16 December 2021
EMA/12384/20222
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Apexxnar

Common name: pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)

Procedure No. EMEA/H/C/005451/0000

Note

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

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Table of contents

List of abbreviations

20vPnC	20-valent pneumococcal polysaccharide conjugate vaccine
13vPnC	13-valent pneumococcal polysaccharide conjugate vaccine
7vPnC	7-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine

Quality:

AlPO4	aluminium phosphate
APQR	Annual Product Quality Review
CPP's	critical process parameters
CPV	Continued Process Verification
CQAs	critical quality attributes
CRM197 (CY process)	diphtheria cross reactive material manufactured with casamino acid-yeast extract based medium
CRM197 (DM process)	diphtheria cross reactive material manufactured with defined medium
DMSO	dimethyl sulfoxide
DOC	sodium deoxycholate
DOE	design of experiments
FP	finished product
AS	active substance
ASI	active substance intermediate
FC's	flexible containers
GMP	Good Manufacturing Practice
HA	hydroxyapatite
HB	hexadecyltrimethylammonium bromide
IPT-Cs	in-process tests for control
IPT-Ms	in-process tests for monitoring
LOQ	limit of quantitation
MBC	monovalent bulk conjugates
MCB	master cell bank
NaBH3CN	sodium cyanoborohydride
NaCl	sodium chloride
NaI	sodium iodide
NaIO4	sodium meta periodate
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
NOR	normal operating range
OD	optical density
OSV	Original Source Vials

PARs	proven acceptable ranges
PE	polyethylene
PFS	pre-filled syringe
PS80	polysorbate 80
PPQ	process performance qualification
PV	Process validation
RM	reference material
SME	subject matter expert
SS	stainless steel
TSE	Transmissible Spongiform Encephalopathy
UFDF	ultrafiltration diafiltration
US FDA	United States Food and Drug Administration
WCB	working cell bank
WFI	water for injection

Non-clinical/ clinical:

4KQ	4-keto-N-quinovosamine
ACVP	American College of Veterinary Pathologists
ADR	Adverse Drug Reaction
AE	Adverse Event
c7vPnC	Complementary 7-Valent Pneumococcal Conjugate Vaccine
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
dLIA	Direct Luminex Immunoassay
ECDC	European Centre for Disease Prevention and Control
e-diary	Electronic Diary
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
FIH	First in Human
GLP	Good Laboratory Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titre
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem-Cell Transplantation
IgG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease

IRT	Interactive Response Technology
ISS	Integrated Summary of Safety
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
LOD	Limit of Detection
MAA	Marketing Authorisation Application
NOAEL	no observed adverse effect level
NZW	New Zealand White
MedDRA	Medical Dictionary for Regulatory Activities
NDCMC	Newly diagnosed chronic medical condition
NI	Non-inferiority margin
NITAGS	National Immunisation Technical Advisory Groups
OC	Other Concern
OPA	Opsonophagocytic Activity
PI	Principal Investigator
PIP	Paediatric Investigation Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
PWG	pathology working group
SA	Scientific Advice
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Tdap	Tetanus, Diphtheria, and acellular Pertussis Vaccine
VE	Vaccine Effectiveness
WHO	World Health Organization
yoa	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 5 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Apexxnar, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

The applicant applied for the following indication:

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

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

The use of TRADENAME should be determined on the basis of official recommendations taking into consideration the risk of invasive disease and pneumonia in different age groups, underlying comorbidities, as well as the variability of serotype epidemiology in different geographical areas."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0159/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0159/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.4.2. Derogation(s) from market exclusivity

Not applicable

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance 'pneumococcal polysaccharide serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F conjugated to CRM197 carrier protein' contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union which was initially agreed.

However, based on the recent positive CHMP opinion (14.10.2021) for pneumococcal vaccine [Vaxneuvance (15-valent, adsorbed)], which contains serotypes 22F and 33F conjugated to CRM197, the applicant was requested to revise the NAS claim, which was done accordingly.

The CHMP now considers that pneumococcal polysaccharide serotypes 8, 10A, 11A, 12F and 15B conjugated to CRM197 carrier protein can be qualified as new active substances.

1.6. Scientific advice

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

Date	Reference	SAWP co-ordinators
13 December 2018	EMEA/H/SA/3940/1/2018/III CORRIGENDUM	*Dr Peter Mol, Dr Filip Josephson*

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

- *Manufacturing comparability*
- *Strategy regarding lots used for shelf life establishment and Process Performance Qualification*
- *Plan to eliminate rabbit pyrogenicity testing for drug product*
- *Preclinical programme to support Phase 3 in adults and children*
- *Concurrence with the phase 3 programme to support indications for IPD and pneumonia for the 20 serotypes contained in the vaccine in adults 18 yoa and older*
- *Success criteria for the phase 3 non inferiority studies*
- *Safety and immunogenicity databased to support licensure in different age groups and pneumococcal vaccine status groups*
- *SmPC claims on high risk adult population and cross-protection for serotype 15C from 15B*

1.7. 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

The application was received by the EMA on	5 February 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Apexxnar on	16 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

20-valent pneumococcal polysaccharide conjugate vaccine (20vPnC) is a protein conjugated polysaccharide vaccine intended for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥ 18 years of age.

Invasive pneumococcal disease (IPD) can occur when *S. pneumoniae* gains access to the blood or otherwise normally sterile sites. Depending on the site where invasion occurs, this can lead to different disease manifestations (e.g. meningitis, bacteraemia, sepsis, bacteraemic pneumonia, and septic arthritis).

S. pneumoniae is the leading bacterial pathogen that causes community-acquired pneumonia (CAP). CAP is amongst the most common causes of acute infection that require hospital administration.

2.1.2. Epidemiology and risk factors

Streptococcus pneumoniae continues to be a major cause of vaccine-preventable disease worldwide, resulting in considerable morbidity and mortality. Older adults (≥65 years of age), adults ≥18 years of age with certain comorbid conditions (e.g. chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma), and immunocompromised adults (e.g. human immunodeficiency virus (HIV), haematopoietic stem-cell transplantation (HSCT) patients) are particularly susceptible to pneumococcal disease.

Studies from Europe have reported a high proportion of ***community-acquired pneumonia (CAP)*** due to *S. pneumoniae* in hospitalised adults. In a recent population-based cohort study from the UK, 36.6% of CAP cases in adults ≥16 years of age were caused by *S. pneumoniae*. Similar proportions were also found in the Netherlands, Germany, Spain, and Sweden and by a meta-analysis of 35 pneumonia studies in adults predominantly conducted in developed countries. Non-bacteraemic pneumococcal pneumonia is much more common than bacteraemic pneumococcal pneumonia. For example, 89.7% and 82.3% of adult cases of pneumococcal CAP large pneumonia surveillance studies in the UK (2013–2018) and Spain (2011–2014) were non-invasive.

Invasive pneumococcal disease (IPD) incidence rates in adults for surveillance years between 2013 and 2019 have been reported for several European countries. The annual incidence per 100,000 population in adults ≥65 years of age was between 22.2 and 51.0 with 30-day case fatality rates for IPD varying between 11% and 30% based on several publications in European countries. According to the ECDC a total of 24,663 IPD cases were reported in the EU/EEA in 2018 (6.4 cases/ 100,000 population). IPD rates were highest at the extremes of age (infants ≤1 yoa: 14.4 cases/ 100,000 population; adults ≥65 yoa: 18.7/ 100,000 population). The case-fatality rate of IPD has not decreased over the past two decades.

Burden of the seven additional non-13vPnC serotypes covered by 20vPnC

According to the ECDC the 10 most common serotypes (≥70% of isolates) causing IPD in Europe in 2018 were in order of decreasing frequency: 8, 3, 19A, 22F, 12F, 9N, 15A, 10A, 23B and 6C. In adults ≥65 yoa 73% of cases were caused by serotypes targeted by PPSV23 and 29% by serotypes

targeted by 13vPnC (source: Invasive pneumococcal disease - Annual Epidemiological Report for 2018; 8 Sep 2020). Notably, despite being targeted by 13vPnC and PPSV23, serotypes 3 and 19A remain amongst the most frequent IPD causing serotypes in Europe in adults ≥ 65 yoa (14.7% and 7.6%, respectively). The seven additional serotypes covered by 20vPnC but not by 13vPnC (8, 10A, 11A, 12F, 15B, 22F, and 33F) are responsible for a substantial proportion of the remaining IPD disease burden In the EU, serotype 8 is of particular concern, causing 14% of all IPD cases in older adults in 2018, followed by 22F (7.4%), 12F (4.0%), 11A (2.8%), 33F (2.5%) and 10A (2.3%). Overall, the serotypes included in 20vPnC represent seven of the 10 most prevalent serotypes that caused IPD in adults ≥65 years of age.

In addition, these serotypes have characteristics that make them medically important, including antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and a tendency to cause more severe disease (e.g. association with meningitis and/or increased mortality rate) (10A, 11A, 22F).

2.1.3. Biologic features

The Gram-positive bacterium *Streptococcus pneumoniae* commonly asymptomatically colonises the human nasopharynx. Carriage rates decline with age (approx. 1/3rd to 2/3rds of children and ≤10% of adults are colonised). Transmission occurs mainly via nasal shedding (mucus droplets). Pneumococcal spread to more distal sites (e.g. middle ear, the lung, bloodstream or brain) can cause a range of disease manifestations (see clinical presentation below). This process depends on complex host-pathogen interactions, involving a multitude of bacterial virulence factors and inflammatory host cascades. The capsule consists of layers of polysaccharides, is the major surface antigen and exists in approx. 100 different chemical compositions called serotypes. It is a prerequisite for virulence (non-encapsulated strains exist but show reduced virulence or are avirulent), prevents mucus entrapment of *S. pneumoniae* and counteracts opsonophagocytosis. Generation of anti-capsular antibodies which enhance opsonophagocytosis forms the basis of currently approved pneumococcal vaccines. Conferred protection is serotype-specific, no serotype-independent pneumococcal vaccines are available.

2.1.4. Clinical presentation, diagnosis

Pneumococcal disease mainly presents as non-invasive disease, such as non-bacteraemic pneumonia, sinusitis or acute otitis media (the latter most commonly in young children). The comparably less frequent albeit generally more severe invasive pneumococcal disease (IPD) occurs when *S. pneumoniae* gains access to more distal, normally sterile anatomical sites. IPD presents as meningitis, bacteraemic pneumonia, bacteraemia without focus and septic arthritis.

Regardless of the presence of bacteraemia, pneumococcal pneumonia is associated with complications and long-term sequelae in all age groups, including respiratory failure requiring hospitalisation, empyema, and necrotizing pneumonia, exacerbations of chronic medical conditions, declines in quality of life, and with a significant increased risk of death within 30 days (acute) and 1 year (long-term) after the event.

2.1.5. Management

Disease Treatment

S. pneumoniae infections are treated based on clinical presentation and susceptibility data to antimicrobials. Broad-spectrum antibiotics are the most commonly used antimicrobials against *S. pneumoniae*. Although *S. pneumoniae* is considered as a "classical" multi-resistant pathogen, increasing resistance rates have been reported which may lead to treatment failures.

Disease Prevention

At time of Marketing Authorisation Application, three pneumococcal vaccines were licensed in the EU:

- The **unconjugated polysaccharide vaccine PPSV23** (Pneumovax23) was initially authorised via national procedures in EU member states in the 1980s. PPSV23 contains capsular polysaccharides for 23 different serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). It is indicated for use in persons 2 years of age and older for whom there is an increased risk of morbidity and mortality from pneumococcal disease due to aging and/or underlying medical conditions.

- The initial pneumococcal **conjugate vaccine**, 7vPnC (Prevenar), was licensed in 2000 for use in children, but is no longer authorised in the EU. **13vPnC (Prevenar 13)** was subsequently developed to expand disease coverage in children (first licensed in 2010) and to better address disease in adults (first licensed in 2011). It targets serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

  Efficacy against IPD and pneumonia was demonstrated in a randomised clinical trial in adults ≥65 years of age. Since its introduction, 13vPnC has demonstrated real-world effectiveness against pneumococcal disease in adults

  -Synflorix was licensed in the EU in 2009 and is indicated for infants and children from 6 weeks up to 5 years of age.

During this procedure, Vaxneuvance received a positive CHMP opinion (14 10 2021), with Commission Decision (authorisation) adopted on 13.12.2021. This pertains to a 15-valent pneumococcal vaccine containing the 13 serotypes included in Prevenar 13 and additionally serotypes 22F and 33F. All 15 serotypes are also contained in 20vPnC (Apexxnar).

2.2. About the product

20vPnC is a pneumococcal conjugate vaccine, modelled after 13vPnC. 20vPnC contains the same 13 serotype-specific capsular polysaccharide antigens included in the authorised 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), plus 7 additional serotype-specific capsular polysaccharides (8, 10A, 11A, 12F, 15B, 22F, and 33F).

Each antigen is covalently linked (i.e. conjugated) to CRM197. This carrier protein modifies the immune response to the polysaccharide from a T cell independent response to a T cell dependent response. The T cell dependent response leads to both an enhanced antibody response and generation of memory B cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria. 20vPnC was developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease.

In adults, the levels of circulating antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

20vPnC is to be administered as a single dose to adults 18 years of age and older. Based on the clinical experience with 13vPnC, if the use of PPSV23 is considered appropriate, 20vPnC should be given first.

The targeted indication for 20vPnC is: Active immunisation for the prevention of invasive disease and pneumonia caused by *S pneumoniae* in adults ≥18 years of age.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the vaccine technology employed from the viewpoint of therapeutic innovation not being considered of major interest as it is an extension of an existing formulation (13vPnC/ Prevenar 13). Moreover, despite the known limitations of an unconjugated polysaccharide vaccine such as PPSV23 and the general advantages of a conjugate vaccine, there is a licensed vaccine available largely covering the same serotypes as 20vPnC.

2.4. Quality aspects

2.4.1. Introduction

This 20-valent pneumococcal polysaccharide conjugate vaccine consists of capsular polysaccharide antigens of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F with each saccharide individually conjugated to diphtheria CRM_{197} protein. The conjugates induce serotype-specific responses to the capsular polysaccharides contained in the vaccine (and within-serogroup for certain serotypes, e.g. serotype 15C) intended to protect against disease due to the vaccine serotypes.

Other ingredients are succinate buffer containing sodium chloride (NaCl), succinic acid and polysorbate 80 in water for injections, at pH 5.8, with aluminium phosphate as an adjuvant.

The vaccine is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes, administered by intramuscular injection.

The target indication for 20-valent pneumococcal conjugate vaccine (20vPnC) is active immunisation for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F in adults 18 years of age and older.

2.4.2. Active Substance (AS)

2.4.2.1. General information

Information on the nomenclature of pneumococcal polysaccharide serotypes is provided in the dossier and previous quality assessment reports for the EU-authorised product, Prevenar 13.

The active substances are the following:

- Pneumococcal polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to diphtheria cross reactive material (CRM_{197}). These are the same serotypes as already included in the 13-valent Pneumococcal conjugate vaccine Prevenar

13 from the same manufacturer. These serotypes are named 13vPnC serotypes in the following text.

- Pneumococcal polysaccharides of serotype 8, 10A, 11A, 12F, 15B, 22F and 33F conjugated to CRM_{197}. These serotypes are named novel serotypes in the following text.

Information on the nomenclature related to CRM_{197}, is provided in the table below.

Table 1: Nomenclature for CRM_{197}

Name	Description
Recommended International Nonproprietary Name (INN)	Diphtheria cross reactive material: CRM_{197}
Compendial Name, if relevant	Not applicable
Chemical Name(s)	Diphtheria cross reactive material (CRM_{197})

Information on the nomenclature of pneumococcal saccharide-CRM_{197} conjugate serotypes is provided in the following table.

Name	**Description**
Compendial name	Monovalent Bulk Conjugate Serotype 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F

2.4.2.1. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The applicant has provided the stability data for all 20 MBC and also for the CRM_{197}. An annual stability programme is foreseen as well.

Overall manufacture

With respect to the manufacturing process, all the individual steps as well as the applicable controls were properly described. The polysaccharide production scheme is a four-stage fermentation process followed by cellular inactivation plus a harvest step. The four stages of the fermentation process are: seed bottles, seed fermentor, intermediate fermentor and production fermentor. After fermentation, the polysaccharides are purified. Purified serotypes are shipped with a validated shipping process. Upon activation, polysaccharides are conjugated to the CRM. Conjugation occurs in aqueous or DMSO conditions.

With respect to the novel serotypes, all individual steps of the fermentation, purification activation and conjugation have also been provided in sufficient detail in the eCTD. Whenever serotype specific steps are involved, these were also described and explained. All in-process controls and in-process monitoring tests were mentioned.

Conjugation of the novel serotypes is mostly also performed under either DMSO or aqueous conditions. Serotype 33F conjugation is performed under specific conditions that are different from the other serotypes, but this is also described in sufficient detail in the dossier.

The production scheme of CRM_{197} is a four-stage fermentation process plus a harvest step followed by ultrafitration, UF concentration and impurity precipitation/ depth filtration in preparation for purification. The four stages of the fermentation process are: primary flasks, secondary/aspirator flasks, seed fermentor and production fermentor.

Purification is a four-stage process. The four stages of the purification process are: batch pooling and concentration/diafiltration column chromatography purification, concentration/diafiltration, and filtration and dispensing. The CRM_{197} is then frozen and stored -75 ± 5°C.

In preparation for conjugation of CRM with serotypes 6A, 6B, 7F, 8, 10A, 11A, 12F, 15B, 19F, 22F and 23F activated saccharides are lyophilised in a three-stage process. The 1 L Type 1 glass bottles containing lyophilised active substance intermediate are stored at -20 ± 5°C from the date of lyophilisation completion. The description of the manufacture of the CRM_{197} is acceptable.

Control of materials

Each manufacturing site has a vendor management programme and appropriate quality systems to ensure control of raw materials used for Good Manufacturing Practice (GMP) manufacturing. Raw materials are purchased from approved suppliers and tested and released. Non-compendial raw materials may be replaced with compendial materials following appropriate qualification of the new sources of the raw materials. Water for injection (WFI) manufactured at the facility is used throughout the process and meets USP/Ph. Eur. requirements.

