirus vaccine), hepatitis A vaccines; influenza vaccines, DTaP, and PedvaxHIB). The concomitantly vaccinated subgroups are however too small to draw valid conclusions.

3.6. Effects Table

Table 71. Effects Table for Prevenar 20

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Percentage of participants with pre-specified pneumococcal IgG Conc. at 1 month after	13 shared serotypes	%	NI criterion met for 4/13 shared serotypes NI criterion met for 8/13 shared serotypes			B7471012 B7471011
	7 additional serotypes	%	NI criterion met for 5/7 additional serotypes NI criterion met for 6/7 additional serotypes			B7471012 B7471011

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
last infant dose						
IgG GMC after last infant dose	13 shared serotypes		NI criterion met for 9/13 shared serotypes NI criterion met for all shared serotypes			B7471012 B7471011
	7 additional serotypes		NI criterion met for all additional serotypes NI criterion met for all additional serotypes			B7471012 B7471011
Percentage of participants with pre-specified pneumococcal IgG Conc. at 1 month after toddler dose	13 shared serotypes	%	NI not formally tested. Only 1 of 13 shared serotypes (serotype 3) had a lower bound <-10% at this time point. The response rate ranged from 82.6% (serotype 3) to 99.6% (serotypes 7F, 14, 19A and 19F). NI not formally tested. Only 1 of 13 shared serotypes (serotype 3) had a lower bound <-10% at this time point. The response rate ranged from 73.6% (serotype 3) to 99.9% (serotype 7F).			B7471012 B7471011
	7 additional serotypes	%	NI not formally tested. The response rate ranged from 96.6% (serotype 12F) to 99.4% (serotype 15B). NI not formally tested. The response rate ranged from 95.2% (serotype 12F) to 99.7% (serotype 15B).			B7471012 B7471011
IgG GMC after toddler dose	13 shared serotypes		NI criterion met for 12/13 shared serotypes NI criterion met for all shared serotypes			B7471012 B7471011
	7 additional serotypes		NI criterion met for all additional serotypes NI criterion met for all additional serotypes			B7471012 B7471011
Notes	Noninferiority of 20vPnC to 13vPnC. For the 13 shared serotypes, NI comparisons were made to the corresponding serotypes in the 13vPnC group. For the 7 additional serotypes, NI comparisons were made to the lowest among the 13 serotypes (except for serotype 3) in the 13vPnC group. For the percentage of participants with a predefined IgG concentration for a serotype, non-inferiority was declared for a serotype if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages is greater than –10% (10% NI margin). For the IgG GMC, non-inferiority was declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC group to the 13vPnC group is greater than 0.5 (2-fold NI margin).					
Unfavourable Effects						
Immediate effects	Within 30min after vaccination	%	<1	<1	Most common: injection site pain, swelling, erythema	B7471012, pooled
Local reactions occurring within 7 days after vaccination						
	injection site pain	%	22.8–42.4 32.8–45.5	24.6–39.9 34.6–45.4	3-dose series 4-dose series	B7471012, pooled
	redness	%	25.3–36.9 22.6–24.5	27.5–33.8 23.2–25.7	3-dose series 4-dose series	B7471012, pooled
	swelling	%	21.4-29.8 15.1–	20.2–24.6 16.0–18.0	3-dose series 4-dose series	B7471012, pooled

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			17.6			
Systemic events occurring within 7 days after vaccination						
	Irritability	%	~71.0 58.5–70.6	68.4–72.5 59.4–71.5	3-dose series 4-dose series	B7471012, pooled
	Drowsiness	%	50.9–61.2 37.7–66.2	48.6–63.7 38.1–65.6	3-dose series 4-dose series	B7471012, pooled
	Decreased appetite	%	24.7–39.3 23.0–26.4	19.4-36.5 22.3–25.9	3-dose series 4-dose series	B7471012, pooled
	Fever	%	8.9 - 24.3 10.3- 6.5	8.5 - 23.7 8.5 -15.7	3-dose series 4-dose series	B7471012, pooled
Other AEs	from Dose 1 to 1 month after the last infant dose		13.8% 31.3%	14.4% 32.1%	3-dose series 4-dose series	B7471012, pooled

Notes: “pooled” refers to the pooled safety database including all studies evaluating a 4-dose series

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This application relies on establishing an immunological bridge to authorised vaccine with known protective efficacy against pneumococcal disease (13vPnC). No efficacy or effectiveness data has been submitted for 20vPnC. 20vPnC was immunogenic in all clinical studies, demonstrated by serotype-specific IgG and OPA antibodies to all 20 serotypes contained in the vaccine. 20vPnC was also able to induce immune memory.