The control of materials has been provided for the 13vPnC serotypes, the novel serotypes and the CRM carrier. All information on raw materials has been provided, also for materials of biological origin. The applicant has given complete and detailed description on the source, history and generation of the cell banks (MCB and WCB) for all the 20 polysaccharides and the CRM carrier.

Control of critical steps and intermediates

Controls of critical process steps are employed during manufacture of pneumococcal polysaccharide serotypes to ensure product quality is maintained. The process controls include release and stability tests and in-process tests with their respective acceptance criteria. If the results of these parameters/controls are outside of the acceptable ranges, an evaluation of the deviation is performed, and the decision about material disposition for further manufacture is based on the investigation conclusion.

In-process tests and acceptance criteria for pneumococcal polysaccharide serotypes are provided. All analytical methods for in process testing of pneumococcal polysaccharides were properly described in the eCTD. Validation of the methods has been done according to ICH Q2(R1).

The release and stability specifications for pneumococcal polysaccharide serotypes are provided and justified.13vPnC serotypes are dispensed and stored in 50 L stainless steel (SS) vessels. Pneumococcal polysaccharide for the novel serotypes is stored in 5 L polyethylene (PE) flexible containers fitted with ports and tubing to facilitate dispensing into the FCs and subsequent dispensing of ASI during active substance manufacturing.

The data presented provide rationale and justification for the pneumococcal polysaccharides commercial shelf life when stored at the recommended temperature of -15 to -25°C. Activated saccharides are filled into 1 L Type 1 glass bottles, lyophilised and closed with a grey butyl stopper. The stopper is secured with a non-product contact cap. The materials of construction for all product-contact components have been demonstrated to be compatible with the activated saccharides through stability studies for each serotype.

Process Validation and/or Evaluation

- 13vPnC serotypes

As part of the 20-valent pneumococcal conjugate vaccine (20vPnC) preparation for licensure, Pfizer did not repeat process validation for the 13 serotypes included in the 13-valent pneumococcal conjugate vaccine (13vPnC) as the processes have been validated before and product quality is monitored by the routine Annual Product Quality Review (APQR) and the Continued Process Verification (CPV) programme which verify that the quality attributes are being appropriately controlled following process validation.

The purpose of process validation was to demonstrate that the pneumococcal polysaccharide conjugate manufacturing process is under control and produces pneumococcal polysaccharide, activated saccharide and monovalent bulk conjugate (MBC) active substance of acceptable quality by meeting all the pre-determined acceptance criteria.

- Novel serotypes

Validation of the novel pneumococcal polysaccharide-CRM_{197} conjugate serotypes manufacturing processes has been successfully completed starting from each of 3 independent, consecutive thaws of the WCB used in production of pneumococcal polysaccharide active substance intermediate. The validation was designed to demonstrate that the manufacturing process, when operating within defined process controls, can consistently produce polysaccharide and polysaccharide-CRM_{197} conjugate meeting pre-determined acceptance criteria and demonstrate expected, reproducible, and consistent process performance.

- CRM_{197}

Validation of the manufacturing process for CRM_{197} has been successfully completed from each of three independent, consecutive thaws of the WCB. The validation was designed to demonstrate that the manufacturing process, when operating within defined process controls, would consistently produce CRM_{197} meeting pre-determined acceptance criteria and demonstrate expected, reproducible and consistent process performance.

Manufacturing process development

For the 13vPnC serotypes the pneumococcal polysaccharide processes used commercially in the 13vPnC vaccine are the result of process development work and learning from commercial experience and the activation and conjugation process used commercially is the result of process development work and learning from commercial experience.

As can be seen in the description of the manufacturing process, the fermentation, activation and conjugation for the novel serotypes are similar to what is used for the 13vPnC serotypes while the purification process is different.

The CRM_{197} processes for all conjugate serotypes are the result of process development work and learning from commercial experience

A comprehensive understanding of the manufacturing processes has been developed through commercial-scale runs and process characterisation studies that include design of experiments (DOE) and using scale-down models of individual unit operations. No design space is claimed.

In alignment with ICH Q10, effective quality systems are in place to support continued quality/process verification and post-approval change management.

A recurring risk review, including a review of the classification of process parameters, takes place periodically throughout the lifecycle of the product. Knowledge management supports interpretation of all relevant data gathered in support of continuous improvement.

Characterisation

The applicant has given detailed information on the characterisation of the pneumococcal polysaccharides, the activated pneumococcal polysaccharides and the conjugated polysaccharides.

2.4.2.2. Specification

The specifications of the conjugated serotypes contain the same attributes for the 13vPnC and novel serotypes.

The proposed release and stability tests for the pneumococcal monovalent bulk conjugates are in compliance with Ph. Eur. 2150.

Analytical procedures and reference standards

A summary of the analytical procedures used for pneumococcal saccharide-CRM_{197} conjugates is provided in the eCTD. Validation or verification of analytical procedures was performed to ensure the quality, identity, purity, and safety of monovalent bulk conjugates (MBC). Analytical procedures were confirmed suitable for their intended use by assessing all relevant validation elements described in ICH Q2(R1), Validation of Analytical Procedures: Text and Methodology. Compendial procedures were verified according to USP <1226> Verification of Compendial Procedures, as well as the relevant Ph. Eur. and JP general chapters.

Non-compendial quantitative analytical procedures were validated for precision, accuracy, specificity, linearity and range. Quantitative procedures used to determine the content of minor constituents were further validated for limit of quantitation. Compendial procedures were confirmed fit for use through method verification.

Batch analysis and justification of specification

All batches fulfil the acceptance criteria and show, within each serotype, reproducible results well within the limits.

Container closure

The monovalent bulk conjugate (MBC) is dispensed and stored in engineered film, 2 L (FCs).

2.4.2.3. Stability

The data presented provide rationale and justification for the novel pneumococcal saccharide-CRM_{197} conjugate serotypes , 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F commercial shelf lives when stored at the recommended temperature of 2-8 °C.

The data presented provide rationale and justification for the liquid CRM_{197} commercial shelf life when stored at the recommended temperature of -75±5 °C.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The 20-valent pneumococcal conjugate (20vPnC) vaccine is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F with each saccharide individually conjugated to diphtheria cross reactive material (CRM_{197}).

The vaccine is supplied in a 1 mL glass syringe with a Luer lock closure. Each 1 mL syringe contains a 0.5 mL dose of vaccine, supplied as a single-dose injection for parenteral administration, with no preservative. A 25G x 5/8" (0.5 x 16 mm) needle or 25G x 1” (0.5 x 25 mm) needle can be included in the packaging.

Pharmaceutical Development

The 20vPnC vaccine contains 20 active substances (monovalent bulk conjugate (MBC) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F), each supplied at a target conjugate concentration of 0.5 g/L saccharide.

No novel excipients are used and no excipients of human or animal origin and no novel excipients are used.

Each prefilled syringe of 20vPnC vaccine is designed to deliver 2.2 µg of each conjugate serotype (except serotype 6B) and 4.4 µg of conjugate serotype 6B in 0.5 mL dose of vaccine. The vaccine is formulated in succinate buffer containing sodium chloride (NaCl) and polysorbate 80 (PS80), at pH 5.8, and containing aluminium phosphate (AlPO4) aluminium as an adjuvant. Each 1 mL syringe contains a 0.5 mL dose of vaccine, supplied as a single-dose injection for parenteral administration, with no preservative.

2.4.3.2. Manufacture of the product and process controls

Pfizer Manufacturing Belgium N.V. Rijksweg 12, Puurs, Belgium is the manufacturer responsible for the batch release.

Manufacturing process controls

The 20vPnC vaccine formulation contains 20 monovalent bulk conjugates (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) in succinate/ sodium chloride (NaCl) buffer, pH 5.8, and aluminium phosphate (AlPO4) at 0.25 mg/mL aluminium as adjuvant with polysorbate 80.

These IPCs are identified at the level of the formulation step and during the filling process. No reprocessing steps have been identified in the finished product manufacturing process.

Process validation / verification

Validation of the 20vPnC vaccine finished product manufacturing process has been successfully completed. The validation was designed to demonstrate that the manufacturing process, when operating within defined process controls, can consistently produce 20vPnC finished product meeting pre-determined acceptance criteria and demonstrate expected, reproducible, and consistent process performance.

2.4.3.3. Product specification

All excipients used for 20vPnC vaccine finished product are compendial except for aluminium phosphate suspension ($AlPO_4$).

The release and stability specification for the compendial and non-compendial excipients have been provided. This is deemed acceptable.

The specifications for the final product have been provided and these have been set in compliance with the Ph. Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150).

Analytical procedures and reference standards

Analytical procedures were provided and adequately described. The results generated for the verification/validation of the analytical procedures were found satisfactory and demonstrate that the analytical procedures are suitable for use in release and stability testing (assays for content/potency, total and bound antigenicity).

Batch analysis and justification of specification

Sufficient batch data have been included for the different batches used in the manufacturing development of the vaccine. Batches have always been tested against the specifications in force at time of testing.

Container closure

The 20vPnC in a prefilled syringe (PFS) is defined as an integral drug-device combination that is governed as a medicinal product under Directive 2001/83/EC, as amended, as the device component forms an integral product intended exclusively for use in combination with the drug product syringe. The PFS is designed and developed in conformance with ISO 13485:2016.

2.4.3.4. Stability of the product

The shelf life claim of 20vPnC finished product is 24 months when stored at the recommended temperature of 2-8°C. The shelf life claim is based on 24 months of real time stability data from 4 primary stability lots of 20vPnC finished product stored at the intended condition of 5±3°C

2.4.3.5. Adventitious agents

Multiple mechanisms and procedures are used to minimize the entry of adventitious agents into the process stream. The adventitious agent control programme includes the engineering systems of the facility and vessels, the control of the materials used in the process, various filtration steps to control microbial load in media, buffers and the process stream, and in-process and environmental testing to monitor the level of adventitious agents in and around the process stream.

20vPnC is composed of components derived from microbial fermentation and is not a viral product. Several ingredients of animal origin are used in the preparation of the vaccine component, and the main theoretical risk associated with these ingredients is contamination of the product by transmissible spongiform encephalopathy (TSE) agents. To minimize this risk, the applicant has been vigilant in assuring proper use and control of animal derived materials by:

- Working with suppliers to collect the most up-to-date information on animal derived materials used in this process;

- Working with the United States Food and Drug Administration (US FDA) for updates on regulations and practices to control TSE in the US;
- Working with other agencies worldwide, including the Committee for Medicinal Products for Human Use (CHMP), when needed, to keep current on any changes in compliance expectations.

Details of the starting material/reagent containing material of animal origin including its source and preparation were discussed and considered satisfactory with regard to TSE. These materials are commercially available and are not specifically produced for the applicant. Other materials of animal origin are used in the production of polymer for the stoppers, filters, manifolds, containers and/or filters components. These components may contain traces of animal tallow derivatives. The tallow is considered compliant with the TSE note for guidance (EMA/410/01, Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products).

Moreover, equipment and materials are cleaned, sterilised and/or chemically decontaminated according to validated procedures, thereby further reducing process risk.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The CMC part, Module3 of the dossier was extensive and of high quality.

The applicant has provided detailed descriptions of the intermediates (20 pneumococcal polysaccharides and carrier protein CRM_{197}) and the 20 active substances (Monovalent bulk conjugates). The starting and raw materials have been appropriately described and all process steps have been described and have been validated during the process validation and development. Specifications have been set for intermediates and individual active substances. Analytical methods were described, and validation summaries provided. All acceptance criteria for specifications are properly justified for intermediates and active substances.

Container closure data are provided, and stability programmes are running. The batches used for shelf life claim are deemed representative for commercial batches and as such, acceptable for setting the shelf life. Depending on the serotype-conjugate, a shelf life from 12 months up to 36 months for individual AS is accepted.

Finished product manufacturing process, the control of materials, the process controls and the process development were adequately described. FP specifications and justifications were provided as well as information on the analytical methods, which were properly validated or qualified. Container closure systems for FP were described and are deemed suitable.

Stability data were provided for clinical and PPQ FP lots. The applicant claims a shelf life of 24 months when stored at 2-8°C, which can be granted based on the available data.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical toxicity assessment for 20vPnC consisted of 9 Good Laboratory Practice (GLP)-compliant studies, which were conducted in accordance with Good Laboratory Practice for Nonclinical Laboratory Studies, in an OECD member state.

GLP inspection: No request for a GLP inspection (routine or triggered) has been made.

The scope of the non-clinical programme is in line with applicable guidelines for the development of a vaccine and is considered adequate. In principle, the vaccine lots used in non-clinical studies should be adequately representative of the formulation intended for clinical investigation. Minor differences are present in the analytical data for nonclinical toxicity study and clinical study drug product lots. However, they are not considered to impact the results of the respective studies.

2.5.2. Pharmacology

Non-clinical studies were performed in mice, rats and rabbits to demonstrate immunogenicity of 20vPnC and the monovalent conjugates of the seven new serotypes contained in 20vPnC (serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F). The responses to each of the seven new antigens contained in 20vPnC were evaluated separately as well as in combination. However, according to the European Centre for Disease Prevention and Control (ECDC) the 10 most common serotypes accounting for 70% of typed isolates circulating in Europe are: 8, 3, 19A, 22F, 12F, 9N, 15A, 10A, 23B and 6C (in order of decreasing frequency). Clinical relevance of any cross-functional immune responses for the serotypes not included in 20vPnC may be determined in a post-marketing setting.

The pharmacology studies were adequately designed to assess relevant immune parameters, including functional immune response leading to protection (i.e. IgG induction and opsonophagocytic activity).

In mice, dose-dependent immune responses to the polysaccharide conjugates for the 7 additional serotypes were determined by increases in OPA titres following two SC administrations three weeks apart.

Immunogenicity of each new serotype conjugate was assessed after 2 or 3 SC injections. Even if presented results support immunogenicity of the newly added conjugate serotype, there are limits in the study because of the route of injection used (SC versus IM), and the number of injections (2 or 3 versus 1 in clinics).

In rats, the 7 additional conjugates in 20vPnC were administered as a combined 7-valent vaccine once every three weeks for a total of three doses. Humoral and functional immune responses were observed as measured by dLIA and OPA. Study VR-VTR-10666 has been conducted in female rats only, by the SC route, and with three repeated injections, which does not mimic the foreseen clinical schema (1 unique IM injection in adults in the clinic.

In general, it was demonstrated that the polysaccharide conjugates for the 7 additional serotypes included in 20vPnC are immunogenic in mice and rats. 20vPnC was also found to be immunogenic in rabbits.

In rabbits, increases in serotype-specific IgG and OPA responses were observed following two IM administrations of 20vPnC three weeks apart. Serum IgG levels increased by at least 2 logs compared to baseline. OPA titres increased by at least 27-fold compared to baseline after immunisation.

The serotype 12F capsular polysaccharide structure was found to contain a partial substitution of N-acetyl-galactosamine by 4KQ using newer methodology as compared to the current published structure. Presence or absence of this substitution in the 12F polysaccharide was not found to impact immunogenicity against clinical 12F isolates.

Standalone safety pharmacology studies were not performed for this submission. This approach is acceptable for vaccines and in line with recent guidance. Furthermore, clinical cage-side observations in combination with microscopic examination of the nervous system and respiratory tract were conducted in the pivotal repeat-dose toxicity study (12GR385) and led to the conclusion that there were no clinical signs indicative of respiratory or neurologic system effects.

The absence of cardiovascular functional endpoints in the pivotal toxicity study is somewhat problematic, since histopathological findings of cardiotoxicity were observed in two animals treated with 20vPnC in that study. These findings are discussed in the toxicology section of this report.

2.5.3. Pharmacokinetics

Pharmacokinetic studies have not been conducted for 20vPnC as according to the relevant EMA and WHO Guidelines they are not required for vaccines

2.5.4. Toxicology

The initial toxicity assessment for 20vPnC consisted of three GLP-compliant studies in NZW rabbits, including an initial pivotal repeat-dose toxicity study, a fertility and developmental toxicity study and a local tolerance study. Following signs of cardiotoxicity in the pivotal toxicity study, a series of investigative studies was conducted

2.5.4.1. Repeat dose toxicity

The toxicity of 20vPnC was evaluated in a pivotal 59-day toxicity study in rabbits when administered by IM injection once every 2 weeks for a total of 5 doses followed by a 4-week dose-free recovery phase. Injection site findings consisting of minimal to moderate chronic-active inflammation and degeneration/necrosis of myofibers as well as injection site reactogenicity were observed. The severity of these reactions in the 20vPnC-dosed animals was comparable to the vehicle group but greater than in rabbits administered saline and was decreased at the end of the recovery phase. All injection site findings and reactogenicity were considered non-adverse in this study.

Microscopic findings of mild to moderate multifocal inflammation with degeneration/necrosis of cardiomyocytes and minimal increased interstitial fibrosis in the papillary muscle of the left ventricle of the heart were observed in one 20vPnC low dose (once the human dose) animal and in one 20vPnC high dose (twice the human dose) animal at the end of the dosing phase. At the end of the recovery phase, marked multifocal interstitial fibrosis was observed in the interventricular septum of one 20vPnC low dose animal. Heart findings were initially attributed to test article administration; however, following multiple investigative activities, the heart findings were considered not related to the vaccine or its components but likely due to stress associated with handling and procedures (see below).

Based on the non-adverse injection site findings and the follow-up investigations on the microscopic heart findings, 2x the clinical dose of 20vPnC (2x 0.5 mL) was considered the NOAEL in this study. However, the heart findings require further explanation, as discussed below.

Investigative repeat-dose toxicity studies

Additional investigative studies were conducted to understand the potential causative factors in the development of the heart findings observed in the pivotal toxicity study.

The weight of evidence from these investigative activities indicates that the heart findings were not related to the vaccine conjugates or other vaccine components. This conclusion is based on evidence that comparable heart findings can occur independent of test article in rabbits, heart findings were not due to direct or immune-mediated cardiotoxicity, and comparable findings may be induced in rabbits with increased handling and study procedures, suggesting the potential contribution of factors extrinsic to test article, such as stress, in the development of heart findings.

These conclusions were supported by an external pathology working group comprised of 3 independent, ACVP board-certified veterinary pathologists who performed a blinded review and evaluation of all heart slides from animals diagnosed with inflammation with degeneration/necrosis of cardiac myocytes along with slides without this finding from the initial repeat-dose toxicity study and the 6 follow-on investigative studies. In addition, slides from 3 animals with mild and moderate myocardial inflammation from the historical database were also included in the review.

It is acknowledged that extensive efforts were made to further examine the unexpected heart findings. The additional studies were well designed and the evaluation by an independent pathology working group is appreciated.

During the evaluation procedure, the applicant provided additional data in support of the notion that the cardiac lesions were rabbit-specific, incidental or caused by stress.

2.5.4.2. Genotoxicity/ carcinogenicity

No genotoxicity or carcinogenicity studies have been conducted with 20vPnC. In line with the relevant EMA and WHO Guidelines, non-clinical studies evaluating genotoxicity or carcinogenicity are not required for vaccines.

2.5.4.3. Reproductive and developmental toxicity

The combined fertility and developmental study (including teratogenicity and postnatal investigations) in rabbits is considered appropriate to detect the effects of 20vPnC on fertility and pre- and postnatal development in pregnant and lactating female F0 animals and on in utero and postnatal development of the offspring. 20vPnC was administered by IM injection at the intended human dose on 4 treatment days (17 and 4 days before mating and on GD 10 and GD 24). Suitability of the animal model was demonstrated by immune response to the vaccine as determined by serum antibody measurements in F0 females, foetuses and pups.

Based on the results of this study, IM administration of 20vPnC before and during gestation to female rabbits did not cause maternal systemic toxicity. Further, there were no 20vPnC-related effects on mating performance or fertility in female rabbits or on embryo-foetal or postnatal survival, growth, or development in the F1 offspring.

2.5.4.4. Local tolerance

Local tolerance was examined in female NZW rabbits after administration of a single 0.5 mL subcutaneous injection of 20vPnC. Non-adverse erythema, oedema, and mass at the injection site were observed in that study. This tissue response at the injection site is considered an expected response to vaccines with aluminium-based adjuvants. In order to better elucidate the effect of the adjuvant, however, it would have been preferable to run a vehicle control group in parallel.

2.5.4.5. Other toxicity studies

No antigenicity, immunotoxicity and dependence studies, and no studies on metabolites and impurities were submitted. According to relevant guidance on non-clinical vaccine development, this is acceptable. Immunogenicity was assessed in the pharmacology studies and in several of the toxicity studies.

2.5.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment has not been submitted. The absence of an ERA for vaccines is in accordance with CHMP guidance EMEA/CHMP/SWP/4447/00 and therefore acceptable. Discussion on non-clinical aspects

2.5.6. Discussion on the non-clinical aspects

In general, the scope of the non-clinical programme is in line with applicable guidelines for the development of a vaccine and is considered adequate.

The vaccine lots used in non-clinical studies should be adequately representative of the formulation intended for clinical investigation and, ideally, should be the same lots as used in clinical studies. According to the Quality part of the dossier, minor differences are present in the analytical data for nonclinical toxicity study and clinical study drug product lots. However, they are not considered to impact the results of the respective studies.

Pharmacology studies conducted with mice, rats and rabbits demonstrated humoral and functional immunogenicity of 20vPnC and the monovalent conjugates of the seven new serotypes contained in it, respectively. In addition, rabbits receiving the full human dose of 20vPnC by two occasions elicited a robust humoral response that was both specific for PnPS and associated with functional killing of the bacterium.

The initial toxicity assessment for 20vPnC consisted of three GLP-compliant studies in rabbits, including a pivotal repeat-dose toxicity study, a fertility and developmental toxicity study and a local tolerance study. Following signs of cardiotoxicity in the pivotal toxicity study, a series of investigative studies was conducted to understand the potential causative factors of the heart findings observed in the pivotal toxicity study. The weight of evidence from these investigative activities indicates that the heart findings were not related to the vaccine conjugates or other vaccine components. This conclusion is based on several observations from the series of investigative studies and was supported by an external pathologist working group.

In the pivotal toxicity study in rabbits, injection site findings consisting of minimal to moderate chronic-active inflammation and degeneration/necrosis of myofibers as well as injection site reactogenicity were observed. The severity of these reactions in the 20vPnC-dosed animals was comparable to the vehicle group and all injection site findings and reactogenicity were considered non-adverse in this study. Microscopic findings of inflammation with degeneration/necrosis of cardiomyocytes and interstitial fibrosis in the heart were observed in three animals treated with 20vPnC.

The submission also contains a combined fertility and developmental study (including teratogenicity and postnatal investigations) in rabbits. Based on the results of this study, IM administration of 20vPnC before and during gestation to female rabbits did not cause maternal systemic toxicity. Further, there were no 20vPnC-related effects on mating performance or fertility in female rabbits or on embryo-foetal or postnatal survival, growth, or development in the F1 offspring.

In a local subcutaneous tolerance study in female rabbits, non-adverse erythema, oedema, and mass at the injection site were observed. This tissue response at the injection site is considered an expected response to vaccines with aluminium-based adjuvants

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical pharmacology studies provided evidence that 20vPnC induces functional antibody activity, which is expected to protect against pneumococcal infection.

The toxicity studies revealed local effects that can be expected for an aluminium-adjuvanted vaccine. Histopathologic findings in the hearts of rabbits were observed in the repeat-dose toxicity studies and were further examined in a serious of investigative studies. It is overall concluded that the findings were incidental, or stress induced and do not raise specific safety concerns.

From a non-clinical point of view, there are no objections against the market approval of 20vPnC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 2: 20vPnC Clinical Trials Included in the Submission

Trial (Countries)	Subject Age/Pneumococcal	Groups: Number of Subjects	Primary and Secondary Immunogenicity Objectives	Exploratory Objectives
B7471007 (USA, Sweden): Phase 3, multicentre, randomised, double-blind study with an age- based 3-cohort design	≥18 years of age / pneumococcal vaccine naïve	Cohort 1 (≥60 years) 20vPnC/saline: 1514 13vPnC/PPSV23: 1495 Cohort 2 (50-59 years) 20vPnC: 334 13vPnC: 111 Cohort 3 (18-49 years) 20vPnC: 336 13vPnC: 112	**Primary Objectives:** - To describe the safety profile of 20vPnC in adults 18 years of age (yoa) and older (all cohorts). - To demonstrate that the immune responses to the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) induced by 20vPnC in adults ≥60 yoa are non-inferior to the immune response induced by 13vPnC - To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults ≥60 yoa are non-inferior to the immune response induced by PPSV23 **Secondary Objectives:** - To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 yoa are non-inferior to the immune responses induced by 20vPnC in adults 60 through 64 yoa. - To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 yoa are non-inferior to the immune responses induced by 20vPnC in adults 60 through 64 yoa - To describe the immune responses to 20vPnC in adults ≥60 yoa and older, 50 through 59 years of age, and 18 through 49 yoa	To further describe the immune responses to 20vPnC, including cross- reactivity to serotype 15C, in adults ≥60 years of age, 50 through 59 years of age, and 18 through 49 years of age To describe the immune responses to the 20 serotypes induced by 20vPnC in adults ≥18 years of age with underlying medical conditions or other factors that put them at increased risk for serious pneumococcal infection (eg, asthma, diabetes mellitus, chronic lung disease, cigarette smoking)
B7471008 (USA): Phase 3, multicentre, randomised, double-blind, lot consistency study with a 4-arm parallel design	18-49 years of age / pneumococcal vaccine naïve	20vPnC Lot 1: 465 20vPnC Lot 2: 475 20vPnC Lot 3: 460 13vPnC: 235	**Primary Objective:** To describe the safety profile of 20vPnC. **Secondary Objectives:** To demonstrate that the immune responses to the 20 serotypes induced by 20vPnC are equivalent across 3 lots To describe the immune response to 20vPnC	To further describe the immune response induced by 20vPnC

B7471006 (USA, Sweden): Phase 3, multicentre, randomised, open-label study with a 3-cohort design based on prior pneumococcal vaccination status	≥65 years of age / <u>Cohort A</u>: vaccinated with PPSV23 ≥1 year and ≤5 years prior to vaccination in the study, and no prior 13vPnC vaccination <u>Cohort B:</u> vaccinated with 13vPnC ≥6 months prior to vaccination in the study, and no prior PPSV23 vaccination <u>Cohort C:</u> vaccinated with 13vPnC followed by PPSV23 (PPSV23 vaccination ≥1 year prior to vaccination in the study)	<u>Cohort A</u> 20vPnC: 253 13vPnC: 122 <u>Cohort B</u> 20vPnC: 248 13vPnC: 127 <u>Cohort C</u> 20vPnC: 125	**Primary Objectives:** To describe the safety profile of 20vPnC. To describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC, or previously vaccinated with both 13vPnC and PPSV23 **Secondary Objective:** To further describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC, or previously vaccinated with both 13vPnC and PPSV23	To further describe the immune responses induced by 20vPnC
B7471002 (USA): Phase 2, multicentre, randomised, active-controlled, double-blind study with a 2-arm parallel design	60-64 years of age / pneumococcal vaccine naïve	20vPnC/saline: 222 13vPnC/PPSV23: 222	**Primary Objective:** To describe the safety profile of 20vPnC in the study population. **Secondary Objective:** To describe the immunogenicity of 20vPnC in the study population	To further describe the immune responses induced by 20vPnC in the study population
B7471005 (USA): Phase 1b, randomised, controlled, double-blind study with a 3-arm parallel design, in adults of Japanese descent	18-49 years of age / pneumococcal vaccine naïve	20vPnC: 35 c7vPnC[a]: 34 13vPnC: 35	**Primary Objective:** To describe the safety profile of 20vPnC and c7vPnC in the study population. **Secondary Objective:** To describe the immunogenicity of 20vPnC and c7vPnC[a] in the study population	To further describe the immune responses induced by 20vPnC and c7vPnC[a] in the study population
B7471001 (USA): Phase 1, first-in-human, randomised, controlled, observer-blinded study with a 2-arm parallel design	18-49 years of age / pneumococcal vaccine naïve	20vPnC: 33 Tdap: 33	**Primary Objective:** To describe the safety profile of 20vPnC in adults. **Secondary Objective:** To describe the immune responses induced by 20vPnC in adults.	To further describe the immune responses induced by 20vPnC in adults

a. Data from subjects who received c7vPnC are not discussed in this submission. Assessor's note: c7vPnC (Phase 1b) = investigational complementary 7-valent pneumococcal conjugate vaccine (c7vPnC) that contains the 7 serotypes also targeted by 20vPnC but not by 13vPnC

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No clinical pharmacokinetic (PK) studies with 20vPnC were conducted as these studies are not routinely conducted as part of the evaluation of vaccines, as described in the CHMP "Guidance on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

2.6.2.2. Pharmacodynamics

Immunogenicity represents the PD effect of the vaccine. Results are described and assessed below in section 2.6.5.

Mechanism of action

20vPnC contains 20 pneumococcal capsular polysaccharides all conjugated to a CRM197 carrier protein, which modifies the immune response to the polysaccharide from a T-cell independent response to a T-cell dependent response. The T-cell dependent response leads to both an enhanced antibody response and generation of memory B cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria.

Vaccination with 20vPnC induces serum antibody production and immunologic memory against the serotypes contained within the vaccine.

In adults, the levels of circulating antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

Assays

In the clinical programme, vaccine-induced, serotype-specific immune responses in the form of opsonophagocytic activity (OPA) and IgG for all 20 serotypes included in 20vPnC were measured using microcolony OPA assay and direct-binding Luminex immunoassays (dLIA), respectively. Evaluation of serotype-specific OPA responses was the primary objective of the Phase 3 studies supporting licensure; evaluation of serotype-specific total IgG responses was only performed in the Phase 1 and 2 studies.

2.6.3. Discussion on clinical pharmacology

Vaccination with 20vPnC induces serum antibody production against 20 pneumococcal serotypes contained in the vaccine. Protection against pneumococcal disease is thought to be mediated by opsonophagocytic mechanisms.

No PK studies were conducted which is acceptable and in accordance with the respective EMA documents.

This MAA is based on an immune-bridging approach between 20vPnC and the previously licensed vaccines with known efficacy (13vPnC and PPSV23). The strategy relies on a comparative evaluation of induction of binding antibodies (Phase 1 & 2 studies) and functional opsonophagocytic antibodies (all clinical studies). As no correlate of protection against pneumococcal disease exists in adults, OPA GMTs are commonly used as surrogate thereof, which is endorsed. Immunogenicity represents the PD effect of the vaccine and is considered main evidence for this MAA since no efficacy studies were conducted (see Clinical Efficacy).

2.6.4. Conclusions on clinical pharmacology

Pivotal evidence for this Marketing Authorisation Application is based on induction of opsonophagocytic antibodies by 20vPnC compared to vaccination with authorised vaccines (13PnC and PPSV23), which is acceptable.

Microcolony OPA assays and direct-binding Luminex immunoassays (dLIA) were used to measure opsonophagocytic activity and IgG, respectively. The microcolony opsonophagocytic assay to detect functional antibodies is considered validated and fit for purpose.

2.6.5. Clinical efficacy (immunogenicity)

2.6.5.1. Dose response studies

No dose-finding studies were performed. 20vPnC contains the same number of pneumococcal polysaccharides per serotype as 13vPnC: 2.2 µg pneumococcal polysaccharide per serotype (4.4 µg for serotype 6B) per single dose of 0.5 mL IM.

Study B7471001 (Phase 1)

Study B7471001 was a phase 1 FIH, randomised, controlled (2-arm parallel design), observer-blinded trial, conducted at one site in the US to compare the safety and immunogenicity of 20vPnC to a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine (Adacel) in 66 healthy adults aged 18 to 49 years (randomised 1:1).

Baseline OPA GMTs of all 20 serotypes were generally similar in the 20vPnC and Tdap groups. There was an increase in OPA GMTs from Day 0 to 1 month after vaccination for all 20 serotypes only in the 20vPnC group. The OPA GMTs measured 1 month after vaccination were higher in the group receiving 20vPnC compared to Tdap with no overlap in 95% CIs. The results were confirmed with OPA GMFRs and the proportion of subjects with an OPA titre ≥ LLOQ. Similar results were observed with IgG GMCs and GMFRs, respectively.

2.6.5.2. Main studies

The immunogenicity data obtained in studies B7471007 and B7471006 are considered as the main evidence for this MAA. Combined, both studies represent the target population for pneumococcal vaccination.

Study B7471007, is the pivotal Phase 3, randomised, active-controlled, double-blind non-inferiority trial in pneumococcal vaccine naïve adults ≥18 years of age (with the majority ≥ 60 years of age). The study also includes non-immunocompromised participants with risk factors for pneumococcal disease. This study provides the main evidence for the immunological bridge via different steps represented by the primary and secondary objectives. Participants (target n= 3880) were enrolled in three cohorts and randomised to receive 20vPnC or control (13vPnC groups in Cohorts 2 and 3 were controls for safety only):

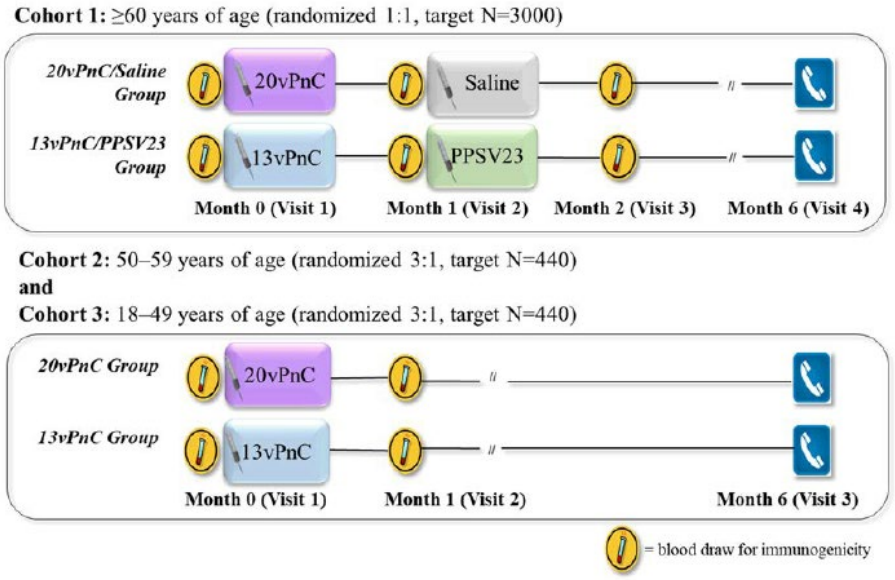

Figure 1: Design of study B7471007

Study B7471006 was a phase 3, randomised, multicentre, controlled, open-label trial to evaluate the safety and immunogenicity of 20vPnC in adults ≥65 years of age with prior pneumococcal vaccination.

Approximately 875 adults ≥65 years of age were targeted to be enrolled into three different cohorts (A, B, C) based on their prior pneumococcal vaccination history.

- Cohort A: Approximately 375 participants who had received PPSV23 ≥1 to ≤5 years previously but had not been vaccinated with 13vPnC were to be randomised (2:1) to receive either 20vPnC or 13vPnC (control for safety only).
- Cohort B: Approximately 375 participants who had received 13vPnC ≥6 months previously, but had not been vaccinated with PPSV23, were to be randomised (2:1) to receive either 20vPnC or PPSV23 (control for safety only).
- Cohort C: Approximately 125 participants who had previously received 13vPnC followed by PPSV23 (PPSV23 vaccination must have been given ≥1 year prior to vaccination in this study) were to receive 20vPnC.

Study B7471007: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Pneumococcal Vaccine–Naïve Adults 18 Years of Age and Older

Study B7471006: A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Adults ≥65 Years of Age With Prior Pneumococcal Vaccination

Methods

- **Study Participants**

The inclusion and exclusion criteria were designed to include the following populations:

B7471007: Pneumococcal Vaccine-Naïve Adults ≥18 Years of Age

B7471006: Adults with prior pneumococcal vaccination (13vPnC and/or PPSV23) ≥65 Years of Age

- **Treatments**

Investigational Product: 20vPnC (Apexxnar)

Control Products

13vPnC (Prevenar13): Prevenar 13 contains the same serotypes (in the same amount) and excipients as 20vPnC. It is approved in the EU for the adult population since 2011.