Non-inferiority criteria were met for most shared serotypes after toddler dose in both pivotal studies B7471012 and B7471011, as measured by the percentage of participants with predefined IgG concentrations and IgG GMC. NI criteria for both parameters were also met for most of the shared serotypes after the last infant dose in the 4-dose regimen. In addition, no substantial differences between vaccines were seen for the response rate for the majority of shared serotypes after toddler dose in study B7471011. However, both pivotal trials formally failed to meet their primary objectives due to multiple failed NI tests. Missing the statistical NI criteria for individual serotypes for response rate and/or IgG GMC does not necessarily predict lack of vaccine efficacy and may not be completely unexpected due to the sheer number of NI comparisons made. From the MA assessment perspective, it is important to note that this uncertainty in prediction would also not rule out a clinically relevant lack of vaccine efficacy as a consequence of failed NI in IgG response. The key issue in this context remains the fact that – in absence of a reliable correlate of protection – the whole setup of the immunology NI evaluation relies on many pre-specifications and assumptions (e.g. IgG-concentration threshold for binary response

description, width of NI-margins, etc), such that actual NI conclusions (positive or negative) need to be *per se* considered rather uninformative as regards disease protective potential (vaccine efficacy).

Moreover, significant differences between vaccines were observed after the last infant dose in the 3-dose regimen (B7471012), demonstrated by multiple (15/40) failed NI tests for both primary parameters, response rate and IgG GMC. Differences between vaccines were also observed after last infant dose in 4-dose regimen, albeit to a lesser extent. Taking into consideration that the burden of IPD is highest in infants <1 year of age, the adequacy of the 3-dose regimen to achieve and maintain protection, especially in the window between the last infant and the toddler dose, raises major concerns. Additional arguments provided by the Applicant did not dissipate major concerns regarding the efficacy of the 2+1 regimen. These uncertainties are not restricted to one or two serotypes but pertain to all serotypes included in the vaccine. Similar uncertainties also apply to the 3+1 regimen, albeit to a lesser extent. Furthermore, consistently lower IgG GMC have been observed for all 13 shared serotypes in 20vPnC group compared to 13vPnC group. The implications of this reduction on the vaccine efficacy and protection against pneumococcal disease is unclear.

In addition to lower immune response to 13 shared serotypes and unknown clinical relevance thereof, several limitations regarding the 'benefit' of additional 7 serotypes should be mentioned. Firstly, the approach for NI comparisons of the 7 additional serotypes against the lowest observed response among the vaccine serotypes in the 13vPnC group (excluding serotype 3) is considered uninformative and might even be potentially misleading, with a clear systematic tendency for overestimation of the 20vPnC benefit. Secondly, two different assays (13-plex dLIA and 7-plex dLIA) were used to obtain antibody titres for the 13 serotypes also contained in 13vPnC and the 7 additional serotypes, respectively. This design does not allow quantitative comparisons between the two sets of serotypes since the influence of specific serotype combinations on the dLIA measurement of serotype-specific IgG concentrations is unclear. Consequently, the determination of NI for the 7 additional serotypes is rather uninformative. Finally, the cut-off value of ≥0.35 µg/mL was derived from 7vPnC data as a surrogate of protection, and the applicability of this level to 7 additional serotypes is less clear. Taken together, immune response of the 7 additional parameters cannot be reliably assessed using parameters of primary interest (response rate and IgG GMC). The assessment of secondary parameters such as IgG and OPA GMFRs clearly shows that 7 additional parameters induce serotype-specific immune response, however the clinical relevance thereof and in how far this translates into protection remains unclear.

Given the overall better immunogenicity results, the 4-dose regimen is more likely to provide protection against the pneumococcal disease. Nonetheless, the effectiveness thereof needs to be confirmed in the post-marketing, especially for the 7 additional serotypes, as the interpretation of data from pivotal studies regarding these serotypes was severely limited.

In addition, a surrogate of protection, IgG of 0.35 µg/mL, after 3 infant doses, has been established for invasive pneumococcal disease (IPD) in children, which can be used to infer protection against IPD. However, for pneumonia and acute otitis media (AOM), no correlate or surrogate of protection exists. 13vPnC has been shown to be effective, as a reduction in disease prevalence in vaccinated children has been observed. Importantly though, no exact vaccine efficacy estimate was determined, nor the immune response required to achieve protection. Therefore, the strategy of NI testing for 20vPnC to 13vPnC, especially when a lower immune response is observed for 20vPnC compared to 13vPnC, introduces the possibility that 20vPnC might not be effective against pneumonia and AOM. Moreover, it is currently unknown whether the threshold of 0.35 µg/mL can also be considered protective for the new serotypes included in this vaccine for any indication.

Finally, due to the overall lower IgG GMCs with 20vPnC, it can be expected that the (assumed) protective effect wanes earlier compared to 13vPnC.

Regarding the administration of a single dose of Prevenar 20 to infants and children fully immunised with Prevenar13, 20vPnC elicited immediate serotype-specific immune response to all 7 additional serotypes, however it is unclear whether a single (priming) dose of 20vPnC is sufficient to achieve protection against the 7 extra serotypes and to induce robust immunological memory. This is particularly important for children under the age of 5, as the burden of pneumococcal disease in this age group is substantial. Previous experience with Prevenar-13 provides support that a single dose can offer some level of protection against additional serotypes, which is considered important for children at higher risk of pneumococcal disease.

Overall, the safety profile of 20vPnC is comparable to 13vPnC. The identified differences between 3-dose and 4-dose regimen are manageable but should be considered together with the observed uncertainties regarding the 3dose regimen detailed above.

Additionally, the CHMP convened a SAG inviting the experts to provide their views on the immunogenicity results for the 2+1 regimen, the potential benefit of 7 additional serotypes, and the need for the 2+1 regimen for 20vPnC. The view of the SAG has been implemented in the assessment report (please refer to the section 2.4.2 for details) and has been taken into consideration for the final benefit/risk assessment on the 2+1 regimen.

3.7.2. Balance of benefits and risks

20vPnC was immunogenic in all clinical studies, demonstrated by serotype-specific IgG antibodies to all 20 serotypes contained in the vaccine. This is important as it suggest that it could potentially provide broader coverage over approved pneumococcal conjugated vaccines against serotypes most responsible for serious pneumococcal disease among children <5 years of age. However, due to many uncertainties, the actual ‘benefit’ of the 7 additional serotypes cannot reliably be assessed by the means of response rate and IgG GMC. Assessment of secondary parameters such as IgG and OPA GMFRs clearly shows that 7 additional parameters induce serotype-specific immune response, however the clinical relevance thereof remains unclear. Although efficacy has not been demonstrated and cannot be inferred for these additional serotypes through immunobridging, based on previous experience with the immune response to the other PCV serogroups the demonstration of IgG titres and functional immune responses are likely to translate into protective efficacy, but the exact level may not be clear.

In addition, consistently lower IgG GMCs have been observed for all 13 shared serotypes in 20vPnC group compared to 13vPnC group. It is uncertain whether the lower immunogenicity has a negative impact on the vaccine effectiveness. This is of particular concern for the 3-dose regimen, as differences between 20vPnC and 13vPnC observed after the last infant dose were significant, demonstrated by multiple (15/40) failed NI tests for both response rate and IgG GMC. Given the high burden of invasive pneumococcal disease in paediatric population in infants <1 year of age, it is crucial that vaccines offer sufficient protection in the window between the last infant and the toddler dose (between 6 and 12 months of age). Furthermore, a substantial disease burden in this age group is also due to pneumonia and acute otitis media. As higher antibody responses are thought to be necessary for the protection against pneumonia and AOM compared to IPD, there is an additional concern that 20vPnC might not offer sufficient protection to infants.

It is important to reiterate that the uncertainties associated with the 2+1 dose regimen, particularly following the last infant dose, pertain not only to one or two serotypes but to the majority of shared serotypes. While the current circulation of the 13vPnC serotypes may be low due to the indirect (herd) protection elicited via high uptake of the toddler dose, it is essential to underscore that this herd immunity is contingent upon the effectiveness of vaccines currently available on the market. Considering

the anticipated replacement of Prevenar-13 by 20vPnC, the numerous uncertainties regarding the efficacy of the latter pose a potential risk to this established herd immunity. Additionally, relying on herd immunity to justify a vaccine with significantly lower immunogenicity and substantial uncertainties about its translation into efficacy is not deemed acceptable. Although herd immunity plays an important role regarding indirect protection, a vaccine should offer direct protection after vaccination. In this specific case, the most critical time frame of individual risk for disease is between the last infant dose and the toddler dose. Since inference of efficacy is contingent upon the demonstration of non-inferiority, efficacy cannot be inferred from the data.