PPSV23 (PNEUMOVAX23): PPSV23 is an unconjugated polysaccharide vaccine. It is nationally approved in the EU since the 1980's. The 0.5 mL dose of vaccine contains 25 micrograms of each of the following 23 pneumococcal polysaccharide serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. Further excipients are phenol and sodium chloride. All seven serotypes additionally included in 20vPnC compared to 13vPnC are included in PPSV23.

Table 3: Treatments used in main clinical studies (all given as 0.5 mL single dose, IM)

Study Code	**Key subject elements**	**Treatments, Planned Sample Size, Randomisation, Timing of Treatment**
B7471007 (pivotal)	Pneumococcal vaccine-naïve adults ≥18 yoa Cohort 1: ≥ 60 yoa Cohort 2: 50-59 yoa Cohort 3: 18-49 yoa	Cohort 1: n= 3000 (1:1, 20vPnC/saline vs 13vPnC/PPSV23); saline or PPSV23 given 1 month after 20vPnC or 13vPnC, respectively Cohort 2: n= 440 (3:1, 20vPnC vs 13vPnC[a]) Cohort 3: n= 440 (3:1, 20vPnC vs 13vPnC[a])
B7471006	Adults ≥ 65 yoa with prior pneumococcal vaccination Cohort A: PPSV23 1-5 years previously Cohort B: 13vPnC ≥6 months previously Cohort C: 13vPnC followed by PPSV23; PPSV23 ≥1 year previously	Cohort A: n= 375 (2:1, 20vPnC vs 13vPnC[a]) Cohort B: n= 375 (2:1, 20vPnC vs PPSV23[a]) Cohort C: n= 125 (20vPnC only) All treatments were given at visit 1.

[a] control for safety only

- **Objectives**

B7471007 Pneumococcal vaccine-naïve adults ≥18 yoa (pivotal);

Primary Immunogenicity Objectives (Cohort 1, ≥60 yoa):

- To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC in adults 60 years of age and older are non-inferior (lower bound of 2-sided 95% CI for OPA GMR >0.5 [2-fold NI margin]) to the immune response induced by 13vPnC.
- To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 years of age and older are non-inferior (lower bound of 2-sided 95% CI for OPA GMR >0.5 [2-fold NI margin]) to the immune response induced by PPSV23.

Secondary Immunogenicity Objective (Cohort 2, 50-59 yoa):

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 years of age are non-inferior (lower bound of 2-sided 95% CI for OPA GMR >0.5 [2-fold NI margin]) to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

Secondary Immunogenicity Objective (Cohort 3, 18-49 yoa):

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 years of age are non-inferior (lower bound of 2-sided 95% CI for OPA GMR >0.5 [2-fold NI margin]) to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

Secondary Immunogenicity Objective (all Cohorts):

- To describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age.

Exploratory Immunogenicity Objectives (all Cohorts):

- To further describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age.
- To describe the immune responses to the 20 serotypes induced by 20vPnC in adults 18 years of age and older with underlying medical conditions or other factors that put them at increased risk for serious pneumococcal infection (e.g., asthma, diabetes mellitus, chronic lung disease, cigarette smoking).

B7471006 Adults ≥ 65 yoa with prior pneumococcal vaccination; open label

Primary Immunogenicity Objective:

- To describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC or previously vaccinated with both (13vPnC and PPSV23).

Secondary Immunogenicity Objective:

- To further describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC or previously vaccinated with both (13vPnC and PPSV23).

Exploratory Immunogenicity Objective:

- To further describe the immune responses induced by 20vPnC.

- **Outcomes/endpoints**

B7471007 Pneumococcal vaccine-naïve adults ≥18 yoa (pivotal); (Cohort 1: ≥60 yoa, Cohort 2: 50-59 yoa, Cohort 3: 18-49 yoa); double-blind

Primary Immunogenicity Endpoint (Cohort 1, ≥60 yoa):

- Serotype-specific OPA titres 1 month after vaccination.

Secondary Immunogenicity Endpoints (Cohort 2, 50-59 yoa; Cohort 3, 18-49 yoa):

- Serotype-specific OPA titres 1 month after vaccination.

Secondary Immunogenicity Endpoints (all Cohorts):

- Fold rise in serotype-specific OPA titres from before to 1 month after vaccination.
- ≥4-Fold rise in serotype-specific OPA titres from before to 1 month after vaccination.
- Serotype-specific OPA titres ≥ LLOQ 1 month after vaccination.

Exploratory Immunogenicity Endpoints (all Cohorts):

- ≥4-Fold rise in pneumococcal serotype 15C OPA titre from before to 1 month after vaccination.
- Pneumococcal serotype 15C OPA titre ≥ LLOQ 1 month after vaccination.
- Pneumococcal serotype 15C OPA titre 1 month after vaccination.
- Fold rise in pneumococcal serotype 15C OPA titre from before to 1 month after vaccination.
- Serotype-specific OPA titres 1 month after vaccination (for participants with an increased risk for serious pneumococcal infection).

B7471006 Adults ≥ 65 yoa with prior pneumococcal vaccination; open label

Primary Immunogenicity Endpoint:

- Pneumococcal serotype-specific OPA titres 1 month after vaccination.

Secondary Immunogenicity Endpoints:

- Fold rise in serotype-specific OPA titres from before to 1 month after vaccination.
- ≥4-Fold rise in serotype-specific OPA titres from before to 1 month after vaccination.
- Serotype-specific OPA titres ≥ LLOQ 1 month after vaccination.

Exploratory Immunogenicity Endpoints:

- ≥4-Fold rise in pneumococcal serotype 15C OPA titres from before to 1 month after vaccination.
- Pneumococcal serotype 15C OPA titre ≥ LLOQ 1 month after vaccination.
- Pneumococcal serotype 15C OPA titre 1 month after vaccination.
- Fold rise in pneumococcal serotype 15C OPA titre from before to 1 month after vaccination.

- **Randomisation and Blinding (masking)**

Randomisation:

B7471007 (pivotal study): Allocation of subjects to vaccine groups used a centre-based interactive response technology (IRT) system (interactive web-based response [IWR]) within the age cohorts.

B7471006: A centre-based interactive response technology system (interactive Web-based response) was used to randomize participants to either 20vPnC or control vaccine group in Cohort A and Cohort B. Every participant received 20vPnC in Cohort C.

Blinding:

Study **B7471006** was an open-label study.

B7471007 (pivotal study): The study was sponsor, participant, and investigator blinded. Vaccination 1 was to be administered in a double-blind fashion, as the appearance and prefilled syringes of 20vPnC and 13vPnC were identical. At Vaccination 2 (Cohort 1 only), the PI was supposed to assign the responsibility of administering saline and PPSV23 to third-party unblinded site staff who was not to participate in the evaluation of any study subject.

- **Statistical methods**

B7471007: Analysis sets

Immunogenicity Populations

Three evaluable immunogenicity populations were defined for the analyses of the immunogenicity data: the evaluable 13-matched immunogenicity population (Cohort 1), the evaluable 7-additional immunogenicity population (Cohort 1), and the evaluable-20 immunogenicity population. In addition, the all-available immunogenicity population was defined as well.

Subjects were to be included in the vaccine group as randomised.

All-Available Immunogenicity Population

This population included all participants who received at least 1 dose of 20vPnC, 13vPnC, PPSV23, or saline and had at least 1 valid and determinate OPA titre after any vaccination. For cohort-specific analysis, the need for all-available tables was assessed separately within each cohort. Only the evaluable population was used for the immunogenicity analyses if there was less than a 5% difference in sample size between the all-available and evaluable populations, (ie, if the evaluable sample size was ≥95% of the all-available sample size).

For the cross-cohort analysis where Cohort 2 or Cohort 3 was being compared to the participants 60 through 64 years of age in Cohort 1, if either cohort in the comparison had less than a 5% difference in sample size between the all-available and evaluable populations (ie, if the evaluable sample size was ≥95% of the all-available sample size), analyses would be based on the evaluable populations only.

Evaluable 13-Matched Immunogenicity Population, Evaluable 7-Additional Immunogenicity Population and Evaluable-20 Immunogenicity Population

The applicant defined specific primary analysis populations for immunogenicity results of the serotypes included in the respective analysis. The populations are defined similarly based on valid respective OPA titres, appropriate randomisation and vaccination(s) etc. (for detailed definitions of the analysis sets please refer to the clinical AR).

Safety population

The safety population will include any subject who:

1. receives 1 dose of any of the following: 20vPnC, 13vPnC, PPSV23, or saline; and

2. has safety follow-up after any vaccination.

Subjects will be included in the vaccine group corresponding to the vaccine actually received. The safety population will be the analysis population for safety and reactogenicity endpoints.

Primary Immunogenicity objective

Hypothesis testing was planned to be performed to assess noninferiority comparing the 20vPnC/saline vaccine group against the 13vPnC/PPSV23 vaccine group in Cohort 1 for each of the 20 serotype-specific OPA titres. The null hypothesis for each serotype specific OPA titre was:

$$H_0: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

where

- ln(0.5) corresponds to a 2-fold margin for noninferiority.
- $\ln(\mu_A)$ is the natural log of the geometric mean OPA titre 1 month after 20vPnC administration for the 20vPnC/saline group.
- $\ln(\mu_B)$ is the natural log of the geometric mean OPA titre 1 month after 13vPnC administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titre from 1 of the shared 13 serotypes in 13vPnC, or,
- $\ln(\mu_B)$ is the natural log of the geometric mean OPA titre 1 month after PPSV23 administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titre from 1 of the 7 additional serotypes.

The primary analysis approach was to be based on a linear regression model. For the comparison of OPA results in Cohort 1, the following terms will be included in the regression model: corresponding baseline OPA titre, age, sex (male or female), smoking status (current smoker, ex-smoker, never smoked), and vaccine group. The difference between these least squares (LS) means on the natural log scale and associated CI estimated from the linear regression model was to be transformed back to the original scale to obtain the GMR and CI. 2-sided 95% CIs were to be used for the noninferiority comparisons of the 20vPnC/saline group to the 13vPnC/PPSV23 group.

As a sensitivity/robustness analysis, the unadjusted serotype-specific OPA GMR and 95%-CI was also planned to be calculated for each of the serotypes by calculating differences in means and 95% CIs on the natural log scale based on the t-distribution, then exponentiating the results.

After the noninferiority between the 20vPnC/saline and 13vPnC/PPSV23 vaccine groups in Cohort 1 for each of the 7 additional serotypes was established, superiority of serotype-specific OPA titres comparing 20vPnC/saline to 13vPnC/PPSV23 was planned to be evaluated for the 7 additional serotypes. The 7 superiority hypotheses were planned to be tested at a 0.025 level (1-sided) with Hochberg's step-up procedure to control the type I error rate. Since the superiority hypotheses for the 7 additional serotypes were planned to be tested only after the noninferiority was achieved for the 7 serotypes, the familywise type I error rate for all hypothesis assessments in Cohort 1 was considered well controlled.

For Cohort 1, subgroup analyses by age group (60 through 64, 65 through 69, 70 through 79, and ≥80 years of age), sex (male and female), and race (white, African American, and others [the rest combined]) for the following immunogenicity endpoints were planned to be performed:

- Serotype-specific OPA GMTs and the associated 95% CIs at baseline and 1 month after vaccination.
- GMFRs and the associated 95% CIs in serotype specific OPA titres from before to 1 month after vaccination.
- Proportion and the associated 95% CIs of subjects with a ≥4-fold rise in serotype-specific OPA titres from before to 1 month after vaccination.
- Proportion and the associated 95% CIs of subjects with serotype specific OPA titres ≥ LLOQ before and 1 month after vaccination.

Additionally, serotype specific OPA GMTs and the associated 95% CIs at baseline and 1 month after vaccination were planned to be summarised by country for subjects ≥65 years of age from Cohort 1.

Secondary Immunogenicity objective

Hypothesis testing was also planned to be performed to assess noninferiority comparing the 20 serotype-specific OPA titres 1 month after vaccination in each of the 20vPnC groups in the younger cohorts (subjects 50 through 59 years of age in Cohort 2 and subjects 18 through 49 years of age in Cohort 3) against subjects 60 through 64 years of age from Cohort 1 one month after vaccination in the 20vPnC/saline group. Again, a 2-fold margin was planned to be used for each of the noninferiority hypothesis tests. The null hypothesis for each serotype specific OPA titre was:

$$H_0: \ln(\mu_C) - \ln(\mu_A) \leq \ln(0.5)$$

where

- ln(0.5) corresponds to a 2-fold margin for noninferiority.
- $\ln(\mu_C)$ is the natural log of the geometric mean OPA titre 1 month after 20vPnC administration for the younger group, subjects 50 through 59 years of age (Cohort 2) or subjects 18 through 49 years of age (Cohort 3).
- $\ln(\mu_A)$ is the natural log of the geometric mean OPA titre 1 month after 20vPnC administration for subjects 60 through 64 years of age from Cohort 1.

The analysis approach was planned to be based on a linear regression model. The following terms were to be included in the regression model: corresponding baseline OPA titre, sex (male or female), smoking status (current smoker, ex-smoker, never smoked), and cohort. Two separate regression models were to be fitted, one for comparing Cohort 2 results to Cohort 1 (subjects 60 through 64 years of age) results, and the other for comparing Cohort 3 results to Cohort 1 (subjects 60 through 64 years of age) results. Only the OPA data from the 20vPnC/saline group in Cohort 1 (subjects 60 through 64 years of age) and the OPA data from the 20vPnC group in Cohort 2/Cohort 3 were to be included in the regression models.

The difference between these least squares (LS) means on the natural log scale and associated CI estimated from the linear regression model were to be transformed back to the original scale to obtain the GMR and CI. 2-sided 95% CIs were to be used for the noninferiority comparison of the 20vPnC group from Cohort 2/Cohort 3 to the 20vPnC/saline group from subjects 60 through 64 years of age in Cohort 1.

Like in the primary analysis setting, as a sensitivity/robustness analysis, the unadjusted serotype-specific OPA GMR and 95%-CI was also planned to be calculated for each of the serotypes by calculating differences in means and 95% CIs on the natural log scale based on the t-distribution, then exponentiating the results.

In the SAP it was noted that these secondary noninferiority assessments comparing the younger age groups (Cohort 3 [subjects 18 through 49 years of age] or Cohort 2 [subjects 50 through 59 years of age]) to the subjects 60 through 64 years of age in Cohort 1 were considered meaningful only after the establishment of overall comparability between 20vPnC and the corresponding controls in Cohort 1. Therefore, there no increase in the type I error rate was formally seen at the planning stage, and no type I error adjustments were seen needed in the immunogenicity assessments for the 2 younger age cohorts (Cohort 2 or Cohort 3).

For Cohort 2 and Cohort 3, subgroup analyses by sex (male and female) and race (white, African American, and others [the rest combined]) for serotype-specific GMTs and the associated 95% CIs were planned to be provided for the 20vPnC group only at both baseline and 1 month after vaccination.

Further secondary and exploratory immunogenicity endpoints and interim analysis

B7471006: Analysis sets

Safety population

The safety population was to include any subject who received 1 dose of 20vPnC, PPSV23, or 13vPnC and had safety follow-up after vaccination. Subjects were to be included in the vaccine group corresponding to the vaccine actually received. The safety population was planned to be used as the analysis population for safety and reactogenicity endpoints.

Evaluable Immunogenicity Populations

The evaluable immunogenicity population was planned to include any subject who

- receives 20vPnC as randomised,

- is enrolled in the appropriate cohort based on prior pneumococcal vaccination history,

- has the Visit 2 blood collection within 27 to 49 days after vaccination,

- has at least 1 valid and determinate OPA titre for any serotype for Visit 2, and

- does not have any other major protocol deviations as determined by the clinician.

The evaluable immunogenicity population was planned to be the primary analysis population for immunogenicity results.

All-available Immunogenicity Populations

The all-available immunogenicity population was planned to include all subjects who receive 20vPnC, and had at least 1 valid and determinate OPA titre 1 month after vaccination. The all-available immunogenicity population was planned to be the secondary analysis population for immunogenicity analysis. Only the evaluable population was to be used for the summary of immunogenicity results if there was less than a 10% difference in sample size between the all-available and evaluable populations.

Statistical analysis methods

Safety/reactogenicity results were summarised by standard statistical analysis methods as described in detail in the SAP, separately for each cohort.

Immunogenicity results of serotype specific OPA titres were to be determined only for subjects who received 20vPnC in each cohort as subjects who received 13vPnC or PPSV23 were included in the study served as the control for safety. Immunogenicity results from the 20vPnC groups were to be summarised side by side from all 3 cohorts. For immunogenicity results of serotype-specific OPA titres, geometric mean titres (GMTs) as well as geometric mean-fold rises (GMFR) were to be computed along with associated 95% CIs.

Standard descriptive statistical methodology was pre-planned to summarise: Subject disposition, demographic characteristics, prior vaccination status, and medical history.

Results

- **Participant flow**

Table 4: Study B7471007 Disposition of All Subjects – Cohort 1 – All Randomised

	Vaccine Group (as Randomized)		
	20vPnC/Saline n[a] (%)	13vPnC/PPSV23 n[a] (%)	Total n[a] (%)
Randomized[b]	1514 (100.0)	1495 (100.0)	3009 (100.0)
Not vaccinated	7 (0.5)	5 (0.3)	12 (0.4)
Vaccinated			
Vaccination 1	1507 (99.5)	1490 (99.7)	2997 (99.6)
Vaccination 2[c]	1461 (96.5)	1446 (96.7)	2907 (96.6)
Completed 1-month follow-up after Vaccination 2/Visit 3	1441 (95.2)	1428 (95.5)	2869 (95.3)
Completed study	1418 (93.7)	1417 (94.8)	2835 (94.2)
Withdrawn from study	96 (6.3)	78 (5.2)	174 (5.8)
Reason for withdrawal			
Adverse event	11 (0.7)	8 (0.5)	19 (0.6)
Death	1 (0.0)	0	1 (0.0)
Lost to follow-up	41 (2.7)	28 (1.9)	69 (2.3)
No longer meets eligibility criteria	3 (0.2)	9 (0.6)	12 (0.4)
Protocol deviation	21 (1.4)	13 (0.9)	34 (1.1)
Withdrawal by subject	19 (1.3)	20 (1.3)	39 (1.3)

a. n=Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Includes a subject who was erroneously injected with a non-protocol defined investigational product at Vaccination 2.