According to the ECDC data from 2019, five serotypes (serotypes 8, 10A, 11A, 12F and 15B) unique to 20vPnC caused 25% of remaining IPD in children age <1 year in Europe. While the *potential benefit* of the additional serotypes notwithstanding the previously mentioned uncertainties is acknowledged, this 'unmet medical need' may be overestimated, as the distribution of serotypes and the transmission dynamics change over time.

While post-authorisation effectiveness evaluation can be used to address some uncertainties present at the time of the assessment, pre-authorisation immunogenicity data should be sufficiently convincing. The benefit: risk of the 3-dose (2+1) regimen is thus considered to be negative. It is important to note, that regardless the uncertainties in relation to the 7 additional serotypes, a broader coverage of a 20-valent vaccine cannot overcome the concerns regarding potential lack of efficacy for the 13 shared serotypes. A vaccine is expected to induce protection against all included serotypes and addition of new serotypes is not considered of benefit if significantly impacting the efficacy against "previous" serotypes in a negative manner.

Given the overall better immunogenicity, the 4-dose (3+1) regimen is in more likelihood to achieve and maintain protection, especially in the window between the last infant and the toddler dose. The efficacy of the 4-dose regimen needs to be confirmed post-marketing, also for the additional 7 serotypes as the interpretation of data from pivotal studies regarding these serotypes was severely limited. To this effect, a post-authorisation commitment [REC] has been drawn up.

20vPnC is in general well tolerated and the reported AEs are considered well manageable.

3.8. Conclusions

The overall benefit: risk of Prevenar 20, 4 dose (3+1) regimen ONLY, for the indication: "Active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age." is positive.

The Applicant has accepted to remove 3-dose regimen from the SmPC (section 4.2) and provided updated PI accordingly. That dosing is only mentioned in the section 5.1 in accordance with the paediatric regulation.

The Applicant agrees to address the following recommendations in the post-authorisation phase:

1. Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Paediatric Vaccine-Type Invasive Pneumococcal Disease in children. Detailed protocol proposals for EMA approval before commencing the studies will be provided by agreed date.
2. The Applicant will discuss the use of 20vPnC in preterm infants in upcoming PSUSAs.

4. Recommendations

Outcome

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

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

Extension of indication to include infants, children and adolescents from 6 weeks to less than 18 years of age for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae*, based on final results from studies B7471003, B7471011, B7471012, B7471013 and B7471014. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

The variation leads to 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 and IIIB and to the RMP.

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

Risk management plan (RMP)

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

An updated RMP should be submitted:

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

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures (resulting from adult indication only):

Description	Due date
1. In order to further investigate the long-term effectiveness of Prevenar 20 for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*, the MAH should conduct and submit the multi-country results of study B7471015, a Phase 4 study using a test-negative design to evaluate the effectiveness of Prevenar 20 against vaccine-type radiologically-confirmed community-acquired pneumonia in adults ≥ 65 years of age.	CSR due 31/12/2027
2. In order to further investigate the long-term effectiveness of Prevenar 20 for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*, the MAH should conduct and submit the European-specific analysis results of study B7471015, a Phase 4 study using a test-negative design to evaluate the effectiveness of Prevenar 20 against vaccine-type radiologically-confirmed community-acquired pneumonia in adults ≥ 65 years of age.	CSR due 31/12/2030
3. In order to further investigate the long-term effectiveness of Prevenar 20 for active immunisation for the prevention of invasive disease caused by *Streptococcus pneumoniae*, the MAH should conduct and submit the results of a Phase 4 observational, real-world study to evaluate the effectiveness of Prevenar 20 against vaccine-type invasive pneumococcal disease in Europe according to an agreed protocol.	CSR due 31/12/2030

CSR: Clinical Study Report

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Prevenar 20-H-C-005451-II-12’

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted) of Prevenar 20, as a relevant example with changes highlighted, as adopted by the CHMP on 25 January 2024.

2. Letter of Undertaking for EMEA/H/C/005451, dated 23 January 2024.

3. Final minutes and answers from the SAG Vaccines meeting on Apexxnar, dd. 06 December 2023.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information (CCI) in "track changes" and with detailed justification by 9 February 2024. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 9 February 2024. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.