Table 5: Study B7471007 Disposition of All Subjects – Cohort 2 – All Randomised

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	334 (100.0)	111 (100.0)	445 (100.0)
Not vaccinated	0	0	0
Vaccinated	334 (100.0)	111 (100.0)	445 (100.0)
Completed 1-month follow up after vaccination/Visit 2	330 (98.8)	110 (99.1)	440 (98.9)
Completed study	323 (96.7)	109 (98.2)	432 (97.1)
Withdrawn from study	11 (3.3)	2 (1.8)	13 (2.9)
Reason for withdrawal			
Lost to follow-up	9 (2.7)	2 (1.8)	11 (2.5)
Protocol deviation	1 (0.3)	0	1 (0.2)
Withdrawal by subject	1 (0.3)	0	1 (0.2)

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.

Table 6: Study B7471007 Disposition of All Subjects – Cohort 3 – All Randomised

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	336 (100.0)	112 (100.0)	448 (100.0)
Not vaccinated	1 (0.3)	0	1 (0.2)
Vaccinated	335 (99.7)	112 (100.0)	447 (99.8)
Completed 1-month follow up after vaccination/Visit 2	325 (96.7)	109 (97.3)	434 (96.9)
Completed study	319 (94.9)	104 (92.9)	423 (94.4)
Withdrawn from study	17 (5.1)	8 (7.1)	25 (5.6)
Reason for withdrawal			
Lost to follow-up	14 (4.2)	8 (7.1)	22 (4.9)
No longer meets eligibility criteria	1 (0.3)	0	1 (0.2)
Protocol deviation	1 (0.3)	0	1 (0.2)
Withdrawal by subject	1 (0.3)	0	1 (0.2)

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.

Table 7: Study B7471006 Disposition of All Subjects – All Randomised

	Vaccine Group (as Randomized)						
	Cohort A			Cohort B			Cohort C
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)	20vPnC n[a] (%)	PPSV23 n[a] (%)	Total n[a] (%)	20vPnC n[a] (%)
Randomized[b]	253 (100.0)	122 (100.0)	375 (100.0)	248 (100.0)	127 (100.0)	375 (100.0)	125 (100.0)
Not vaccinated	0	0	0	2 (0.8)	0	2 (0.5)	0
Vaccinated	253 (100.0)	122 (100.0)	375 (100.0)	246 (99.2)	127 (100.0)	373 (99.5)	125 (100.0)
Completed 1-month follow-up after vaccination	251 (99.2)	120 (98.4)	371 (98.9)	245 (98.8)	127 (100.0)	372 (99.2)	125 (100.0)
Completed study	250 (98.8)	119 (97.5)	369 (98.4)	245 (98.8)	126 (99.2)	371 (98.9)	125 (100.0)
Withdrawn from study	3 (1.2)	3 (2.5)	6 (1.6)	3 (1.2)	1 (0.8)	4 (1.1)	0
Reason for withdrawal							
Lost to follow-up	1 (0.4)	1 (0.8)	2 (0.5)	0	0	0	0
No longer meets eligibility criteria	0	1 (0.8)	1 (0.3)	0	0	0	0
Protocol deviation	1 (0.4)	1 (0.8)	2 (0.5)	2 (0.8)	0	2 (0.5)	0
Withdrawal by subject	1 (0.4)	0	1 (0.3)	1 (0.4)	1 (0.8)	2 (0.5)	0

a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.

- **Baseline data**

Table 8: Study B7471007 Demographic Characteristics and Smoking History – Cohort 1 – Safety Population

	Vaccine Group (as Administered)		
	20vPnC/Saline (N[a]=1507) n[b] (%)	13vPnC/PPSV23 (N[a]=1490) n[b] (%)	Total (N[a]=2997) n[b] (%)
Sex			
Male	610 (40.5)	611 (41.0)	1221 (40.7)
Female	897 (59.5)	879 (59.0)	1776 (59.3)
Race			
White	1295 (85.9)	1237 (83.0)	2532 (84.5)
Black or African American	177 (11.7)	212 (14.2)	389 (13.0)
Asian	19 (1.3)	15 (1.0)	34 (1.1)
American Indian or Alaska Native	6 (0.4)	9 (0.6)	15 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.0)	1 (0.0)	2 (0.0)
Multiracial	7 (0.5)	9 (0.6)	16 (0.5)
Not reported	2 (0.1)	7 (0.5)	9 (0.3)
Ethnicity			
Hispanic/Latino	167 (11.1)	169 (11.3)	336 (11.2)
Non-Hispanic/non-Latino	1324 (87.9)	1308 (87.8)	2632 (87.8)
Not reported	16 (1.1)	13 (0.9)	29 (1.0)
Age group			
60 to 64 Years	993 (65.9)	992 (66.6)	1985 (66.2)
65 to 69 Years	319 (21.2)	305 (20.5)	624 (20.8)
70 to 79 Years	160 (10.6)	159 (10.7)	319 (10.6)
≥80 Years	35 (2.3)	34 (2.3)	69 (2.3)
Age at Vaccination 1 (years)			
Mean (SD)	64.6 (4.82)	64.6 (4.81)	64.6 (4.82)
Median	63.0	63.0	63.0
Min, max	(60, 91)	(60, 89)	(60, 91)
Smoking History			
Current smoker	170 (11.3)	192 (12.9)	362 (12.1)
Time since the current smoker started smoking (years)			
Mean (SD)	38.4 (15.36)	37.4 (14.44)	37.9 (14.86)
Median	43.7	42.3	42.8
Min, max	(0.2, 62.8)	(0.4, 67.7)	(0.2, 67.7)
Ex-smoker	446 (29.6)	472 (31.7)	918 (30.6)
Time since the ex-smoker stopped smoking (years)			
Mean (SD)	23.5 (14.62)	24.7 (14.84)	24.1 (14.74)
Median	22.8	25.6	23.8
Min, max	(0.1, 59.6)	(0.0, 56.4)	(0.0, 59.6)
Never smoked	891 (59.1)	826 (55.4)	1717 (57.3)

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

Table 9: Study B7471007 Demographic Characteristics and Smoking History – Cohort 2 – Safety Population

	Vaccine Group (as Administered)		
	20vPnC (N^a=334) n^b (%)	13vPnC (N^a=111) n^b (%)	Total (N^a=445) n^b (%)
Sex			
Male	139 (41.6)	42 (37.8)	181 (40.7)
Female	195 (58.4)	69 (62.2)	264 (59.3)
Race			
White	278 (83.2)	90 (81.1)	368 (82.7)
Black or African American	35 (10.5)	15 (13.5)	50 (11.2)
Asian	10 (3.0)	2 (1.8)	12 (2.7)
American Indian or Alaska Native	0	3 (2.7)	3 (0.7)
Multiracial	6 (1.8)	1 (0.9)	7 (1.6)
Not reported	5 (1.5)	0	5 (1.1)
Ethnicity			
Hispanic/Latino	12 (3.6)	8 (7.2)	20 (4.5)
Non-Hispanic/non-Latino	319 (95.5)	101 (91.0)	420 (94.4)
Not reported	3 (0.9)	2 (1.8)	5 (1.1)
Age at vaccination (years)			
Mean (SD)	54.9 (2.77)	55.0 (3.11)	54.9 (2.85)
Median	55.0	56.0	55.0
Min, max	(50, 59)	(48, 59)	(48, 59)
Smoking History			
Current smoker	52 (15.6)	17 (15.3)	69 (15.5)
Time since the current smoker started smoking (years)			
Mean (SD)	31.6 (11.42)	28.7 (13.54)	30.9 (11.94)
Median	35.6	30.7	34.7
Min, max	(1.7, 48.7)	(0.6, 50.6)	(0.6, 50.6)
Ex-smoker	67 (20.1)	22 (19.8)	89 (20.0)
Time since the ex-smoker stopped smoking (years)			
Mean (SD)	18.5 (11.57)	18.8 (13.30)	18.5 (11.94)
Median	19.7	19.6	19.7
Min, max	(0.5, 41.6)	(0.1, 40.6)	(0.1, 41.6)
Never smoked	215 (64.4)	72 (64.9)	287 (64.5)

Note: One Subject was incorrectly enrolled in Cohort 2 (50-59 years of age), rather than in Cohort 3 (18-49 years of age),and is included in the cohort 2 data analysis.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n=Number of subjects with the specified characteristic.

Table 10: Study B7471007 Demographic Characteristics and Smoking History – Cohort 3 – Safety Population

Sex			
Male	121 (36.1)	35 (31.3)	156 (34.9)
Female	214 (63.9)	77 (68.8)	291 (65.1)
Race			
White	274 (81.8)	101 (90.2)	375 (83.9)
Black or African American	34 (10.1)	7 (6.3)	41 (9.2)
Asian	11 (3.3)	1 (0.9)	12 (2.7)
American Indian or Alaska Native	1 (0.3)	1 (0.9)	2 (0.4)
Native Hawaiian or other Pacific Islander	3 (0.9)	1 (0.9)	4 (0.9)
Multiracial	8 (2.4)	1 (0.9)	9 (2.0)
Not reported	4 (1.2)	0	4 (0.9)
Ethnicity			
Hispanic/Latino	24 (7.2)	7 (6.3)	31 (6.9)
Non-Hispanic/non-Latino	300 (89.6)	102 (91.1)	402 (89.9)
Not reported	11 (3.3)	3 (2.7)	14 (3.1)
Age at vaccination (years)			
Mean (SD)	34.0 (8.77)	33.9 (8.03)	34.0 (8.58)
Median	34.0	32.0	33.0
Min, max	(18, 60)	(19, 49)	(18, 60)
Smoking History			
Current smoker	49 (14.6)	22 (19.6)	71 (15.9)
Time since the current smoker started smoking (years)			
Mean (SD)	14.8 (8.88)	13.5 (8.99)	14.4 (8.87)
Median	13.6	15.1	13.6
Min, max	(0.2, 34.5)	(0.1, 33.6)	(0.1, 34.5)
Ex-smoker	47 (14.0)	22 (19.6)	69 (15.4)
Time since the ex-smoker stopped smoking (years)			
Mean (SD)	8.1 (6.92)	6.8 (5.85)	7.7 (6.58)
Median	6.6	5.6	6.6
Min, max	(0.3, 25.5)	(0.5, 20.6)	(0.3, 25.5)
Never smoked	239 (71.3)	68 (60.7)	307 (68.7)

Note: One Subject was incorrectly enrolled in Cohort 3 (18-49 years of age), rather than in Cohort 1 (≥60 years of age), and is included in he Cohort 3 data analysis.
a. N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n=Number of subjects with the specified characteristic.

In study B7471007 the following frequencies of subjects with one or more risk factor(s) other than smoking (evaluable 13-Matched Immunogenicity Population for Cohort 1 and evaluable 20-Matched Immunogenicity Population for Cohorts 2 and 3) were reported: Cohort 1: 20vPnC/Saline (354/1435; 24.7%) vs 13vPnC/PPSV23 (404/1420; 28.5%). Cohort 2: 20vPnC (65/321; 20.2%) vs 13vPnC (21/108; 19.4%). Cohort 3: 20vPnC (39/317; 12.3%) vs 13vPnC (13/106; 12.3%). The three most common medical conditions or disease with multiple medical conditions reported (with total frequencies in brackets for cohorts 1, 2 and 3, respectively) were Type 2 diabetes mellitus (14.3%, 11.5%, 2.8%), asthma (6.1%, 5.6%, 7.6%) and chronic cardiovascular disease (4.9%, 3.7%, 0.9%).

Table 11: Study B7471006 Demographic Characteristics and Smoking History- Safety Population

	Vaccine Group (as Administered)						
	Cohort A			Cohort B			Cohort C
	20vPnC (N[a]=253)	13vPnC (N[a]=122)	Total (N[a]=375)	20vPnC (N[a]=246)	PPSV23 (N[a]=127)	Total (N[a]=373)	20vPnC (N[a]=125)
	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Sex							
Male	113 (44.7)	58 (47.5)	171 (45.6)	108 (43.9)	59 (46.5)	167 (44.8)	60 (48.0)
Female	140 (55.3)	64 (52.5)	204 (54.4)	138 (56.1)	68 (53.5)	206 (55.2)	65 (52.0)
Race							
White	236 (93.3)	110 (90.2)	346 (92.3)	226 (91.9)	118 (92.9)	344 (92.2)	117 (93.6)
Black or African American	15 (5.9)	8 (6.6)	23 (6.1)	14 (5.7)	6 (4.7)	20 (5.4)	4 (3.2)
Asian	1 (0.4)	2 (1.6)	3 (0.8)	0	2 (1.6)	2 (0.5)	0
American Indian or Alaskan Native	1 (0.4)	0	1 (0.3)	1 (0.4)	0	1 (0.3)	0
Native Hawaiian or other Pacific Islander	0	1 (0.8)	1 (0.3)	1 (0.4)	1 (0.8)	2 (0.5)	0
Multiracial	0	0	0	1 (0.4)	0	1 (0.3)	3 (2.4)
Not reported	0	1 (0.8)	1 (0.3)	3 (1.2)	0	3 (0.8)	1 (0.8)
Ethnicity							
Hispanic/Latino	4 (1.6)	3 (2.5)	7 (1.9)	6 (2.4)	1 (0.8)	7 (1.9)	2 (1.6)
Non-Hispanic/non-Latino	247 (97.6)	117 (95.9)	364 (97.1)	231 (93.9)	122 (96.1)	353 (94.6)	113 (90.4)
Not reported	2 (0.8)	2 (1.6)	4 (1.1)	9 (3.7)	4 (3.1)	13 (3.5)	10 (8.0)
Country							
USA	163 (64.4)	79 (64.8)	242 (64.5)	246 (100.0)	127 (100.0)	373 (100.0)	125 (100.0)
Sweden	90 (35.6)	43 (35.2)	133 (35.5)	0	0	0	0
Age group							
65 to 69 years	143 (56.5)	63 (51.6)	206 (54.9)	136 (55.3)	72 (56.7)	208 (55.8)	70 (56.0)
70 to 79 years	105 (41.5)	57 (46.7)	162 (43.2)	86 (35.0)	43 (33.9)	129 (34.6)	47 (37.6)
≥80 years	5 (2.0)	2 (1.6)	7 (1.9)	24 (9.8)	12 (9.4)	36 (9.7)	8 (6.4)
Age at vaccination (years)							
Mean (SD)	69.6 (3.88)	70.2 (4.09)	69.8 (3.96)	70.7 (5.71)	70.6 (5.73)	70.7 (5.71)	70.8 (4.26)
Median	69.0	69.0	69.0	68.0	68.0	68.0	69.0
Min, Max	(65, 84)	(65, 80)	(65, 84)	(65, 92)	(65, 90)	(65, 92)	(65, 81)
Smoking History							
Current smoker	24 (9.5)	7 (5.7)	31 (8.3)	13 (5.3)	6 (4.7)	19 (5.1)	5 (4.0)
Time since the current smoker started smoking (years)							
Mean (SD)	46.2 (13.68)	39.6 (18.13)	44.7 (14.74)	37.5 (16.86)	47.5 (6.23)	40.6 (14.94)	50.9 (7.02)
Median	49.1	47.1	49.0	43.7	47.8	45.7	51.7
Min, max	(2.0, 63.0)	(1.9, 56.1)	(1.9, 63.0)	(2.7, 52.8)	(39.6, 57.2)	(2.7, 57.2)	(43.7, 58.7)
Ex-smoker	94 (37.2)	43 (35.2)	137 (36.5)	95 (38.6)	36 (28.3)	131 (35.1)	43 (34.4)
Time since the ex-smoker stopped smoking (years)							
Mean (SD)	24.7 (14.31)	26.0 (14.93)	25.1 (14.46)	27.8 (15.58)	30.8 (14.70)	28.6 (15.35)	33.4 (15.44)
Median	25.1	24.9	24.9	25.7	30.7	27.7	33.8
Min, max	(0.1, 52.0)	(0.3, 52.0)	(0.1, 52.0)	(0.1, 62.6)	(4.9, 55.6)	(0.1, 62.6)	(3.8, 58.7)
Never smoked	135 (53.4)	72 (59.0)	207 (55.2)	138 (56.1)	85 (66.9)	223 (59.8)	77 (61.6)

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

- **Outcomes and estimation**

Study B7471007

In total 3902 participants were enrolled in the following cohorts based on age:

- Cohort 1: subjects ≥ 60 yoa (n=3009; randomised 1:1 to receive either 20vPnC/saline or 13vPnC/PPSV23)
- Cohort 2: 50-59 yoa (n=445; randomised 3:1 to receive 20vPnC or 13vPnC)
- Cohort 3: 18-49 yoa (n=448; randomised 3:1 to receive 20vPnC or 13vPnC)

Primary objectives: Non-inferiority of 20vPnC to comparator in adults ≥60 years of age (Cohort 1)

13 shared serotypes:

20vPnC met the primary immunogenicity objective for the 13 matched vaccine serotypes. One month after 20vPnC or 13vPnC, the immune responses to all 13 matched serotypes induced by 20vPnC were non-inferior to those induced by 13vPnC, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC relative to 13vPnC group) >0.5 (2-fold NI margin).

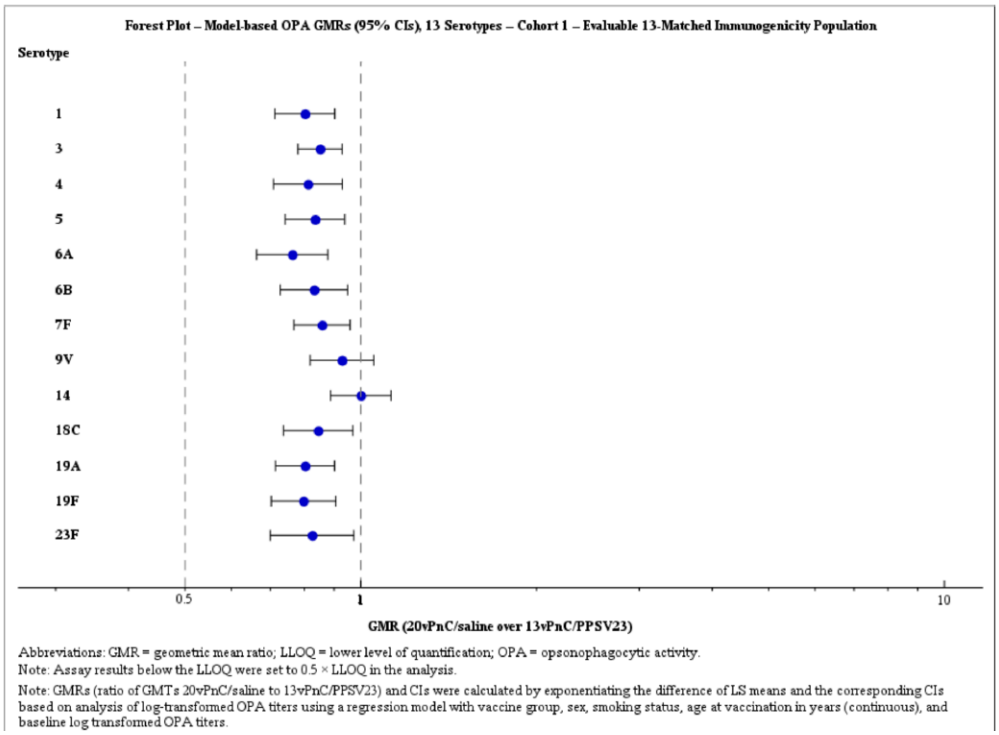

Figure 2: Model-Based OPA GMRs of 20vPnC to 13vPnC for the 13 Matched Serotypes 1 Month After Vaccination – B7471007 Cohort 1 (≥60 Years of Age)

Table 12: Pneumococcal OPA GMTs and GMRs for the 13vPnC Serotypes 1 Month After Vaccination – Linear Regression Model – Cohort 1

Sero type	Vaccination 1 20vPnC/Saline			Vaccination 1 13vPnC/PPSV23			Vaccine Comparison	
	n	GMT	(95% CI)	n	GMT	(95% CI)	GMR	(95% CI)
1	1430	123.4	(112.3, 135.5)	1419	153.8	(140.2, 168.8)	0.80	(0.71, 0.90)
3	1415	40.7	(38.0, 43.6)	1411	47.8	(44.7, 51.2)	0.85	(0.78, 0.93)
4	1415	508.7	(456.5, 566.9)	1409	626.9	(563.5, 697.4)	0.81	(0.71, 0.93)
5	1418	91.6	(83.4, 100.5)	1395	109.7	(100.1, 120.3)	0.83	(0.74, 0.94)
6A	1403	889.0	(795.0, 994.1)	1390	1165.1	(1043.3, 1301.0)	0.76	(0.66, 0.88)
6B	1413	1115.2	(1003.1, 1239.8)	1401	1341.3	(1208.5, 1488.8)	0.83	(0.73, 0.95)
7F	1409	968.8	(887.0, 1058.3)	1391	1129.2	(1034.7, 1232.4)	0.86	(0.77, 0.96)
9V	1399	1455.5	(1317.5, 1608.0)	1391	1567.8	(1420.5, 1730.5)	0.93	(0.82, 1.05)
14	1418	746.7	(679.0, 821.2)	1408	746.7	(679.8, 820.1)	1.00	(0.89, 1.13)
18C	1420	1252.6	(1123.1, 1397.0)	1403	1482.3	(1330.5, 1651.5)	0.85	(0.74, 0.97)
19A	1420	517.9	(472.2, 568.0)	1398	645.3	(588.9, 707.1)	0.80	(0.71, 0.90)
19F	1421	265.8	(240.2, 294.1)	1403	333.3	(301.5, 368.3)	0.80	(0.70, 0.91)
23F	1424	276.5	(242.5, 315.2)	1409	335.1	(294.4, 381.4)	0.83	(0.70, 0.97)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. n = Number of subjects with valid and determinate OPA titres for the specified serotype.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, smoking status, age at vaccination in years (continuous), and baseline log transformed OPA titres.
GMRs (ratio of GMTs 20vPnC/saline to 13vPnC/PPSV23) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Seven additional serotypes:

20vPnC met the primary immunogenicity objective for 6 of the 7 additional serotypes. One month after 20vPnC or PPSV23, the immune responses to 6 of the 7 additional vaccine serotypes induced by 20vPnC were non-inferior to those induced by PPSV23, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model based OPA GMRs (20vPnC/saline relative to 13vPnC/PPSV23 group) >0.5.

Although superiority of 20vPnC to PPSV23 couldn't be formally evaluated due to a missed NI for 1 serotype (serotype 8) as per the statistical analysis plan, the lower bounds of the 2-sided 95% CIs for the GMRs were >1, with nominal p values for superiority <0.001 for the 6 serotypes.

Figure 3: Model-Based OPA GMRs of 20vPnC to PPSV23 for the 7 Additional Serotypes 1 Month After Vaccination – B7471007 Cohort 1 (≥60 Years of Age)

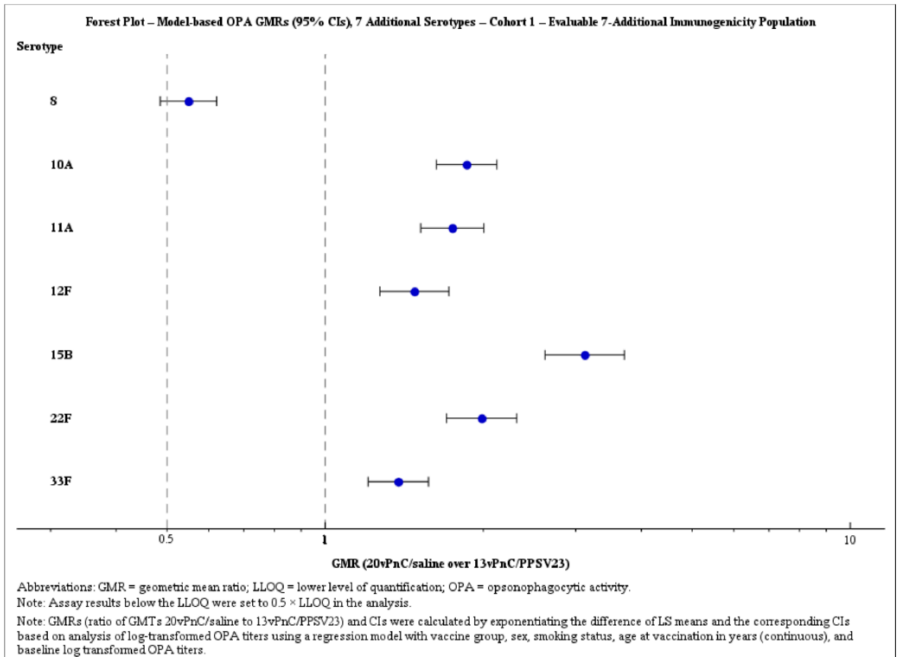

Table 13: Pneumococcal OPA GMTs and GMRs for the 7 Additional Serotypes 1 Month After Vaccination – Linear Regression Model – Cohort 1

Sero type	Vaccination 1 20vPnC/Saline			Vaccination 2 13vPnC/PPSV23			Vaccine Comparison		
	n	GMT	(95% CI)	n	GMT	(95% CI)	GMR	(95% CI)	p-Value
8	1374	465.6	(422.5, 513.1)	1319	848.1	(769.1, 935.2)	0.55	(0.49, 0.62)	>0.999
10A	1310	2007.6	(1808.0, 2229.1)	1263	1079.9	(972.1, 1199.7)	1.86	(1.63, 2.12)	<0.001
11A	1198	4426.8	(3965.5, 4941.8)	1209	2534.9	(2276.8, 2822.3)	1.75	(1.52, 2.01)	<0.001
12F	1294	2538.7	(2255.3, 2857.7)	1222	1716.6	(1521.8, 1936.3)	1.48	(1.27, 1.72)	<0.001
15B	1283	2398.2	(2090.6, 2751.2)	1249	768.5	(669.7, 881.9)	3.12	(2.62, 3.71)	<0.001
22F	1274	3666.2	(3244.4, 4143.0)	1227	1846.2	(1636.6, 2082.6)	1.99	(1.70, 2.32)	<0.001
33F	1157	5125.9	(4611.3, 5698.0)	1201	3720.6	(3356.2, 4124.6)	1.38	(1.21, 1.57)	<0.001

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. n = Number of subjects with valid and determinate OPA titres for the specified serotype.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, smoking status, age at vaccination in years (continuous), and baseline log transformed OPA titres.
GMRs (ratio of GMTs 20vPnC/saline to 13vPnC/PPSV23) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Table 14: Proportion of Subjects Achieving a ≥4-Fold Rise in Serotype-Specific OPA Titres From Before Vaccination to 1 Month After Vaccination – 7 additional serotypes – Cohort 1

Serotype	20vPnC/Saline				13vPnC/PPSV23			
	N	n	%	(95% CI)	N	n	%	(95% CI)
8	1353	1053	77.8	(75.5, 80.0)	1293	1122	86.8	(84.8, 88.6)
10A	1208	912	75.5	(73.0, 77.9)	1164	764	65.6	(62.8, 68.4)
11A	973	576	59.2	(56.0, 62.3)	993	515	51.9	(48.7, 55.0)
12F	1226	1072	87.4	(85.5, 89.2)	1147	924	80.6	(78.1, 82.8)
15B	1228	955	77.8	(75.3, 80.1)	1178	752	63.8	(61.0, 66.6)
22F	1178	974	82.7	(80.4, 84.8)	1156	888	76.8	(74.3, 79.2)
33F	1020	613	60.1	(57.0, 63.1)	1080	599	55.5	(52.4, 58.5)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations. n = Number of subjects with a ≥4-fold rise in titres from before Vaccination 1 to 1 month after vaccination for the specified serotype.

Note: For the 20vPnC/saline group, fold rise is calculated using assay results from before Vaccination 1 to 1 month after Vaccination 1; for subjects in the 13vPnC/PPSV23 group, fold rise is calculated using assay results from before Vaccination 1 to 1 month after Vaccination 2.; 95% CI: Exact 2-sided CI based on the Clopper and Pearson method.

Additional results for serotype 8:

For serotype 8, the model-based GMR (2-sided 95% CI) was 0.55 (0.49, 0.62), narrowly missing the statistical non-inferiority criterion. Based on additional analyses that further characterize the immune responses to serotype 8, the immune response is expected to provide protection similar to the other 19 vaccine serotypes in 20vPnC that met non-inferiority:

- A GMFR of 22.1 was observed for serotype 8 from before to 1 month after 20vPnC, which is within the range of the observed GMFRs (5.8 for serotype 3 to 42.6 for serotype 6A) for the 13 matched serotypes from before to 1 month after 13vPnC.
- After 20vPnC, 77.8% of subjects achieved a ≥4-fold rise in OPA titres from before to 1 month after vaccination for serotype 8, which is within the range of proportions observed (54.0% for serotype 14 to 84.0% for serotype 6A) for the 13 matched serotypes after 13vPnC.

Secondary objectives: Non-inferiority of 20vPnC in younger age groups (Cohort 2 and 3) compared with adults 60 through 64 years of age (subset of Cohort 1)

20vPnC met the secondary immunogenicity objective for all 20 vaccine serotypes based on

- comparison of the immune responses in subjects 50 through 59 years of age (Cohort 2) to those in subjects 60 through 64 years of age in Cohort 1 (Figure 4, **Table 15**),
- and comparison of the immune responses in subjects 18 through 49 years of age (Cohort 3) to those in subjects 60 through 64 years of age in Cohort 1 (Figure 5, **Table 16**).

One month after 20vPnC, the immune responses to all 20 vaccine serotypes in Cohort 2 and Cohort 3 were non-inferior to those in Cohort 1 subjects 60 through 64 years of age. The lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (younger cohort relative to Cohort 1 subjects 60 through 64 years of age) were >0.5 (2-fold NI margin). The finding of higher responses in younger adults compared with older adults is consistent with the experience with 13vPnC.

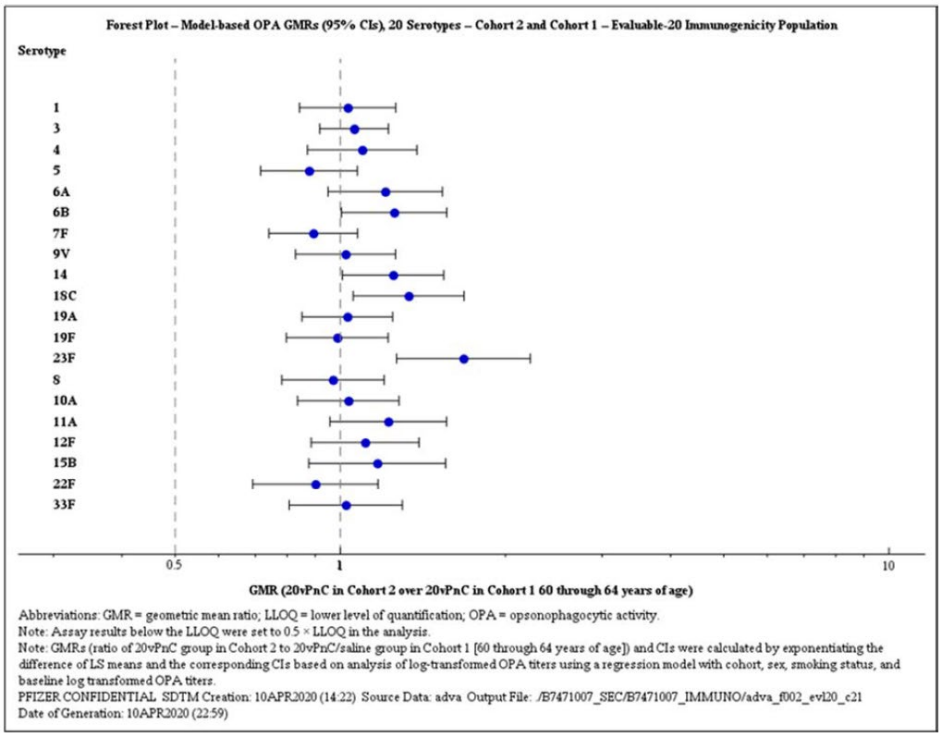

Figure 4: Model-Based OPA GMRs of Cohort 2 (50 Through 59 Years of Age) to Cohort 1 Subjects 60 Through 64 Years of Age for the 20vPnC Serotypes 1 Month After Vaccination

Table 15: Comparisons of Pneumococcal OPA GMTs 1 Month After 20vPnC Vaccination in Cohort 2 and Cohort 1 Subjects 60 Through 64 Years of Age – Linear Regression

	20vPnC Group in Cohort 2			20vPnC/Saline Group in Cohort 1 (60 - 64 Years of Age)			Comparison	
Serotype	**n**	**GMT**	**(95% CI)**	**n**	**GMT**	**(95% CI)**	**GMR**	**(95% CI)**
13vPnC								
1	320	135.9	(113.1, 163.4)	941	131.8	(117.2, 148.3)	1.03	(0.84, 1.26)
3	318	43.3	(38.0, 49.4)	935	40.9	(37.6, 44.5)	1.06	(0.92, 1.22)
4	318	633.3	(513.9, 780.4)	931	577.9	(505.5, 660.6)	1.10	(0.87, 1.38)
5	313	84.6	(70.3, 101.8)	935	96.5	(85.8, 108.6)	0.88	(0.72, 1.07)
6A	318	1203.9	(968.1, 1497.1)	921	997.1	(866.5, 1147.5)	1.21	(0.95, 1.53)
6B	318	1502.7	(1228.2, 1838.5)	933	1199.0	(1054.3, 1363.4)	1.25	(1.00, 1.56)
7F	313	1047.0	(884.0, 1240.2)	924	1173.0	(1052.9, 1306.9)	0.89	(0.74, 1.07)
9V	312	1725.7	(1424.4, 2090.6)	922	1687.9	(1493.7, 1907.3)	1.02	(0.83, 1.26)
14	313	926.2	(761.8, 1126.0)	933	742.3	(655.8, 840.2)	1.25	(1.01, 1.54)
18C	315	1805.0	(1459.6, 2232.2)	937	1355.2	(1184.3, 1550.7)	1.33	(1.06, 1.68)
19A	318	618.4	(519.9, 735.5)	932	600.3	(537.5, 670.6)	1.03	(0.85, 1.25)

19F	320	286.7	(236.0, 348.2)	937	290.4	(256.4, 329.0)	0.99	(0.80, 1.22)
23F	319	549.1	(425.4, 708.9)	937	327.5	(278.2, 385.6)	1.68	(1.27, 2.22)
Additional								
8	314	486.9	(400.6, 591.9)	901	502.3	(442.8, 569.8)	0.97	(0.78, 1.20)
10A	296	2520.4	(2076.0, 3060.0)	857	2437.0	(2149.8, 2762.5)	1.03	(0.84, 1.28)
11A	271	6416.9	(5131.9, 8023.6)	796	5248.9	(4564.5, 6035.9)	1.22	(0.96, 1.56)
12F	292	3445.1	(2807.8, 4227.1)	855	3105.2	(2722.7, 3541.4)	1.11	(0.88, 1.39)
15B	284	3355.9	(2582.0, 4361.8)	830	2873.7	(2438.1, 3387.1)	1.17	(0.88, 1.56)
22F	284	3808.1	(2998.2, 4836.8)	835	4228.4	(3629.6, 4926.0)	0.90	(0.69, 1.17)
33F	266	5571.3	(4495.7, 6904.2)	765	5445.2	(4749.2, 6243.2)	1.02	(0.81, 1.30)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. n = Number of subjects with a determinate OPA titre to the given serotype.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with cohort, sex, smoking status, and baseline log transformed OPA titres.

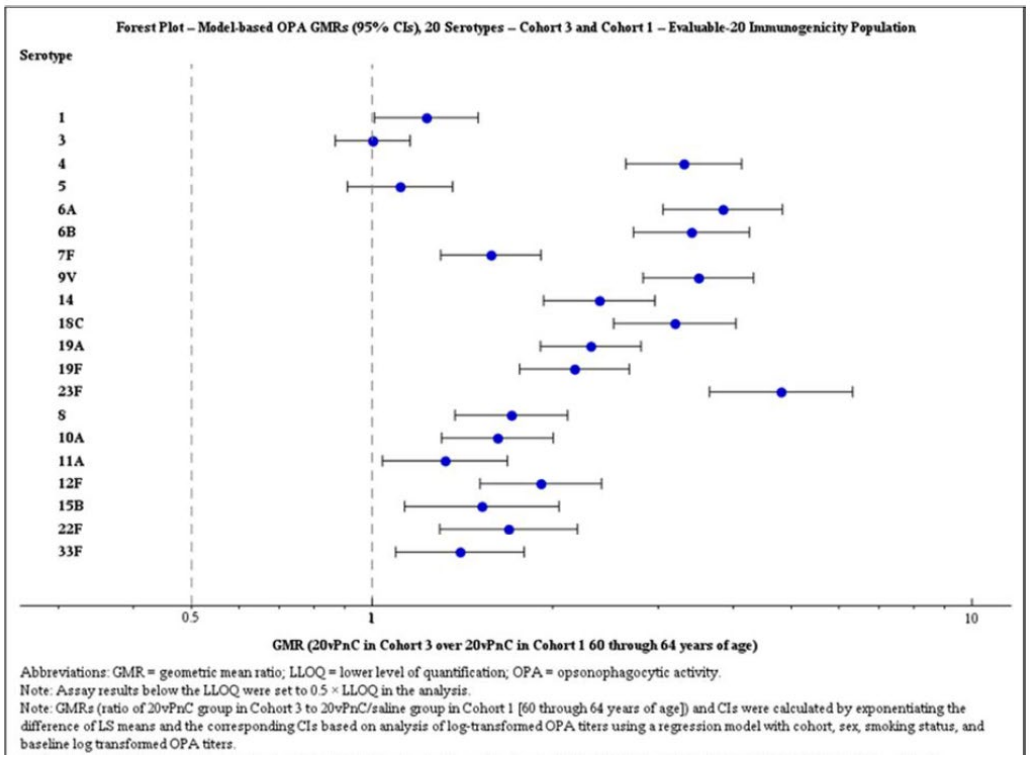

Figure 5: Model-Based OPA GMRs of Cohort 3 (18 Through 49 Years of Age) to Cohort 1 Subjects 60 Through 64 Years of Age for the 20vPnC Serotypes 1 Month After Vaccination

Table 16: Comparisons of Pneumococcal OPA GMTs 1 Month After 20vPnC Vaccination in Cohort 3 and Cohort 1 Subjects 60 Through 64 Years of Age – Linear Regression Model

Serotype	20vPnC Group in Cohort 3			20vPnC/Saline Group in Cohort 1 (60 - 64 Years of Age)			Comparison	
	n	GMT	(95% CI)	n	GMT	(95% CI)	GMR	(95% CI)
13vPnC								
1	316	162.6	(135.1, 195.6)	941	132.0	(117.7, 148.1)	1.23	(1.01, 1.50)
3	316	42.1	(36.9, 48.1)	935	42.0	(38.7, 45.7)	1.00	(0.87, 1.16)
4	315	1966.7	(1599.5, 2418.3)	931	594.5	(522.9, 675.9)	3.31	(2.65, 4.13)
5	317	107.9	(89.4, 130.1)	935	96.9	(86.2, 109.0)	1.11	(0.91, 1.36)
6A	315	3930.5	(3176.0, 4864.4)	921	1022.8	(896.1, 1167.4)	3.84	(3.06, 4.83)
6B	314	4260.0	(3461.3, 5243.1)	933	1250.4	(1102.3, 1418.4)	3.41	(2.73, 4.26)
7F	311	1872.8	(1564.2, 2242.4)	924	1187.2	(1064.4, 1324.2)	1.58	(1.30, 1.91)
9V	315	6041.4	(4962.5, 7354.9)	922	1726.7	(1529.2, 1949.7)	3.50	(2.83, 4.33)
14	316	1848.4	(1514.7, 2255.7)	933	772.8	(684.7, 872.3)	2.39	(1.93, 2.96)
18C	312	4460.5	(3584.6, 5550.4)	937	1395.3	(1220.9, 1594.5)	3.20	(2.53, 4.04)

19A	312	1415.0	(1181.8, 1694.2)	932	611.3	(547.8, 682.3)	2.31	(1.91, 2.81)
19F	315	654.8	(538.2, 796.8)	937	301.2	(266.7, 340.1)	2.17	(1.76, 2.68)
23F	315	1559.2	(1208.1, 2012.2)	937	324.5	(277.1, 380.1)	4.80	(3.65, 6.32)
Additional								
8	306	867.0	(709.7, 1059.2)	901	508.1	(448.8, 575.3)	1.71	(1.38, 2.12)
10A	292	4157.3	(3410.9, 5067.0)	857	2569.7	(2274.0, 2903.7)	1.62	(1.31, 2.00)
11A	263	7169.3	(5735.7, 8961.1)	796	5419.7	(4737.7, 6199.7)	1.32	(1.04, 1.68)
12F	273	5875.4	(4719.8, 7314.1)	855	3074.5	(2697.9, 3503.7)	1.91	(1.51, 2.41)
15B	279	4601.0	(3487.9, 6069.4)	830	3019.0	(2562.8, 3556.4)	1.52	(1.13, 2.05)
22F	273	7568.2	(5927.4, 9663.2)	835	4482.5	(3862.7, 5201.8)	1.69	(1.30, 2.20)
33F	251	7976.9	(6341.7, 10033.7)	765	5693.2	(4970.1, 6521.5)	1.40	(1.10, 1.79)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. n = Number of subjects with a determinate OPA titre to the given serotype.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titers using a regression model with cohort, sex, smoking status, and baseline log transformed OPA titres.
GMRs (ratio of 20vPnC group in Cohort 3 to 20vPnC/saline group in Cohort 1 [60 through 64 years of age]) and 2- sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Additional data to illustrate the immune response of 20vPnC compared to 13vPnC (ad hoc analysis by the Rapporteur)

For cohort 2 and 3 no comparison between both vaccines was intended in the study, nevertheless GMT data for both cohorts for 13vPnC were available and are shown below.

Immune response elicited by 20vPnC is consistently numerically lower in all cohorts compared to 13vPnC for the 13vPnC serotypes. In Cohort 2, including 50-59-year-old subjects, the difference seems even more pronounced, although the conclusions are somewhat hampered by the smaller sample size for 13vPnC. The observations of reduced response are further confirmed with the proportion of subjects with a ≥4-fold rise. Similar reductions have also been observed in the lot consistency study B7471008 (13vPnC was included mainly as control arm for the safety assessment, see section 2.6.5.5 for further details of this study) and a paediatric study, submitted by the applicant (B7471003), although this population is not part of the current indication (study not further described in this report).

Table 17: Pneumococcal OPA GMFRs From Before Vaccination to 1 Month After Vaccination – Cohort 2 – Evaluable-20 Immunogenicity Population

			Sampling Time Point					
			Before Vaccination		**1 Month After Vaccination**		**1 Month After Vaccination/ Before Vaccination**	
Serotype	**Vaccine Group** (as Randomised)	**n[a]**	**GMT[b]**	**(95% CI[b])**	**GMT[b]**	**(95% CI[b])**	**GMFR[b]**	**(95% CI[b])**
13vPnC								
1	20vPnC	319	11.6	(10.7, 12.6)	167.0	(140.1, 199.0)	14.4	(12.0, 17.3)
	13vPnC	107	10.8	(9.8, 12.0)	191.4	(138.3, 265.1)	17.7	(12.8, 24.3)
3	20vPnC	317	9.5	(8.6, 10.6)	48.5	(42.6, 55.3)	5.1	(4.4, 5.9)
	13vPnC	108	8.3	(7.3, 9.4)	44.7	(34.7, 57.7)	5.4	(4.2, 7.0)
4	20vPnC	304	16.6	(14.4, 19.1)	719.7	(590.6, 877.2)	43.4	(34.4, 54.9)
	13vPnC	106	16.7	(13.1, 21.2)	1141.9	(809.8, 1610.2)	68.5	(46.0, 102.1)
5	20vPnC	312	16.3	(15.4, 17.2)	96.4	(81.0, 114.8)	5.9	(5.0, 7.0)
	13vPnC	108	15.5	(14.2, 16.9)	175.3	(130.8, 235.0)	11.3	(8.4, 15.2)
6A	20vPnC	312	27.5	(24.2, 31.2)	1383.8	(1130.1, 1694.4)	50.3	(40.2, 63.0)
	13vPnC	104	28.2	(23.2, 34.3)	1603.3	(1170.5, 2196.2)	56.8	(39.8, 81.2)
6B	20vPnC	299	56.2	(46.9, 67.2)	1782.2	(1491.1, 2130.1)	31.7	(25.3, 39.7)
	13vPnC	103	58.8	(44.3, 78.0)	2216.4	(1667.8, 2945.4)	37.7	(25.9, 54.8)
7F	20vPnC	300	85.6	(76.2, 96.2)	1097.2	(941.0, 1279.2)	12.8	(10.7, 15.4)
	13vPnC	106	72.9	(61.9, 85.9)	1835.4	(1407.3, 2393.8)	25.2	(18.5, 34.2)
9V	20vPnC	288	160.3	(137.3, 187.1)	1933.8	(1609.6, 2323.4)	12.1	(9.9, 14.7)
	13vPnC	97	170.7	(127.1, 229.2)	3489.9	(2436.4, 4998.9)	20.4	(13.5, 30.9)
14	20vPnC	300	101.5	(83.6, 123.2)	1058.5	(880.5, 1272.5)	10.4	(8.3, 13.0)
	13vPnC	103	139.5	(98.8, 197.1)	1361.1	(1014.2, 1826.5)	9.8	(6.7, 14.3)
18C	20vPnC	308	42.2	(35.0, 50.9)	2040.0	(1701.0, 2446.5)	48.3	(37.9, 61.5)

	13vPnC	106	38.1	(28.1, 51.5)	2617.3	(1889.5, 3625.4)	68.8	(43.6, 108.5)
19A	20vPnC	310	28.7	(24.4, 33.8)	679.4	(584.6, 789.6)	23.6	(19.2, 29.1)
	13vPnC	105	29.5	(22.1, 39.4)	1154.5	(903.4, 1475.4)	39.1	(27.7, 55.3)
19F	20vPnC	316	34.2	(30.9, 37.8)	315.5	(260.9, 381.5)	9.2	(7.6, 11.3)
	13vPnC	106	30.6	(26.9, 34.9)	568.8	(401.3, 806.2)	18.6	(13.0, 26.5)
23F	20vPnC	313	11.8	(10.1, 13.7)	563.1	(445.4, 711.9)	47.8	(37.2, 61.3)
	13vPnC	106	11.4	(8.9, 14.6)	881.6	(592.8, 1311.3)	77.4	(51.3, 116.7)
Additional								
8	20vPnC	310	22.7	(20.3, 25.5)	542.7	(450.8, 653.3)	23.9	(19.3, 29.6)
	13vPnC	106	21.9	(18.2, 26.5)	23.6	(18.9, 29.4)	1.1	(0.9, 1.4)
10A	20vPnC	273	162.9	(131.5, 201.9)	2923.9	(2433.7, 3512.9)	17.9	(14.2, 22.6)
	13vPnC	96	168.3	(115.2, 245.9)	151.5	(102.3, 224.3)	0.9	(0.7, 1.2)
11A	20vPnC	213	643.9	(497.1, 834.1)	6714.7	(5281.8, 8536.4)	10.4	(7.7, 14.2)
	13vPnC	73	979.9	(602.6, 1593.3)	1121.1	(694.1, 1810.6)	1.1	(0.8, 1.6)
12F	20vPnC	279	37.0	(32.3, 42.3)	3964.7	(3323.4, 4729.7)	107.3	(85.8, 134.1)
	13vPnC	101	38.0	(29.7, 48.5)	44.8	(33.3, 60.2)	1.2	(1.0, 1.4)
15B	20vPnC	263	50.9	(39.5, 65.5)	3668.0	(2876.7, 4676.9)	72.1	(51.9, 100.1)
	13vPnC	85	39.7	(26.3, 59.9)	51.9	(33.9, 79.4)	1.3	(1.0, 1.7)
22F	20vPnC	256	71.9	(54.5, 94.8)	4568.1	(3594.1, 5806.1)	63.5	(44.8, 90.1)
	13vPnC	90	84.3	(52.7, 134.8)	69.3	(42.2, 113.7)	0.8	(0.6, 1.1)
33F	20vPnC	233	678.2	(560.0, 821.5)	6202.9	(5008.8, 7681.6)	9.1	(7.1, 11.7)
	13vPnC	86	778.7	(575.1, 1054.3)	719.0	(524.2, 986.1)	0.9	(0.7, 1.2)

Abbreviations: GMFR = geometric mean fold rise; GMT = geometric mean titre; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections.
b. GMTs, GMFRs, and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titres or fold rises and the corresponding CIs (based on the Student t distribution).

Table 18: Pneumococcal OPA GMFRs From Before Vaccination to 1 Month After Vaccination – Cohort 3 – Evaluable-20 Immunogenicity Population

			Sampling Time Point					
			Before Vaccination		1 Month After Vaccination		1 Month After Vaccination/ Before Vaccination	
Serotype	**Vaccine Group** (as Randomised)	**n[a]**	**GMT[b]**	**(95% CI[b])**	**GMT[b]**	**(95% CI[b])**	**GMFR[b]**	**(95% CI[b])**
13vPnC								
1	20vPnC	315	10.5	(9.9, 11.1)	195.2	(166.8, 228.5)	18.6	(16.0, 21.8)
	13vPnC	105	10.6	(9.5, 11.8)	288.9	(216.2, 386.2)	27.3	(20.5, 36.3)
3	20vPnC	312	9.7	(8.8, 10.7)	46.8	(41.4, 52.9)	4.8	(4.2, 5.5)
	13vPnC	105	10.4	(8.5, 12.6)	53.0	(42.4, 66.3)	5.1	(4.0, 6.5)
4	20vPnC	302	17.0	(14.5, 19.9)	2235.5	(1908.8, 2618.1)	131.8	(106.4, 163.4)
	13vPnC	103	20.1	(14.6, 27.8)	3144.1	(2322.1, 4256.9)	156.4	(104.3, 234.5)
5	20vPnC	315	15.6	(14.9, 16.4)	123.8	(104.8, 146.2)	7.9	(6.7, 9.4)
	13vPnC	106	14.7	(14.4, 15.1)	161.7	(120.0, 217.9)	11.0	(8.2, 14.7)
6A	20vPnC	305	31.9	(27.6, 36.9)	4676.8	(4060.3, 5386.9)	146.5	(120.6, 178.0)
	13vPnC	103	30.2	(23.9, 38.3)	4971.2	(3627.5, 6812.6)	164.4	(114.3, 236.5)
6B	20vPnC	286	76.2	(61.4, 94.6)	5355.2	(4575.5, 6267.7)	70.3	(55.7, 88.7)
	13vPnC	97	92.6	(62.4, 137.3)	6654.3	(5041.2, 8783.5)	71.9	(46.5, 111.1)
7F	20vPnC	284	102.1	(88.6, 117.5)	2015.4	(1719.2, 2362.5)	19.7	(16.1, 24.3)
	13vPnC	97	109.8	(82.7, 146.0)	3301.8	(2634.0, 4138.9)	30.1	(21.4, 42.2)
9V	20vPnC	281	201.2	(169.6, 238.6)	7065.4	(5999.3, 8321.0)	35.1	(27.9, 44.2)
	13vPnC	99	209.8	(154.5, 284.9)	8475.1	(6280.3, 11437)	40.4	(26.7, 61.2)
14	20vPnC	291	147.6	(117.3, 185.9)	2158.3	(1854.9, 2511.4)	14.6	(11.3, 18.9)
	13vPnC	100	180.5	(118.7, 274.6)	2823.9	(2210.5, 3607.6)	15.6	(9.7, 25.4)
18C	20vPnC	299	44.6	(35.9, 55.2)	4980.5	(4202.1, 5903.2)	111.8	(86.8, 143.8)
	13vPnC	96	55.5	(36.6, 84.0)	5656.6	(4166.5, 7679.6)	102.0	(62.7, 165.9)
19A	20vPnC	299	42.4	(34.3, 52.4)	1658.7	(1441.5, 1908.6)	39.1	(30.9, 49.6)
	13vPnC	105	40.8	(29.0, 57.5)	1962.4	(1529.3, 2518.1)	48.1	(32.5, 71.0)
19F	20vPnC	310	41.5	(36.8, 46.7)	738.9	(626.5, 871.3)	17.8	(14.7, 21.6)
	13vPnC	105	45.7	(35.8, 58.5)	837.7	(623.0, 1126.3)	18.3	(13.1, 25.5)
23F	20vPnC	309	15.0	(12.3, 18.3)	1774.2	(1461.3, 2154.1)	118.2	(92.7, 150.7)
	13vPnC	104	12.1	(8.9, 16.4)	2556.7	(1888.9, 3460.7)	212.0	(144.4, 311.2)
Additional								
8	20vPnC	300	28.7	(24.9, 33.1)	991.3	(833.5, 1178.9)	34.6	(27.8, 43.0)

	13vPnC	103	28.8	(22.2, 37.4)	30.7	(23.3, 40.6)	1.1	(0.8, 1.4)
10A	20vPnC	260	219.3	(174.8, 275.0)	4985.9	(4277.7, 5811.3)	22.7	(17.8, 29.0)
	13vPnC	86	177.4	(119.1, 264.2)	272.1	(176.5, 419.6)	1.5	(1.1, 2.1)
11A	20vPnC	220	1632.3	(1296.8, 2054.6)	8521.7	(7045.7, 10307)	5.2	(3.9, 6.9)
	13vPnC	64	2152.6	(1415.4, 3273.8)	2254.7	(1509.0, 3368.9)	1.0	(0.7, 1.5)
12F	20vPnC	252	42.4	(35.9, 50.2)	7263.1	(6105.7, 8639.9)	171.1	(135.1, 216.8)
	13vPnC	88	52.4	(37.6, 73.1)	60.0	(41.8, 86.0)	1.1	(0.9, 1.4)
15B	20vPnC	248	76.8	(57.3, 102.8)	4989.4	(3929.9, 6334.7)	65.0	(44.8, 94.4)
	13vPnC	90	56.3	(35.1, 90.2)	75.0	(44.9, 125.0)	1.3	(0.9, 1.9)
22F	20vPnC	241	140.4	(103.9, 189.7)	9730.9	(7878.4, 12019)	69.3	(48.4, 99.4)
	13vPnC	83	129.7	(75.0, 224.1)	173.7	(98.8, 305.3)	1.3	(0.9, 2.0)
33F	20vPnC	213	1393.3	(1151.9, 1685.2)	10425	(8494.4, 12795)	7.5	(5.8, 9.7)
	13vPnC	78	1882.4	(1351.5, 2621.9)	1675.0	(1232.0, 2277.3)	0.9	(0.7, 1.2)

Abbreviations: GMFR = geometric mean fold rise; 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.

a. n = Number of subjects with valid and determinate assay results for both before and 1 month after vaccination blood sample collections.

b. GMTs, GMFRs, and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titers or fold rises and the corresponding CIs (based on the Student t distribution).

Table 19: Proportion of Subjects Achieving a ⩾4-Fold Rise in Serotype-Specific OPA Titres From Before Vaccination to 1 Month After Vaccination – Cohort 2 – Evaluable-20 Immunogenicity Population

	Vaccine Group (as Randomised)							
	20vPnC				13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	319	239	74.9	(69.8, 79.6)	107	84	78.5	(69.5, 85.9)
3	317	187	59.0	(53.4, 64.5)	108	65	60.2	(50.3, 69.5)
4	304	256	84.2	(79.6, 88.1)	106	90	84.9	(76.6, 91.1)
5	312	171	54.8	(49.1, 60.4)	108	78	72.2	(62.8, 80.4)
6A	312	268	85.9	(81.5, 89.6)	104	92	88.5	(80.7, 93.9)
6B	299	236	78.9	(73.9, 83.4)	103	85	82.5	(73.8, 89.3)
7F	300	219	73.0	(67.6, 77.9)	106	91	85.8	(77.7, 91.9)
9V	288	212	73.6	(68.1, 78.6)	97	74	76.3	(66.6, 84.3)
14	300	187	62.3	(56.6, 67.8)	103	62	60.2	(50.1, 69.7)
18C	308	254	82.5	(77.8, 86.5)	106	88	83.0	(74.5, 89.6)
19A	310	248	80.0	(75.1, 84.3)	105	91	86.7	(78.6, 92.5)
19F	316	203	64.2	(58.7, 69.5)	106	83	78.3	(69.2, 85.7)
23F	313	254	81.2	(76.4, 85.3)	106	93	87.7	(79.9, 93.3)
Additional								
8	310	246	79.4	(74.4, 83.7)	106	8	7.5	(3.3, 14.3)
10A	273	215	78.8	(73.4, 83.5)	96	6	6.3	(2.3, 13.1)
11A	213	130	61.0	(54.1, 67.6)	73	9	12.3	(5.8, 22.1)
12F	279	260	93.2	(89.6, 95.9)	101	6	5.9	(2.2, 12.5)
15B	263	217	82.5	(77.4, 86.9)	85	9	10.6	(5.0, 19.2)
22F	256	206	80.5	(75.1, 85.1)	90	5	5.6	(1.8, 12.5)
33F	233	149	63.9	(57.4, 70.1)	86	8	9.3	(4.1, 17.5)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.

b. n = Number of subjects with a ⩾4-fold rise in titres from before vaccination to 1 month after vaccination for the specified serotype.

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

Table 20: Proportion of Subjects Achieving a ⩾4-Fold Rise in Serotype-Specific OPA Titres From Before Vaccination to 1 Month After Vaccination – Cohort 3 – Evaluable-20 Immunogenicity Population

	Vaccine Group (as Randomised)							
	20vPnC				13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	315	271	86.0	(81.7, 89.7)	105	92	87.6	(79.8, 93.2)
3	312	177	56.7	(51.0, 62.3)	105	66	62.9	(52.9, 72.1)
4	302	276	91.4	(87.6, 94.3)	103	94	91.3	(84.1, 95.9)
5	315	204	64.8	(59.2, 70.0)	106	79	74.5	(65.1, 82.5)
6A	305	295	96.7	(94.1, 98.4)	103	98	95.1	(89.0, 98.4)
6B	286	255	89.2	(85.0, 92.5)	97	84	86.6	(78.2, 92.7)
7F	284	216	76.1	(70.7, 80.9)	97	82	84.5	(75.8, 91.1)
9V	281	236	84.0	(79.2, 88.1)	99	80	80.8	(71.7, 88.0)
14	291	181	62.2	(56.4, 67.8)	100	62	62.0	(51.7, 71.5)
18C	299	261	87.3	(83.0, 90.8)	96	83	86.5	(78.0, 92.6)
19A	299	247	82.6	(77.8, 86.7)	105	85	81.0	(72.1, 88.0)
19F	310	243	78.4	(73.4, 82.8)	105	81	77.1	(67.9, 84.8)
23F	309	271	87.7	(83.5, 91.1)	104	95	91.3	(84.2, 96.0)
Additional								
8	300	249	83.0	(78.3, 87.1)	103	11	10.7	(5.5, 18.3)
10A	260	205	78.8	(73.4, 83.6)	86	15	17.4	(10.1, 27.1)
11A	220	104	47.3	(40.5, 54.1)	64	3	4.7	(1.0, 13.1)
12F	252	236	93.7	(89.9, 96.3)	88	5	5.7	(1.9, 12.8)
15B	248	182	73.4	(67.4, 78.8)	90	10	11.1	(5.5, 19.5)
22F	241	202	83.8	(78.5, 88.2)	83	11	13.3	(6.8, 22.5)
33F	213	129	60.6	(53.7, 67.2)	78	8	10.3	(4.5, 19.2)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.

b. n = Number of subjects with a ⩾4-fold rise in titres from before vaccination to 1 month after vaccination for the specified serotype.

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

Selected exploratory endpoint: Immune response by risk status

Approximately one-third of the total evaluable subjects across all 3 cohorts combined had risk factors for serious pneumococcal disease (648 subjects), including diabetes mellitus (13.9%), smoking (12.8%), chronic pulmonary disease including asthma (8.5%), medical conditions related to chronic cardiovascular disease (5.3%), and liver disease (0.4%).

The initial analysis was criticised by the Rapporteurs and the applicant has performed an additional unplanned ad hoc analysis for the participants with and without risk factors by each age cohort in the B7471007 study (≥60 years [Cohort 1], 50–59 years [Cohort 2], and 18–49 years of age [Cohort 3]). The study was not designed or powered for any formal between-group comparisons in this ad hoc analysis. The 13vPnC arms in Cohorts 2 and 3 were included for safety only, however the immunogenicity in all cohorts was measured to maintain blinding during the assay work. Additionally, because the number of participants 18 through 49 years of age in B7471007 is somewhat small when split into those subpopulations, an analysis was performed among participants in this age range from B7471007 pooled with the participants from B7471008 (all 18–49 years of age) to increase the precision. Note that the 13vPnC control group in Study B7471008 was included for safety only, however the immunogenicity in all groups was measured to maintain blinding during the assay work. There was no other study that overlapped with the adults 50 through 59 years of age. Post hoc supplemental data on the proportion of subjects with ≥4-fold rises in OPA titres from before to 1 month after vaccination are summarised in the tables below.

Substantial increases in OPA GMTs from before to 1 month after 20vPnC were observed in subjects with and without risk factors in all cohorts. 20vPnC elicited OPA GMTs in the participants with risk factors that were observed to be slightly lower for several serotypes than in participants without risk factors. This trend was consistent in both the 20vPnC group and the corresponding control group — 13vPnC for the 13 serotypes and PPSV23 for the 7 additional serotypes. In participants ≥60 years of age with risk factors, approximately 50% to 80% of participants responded to 20vPnC with a ≥4-fold increase in OPA titre to the vaccine serotypes, as did approximately 40% to 90% of those 50 through 59 and 18 through 49 years of age. The sample size becomes relatively small in the subsets of the younger populations (for example, as low as 30 participants in 50 through 59 years of age) so that results in a few subjects may have a disproportionate effect and increased overall variabilities in the summary.

Table 21: Pneumococcal OPA GMTs and GMRs for the 13vPnC Serotypes 1 Month After Vaccination by Risk Status – Linear Regression Model – Cohort 1

Serotype	Risk Status[a]	Vaccine Group (as Randomised)						Vaccine Comparison 20vPnC/13vPnC	
		20vPnC			13vPnC				
		n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d]	(95% CI[d])
1	Overall	1430	149.2	(137.0, 162.4)	1419	183.4	(168.4, 199.7)	0.81	(0.72, 0.92)
	With Risk Factors	464	113.4	(97.1, 132.4)	516	143.1	(123.5, 165.8)	0.79	(0.64, 0.98)
	Without Risk Factors	966	172.1	(155.6, 190.3)	903	214.6	(193.4, 238.2)	0.80	(0.70, 0.92)
3	Overall	1415	42.6	(40.1, 45.4)	1411	49.9	(46.9, 53.1)	0.85	(0.78, 0.93)
	With Risk Factors	457	40.4	(36.0, 45.3)	512	49.8	(44.7, 55.4)	0.81	(0.69, 0.95)
	Without Risk Factors	958	43.7	(40.6, 47.1)	899	50.2	(46.5, 54.1)	0.87	(0.79, 0.97)
4	Overall	1415	601.1	(545.3, 662.7)	1409	731.0	(663.1, 805.8)	0.82	(0.72, 0.94)
	With Risk Factors	459	488.7	(409.7, 583.0)	512	648.8	(549.5, 765.9)	0.75	(0.59, 0.96)
	Without Risk Factors	956	661.6	(588.9, 743.3)	897	785.8	(696.7, 886.2)	0.84	(0.71, 0.99)
5	Overall	1418	101.0	(92.9, 109.8)	1395	119.8	(110.1, 130.3)	0.84	(0.75, 0.95)
	With Risk Factors	458	94.0	(81.7, 108.2)	506	113.6	(99.4, 129.8)	0.83	(0.68, 1.00)
	Without Risk Factors	960	104.6	(94.2, 116.1)	889	124.2	(111.4, 138.4)	0.84	(0.73, 0.98)
6A	Overall	1403	990.3	(896.0, 1094.6)	1390	1283.2	(1160.4, 1418.9)	0.77	(0.67, 0.89)
	With Risk Factors	456	981.5	(821.4, 1172.8)	508	1229.4	(1039.6, 1453.8)	0.80	(0.63, 1.02)
	Without Risk Factors	947	998.5	(884.5, 1127.2)	882	1330.2	(1172.5, 1509.1)	0.75	(0.63, 0.89)
6B	Overall	1413	1227.7	(1116.8, 1349.7)	1401	1460.5	(1328.4, 1605.8)	0.84	(0.74, 0.96)
	With Risk Factors	455	1231.0	(1040.7, 1456.2)	507	1428.0	(1219.0, 1672.8)	0.86	(0.68, 1.09)
	Without Risk Factors	958	1226.4	(1093.2, 1375.7)	894	1494.8	(1327.2, 1683.6)	0.82	(0.70, 0.97)
7F	Overall	1409	1025.2	(947.4, 1109.5)	1391	1193.2	(1102.3, 1291.7)	0.86	(0.77, 0.96)
	With Risk Factors	459	895.0	(780.8, 1025.9)	504	1080.4	(948.9, 1230.2)	0.83	(0.69, 1.00)
	Without Risk Factors	950	1091.2	(990.4, 1202.2)	887	1261.7	(1141.3, 1394.7)	0.86	(0.75, 0.99)
9V	Overall	1399	1550.1	(1418.1, 1694.3)	1391	1663.1	(1520.3, 1819.3)	0.93	(0.82, 1.06)
	With Risk Factors	450	1348.8	(1146.5, 1586.8)	504	1565.9	(1341.5, 1827.9)	0.86	(0.69, 1.08)
	Without Risk Factors	949	1659.7	(1492.6, 1845.4)	887	1732.2	(1551.3, 1934.2)	0.96	(0.82, 1.11)
14	Overall	1418	761.8	(699.6, 829.5)	1408	761.5	(699.2, 829.3)	1.00	(0.89, 1.13)
	With Risk Factors	461	837.4	(725.6, 966.3)	512	717.6	(625.8, 822.9)	1.17	(0.96, 1.42)
	Without Risk Factors	957	727.9	(654.6, 809.4)	896	794.5	(712.4, 886.1)	0.92	(0.79, 1.06)
18C	Overall	1420	1358.0	(1231.8, 1497.2)	1403	1601.5	(1451.9, 1766.4)	0.85	(0.74, 0.97)
	With Risk Factors	460	1136.9	(959.0, 1347.8)	512	1508.9	(1284.5, 1772.6)	0.75	(0.60, 0.95)
	Without Risk Factors	960	1482.2	(1315.5, 1669.9)	891	1671.5	(1477.0, 1891.6)	0.89	(0.75, 1.05)
19A	Overall	1420	579.1	(533.0, 629.3)	1398	715.6	(658.2, 778.1)	0.81	(0.72, 0.91)
	With Risk Factors	460	502.0	(434.4, 580.1)	507	627.2	(546.4, 720.0)	0.80	(0.66, 0.98)
	Without Risk Factors	960	622.6	(562.6, 689.0)	891	779.4	(701.5, 866.0)	0.80	(0.69, 0.92)
19F	Overall	1421	295.1	(269.5, 323.1)	1403	367.0	(335.1, 402.0)	0.80	(0.71, 0.91)
	With Risk Factors	459	263.2	(224.1, 309.1)	510	356.6	(306.3, 415.2)	0.74	(0.59, 0.92)
	Without Risk Factors	962	312.9	(280.2, 349.3)	893	377.3	(336.6, 423.0)	0.83	(0.71, 0.97)
23F	Overall	1424	299.8	(266.6, 337.1)	1409	361.6	(321.4, 406.7)	0.83	(0.70, 0.98)
	With Risk Factors	461	295.1	(240.0, 363.0)	511	334.1	(274.5, 406.6)	0.88	(0.66, 1.17)
	Without Risk Factors	963	299.3	(259.5, 345.4)	898	377.5	(325.7, 437.6)	0.79	(0.65, 0.97)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. n = Number of subjects with valid and determinate OPA titters for the specified serotype.

c. GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, age at vaccination in years (continuous), and baseline log transformed OPA titres.

d. GMRs (ratio of GMTs 20vPnC to 13vPnC) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Table 22: Pneumococcal OPA GMTs and GMRs for the 7 Additional Serotypes 1 Month After Vaccination by Risk Status – Linear Regression Model – Cohort 1

Serotype	Risk Status[a]	Vaccine Group (as Randomised) 20vPnC n[b]	20vPnC GMT[c]	20vPnC (95% CI[c])	PPSV23 n[b]	PPSV23 GMT[c]	PPSV23 (95% CI[c])	Vaccine Comparison 20vPnC/PPSV23 GMR[d]	GMR (95% CI[d])
8	Overall	1374	523.8	(479.9, 571.6)	1319	948.6	(867.5, 1037.3)	0.55	(0.49, 0.63)
	With Risk Factors	446	421.0	(358.1, 494.8)	484	816.2	(698.4, 953.8)	0.52	(0.41, 0.65)
	Without Risk Factors	928	582.9	(525.9, 646.0)	835	1046.7	(939.1, 1166.7)	0.56	(0.48, 0.65)
10A	Overall	1310	2114.1	(1926.0, 2320.7)	1263	1133.1	(1030.4, 1245.9)	1.87	(1.64, 2.13)
	With Risk Factors	423	1891.2	(1604.7, 2229.0)	461	1044.8	(892.3, 1223.4)	1.81	(1.44, 2.27)
	Without Risk Factors	887	2219.0	(1980.9, 2485.7)	802	1179.2	(1046.4, 1328.9)	1.88	(1.60, 2.21)
11A	Overall	1198	4689.2	(4248.4, 5175.7)	1209	2675.7	(2426.4, 2950.6)	1.75	(1.53, 2.01)
	With Risk Factors	379	3593.5	(3007.9, 4293.2)	439	2535.7	(2146.9, 2994.9)	1.42	(1.11, 1.81)
	Without Risk Factors	819	5349.6	(4751.6, 6022.9)	770	2768.9	(2453.4, 3125.0)	1.93	(1.63, 2.28)
12F	Overall	1294	3077.7	(2765.9, 3424.7)	1222	2064.9	(1849.1, 2306.0)	1.49	(1.28, 1.74)
	With Risk Factors	427	2244.4	(1848.5, 2725.1)	451	1630.6	(1347.6, 1972.9)	1.38	(1.05, 1.81)
	Without Risk Factors	867	3636.2	(3204.8, 4125.7)	771	2414.9	(2111.4, 2762.1)	1.51	(1.26, 1.81)
15B	Overall	1283	2623.6	(2320.5, 2966.2)	1249	837.9	(739.2, 949.8)	3.13	(2.63, 3.73)
	With Risk Factors	426	2155.0	(1744.2, 2662.6)	452	888.3	(722.7, 1091.8)	2.43	(1.81, 3.26)
	Without Risk Factors	857	2899.0	(2492.6, 3371.7)	797	819.6	(699.6, 960.2)	3.54	(2.85, 4.39)
22F	Overall	1274	4270.4	(3827.0, 4765.2)	1227	2114.2	(1893.4, 2360.7)	2.02	(1.73, 2.36)
	With Risk Factors	410	3643.3	(2985.9, 4445.4)	450	1705.2	(1410.1, 2061.9)	2.14	(1.62, 2.81)
	Without Risk Factors	864	4680.0	(4106.3, 5333.8)	777	2435.7	(2127.3, 2788.6)	1.92	(1.60, 2.31)
33F	Overall	1157	5640.5	(5126.5, 6206.0)	1201	4081.2	(3717.6, 4480.4)	1.38	(1.21, 1.58)
	With Risk Factors	380	4535.6	(3850.6, 5342.6)	428	3496.9	(2999.5, 4076.8)	1.30	(1.04, 1.62)
	Without Risk Factors	777	6299.7	(5601.8, 7084.7)	773	4444.7	(3952.3, 4998.5)	1.42	(1.20, 1.67)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. n = Number of subjects with valid and determinate OPA titres for the specified serotype.

c. GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, age at vaccination in years (continuous), and baseline log transformed OPA titres.

d. GMRs (ratio of GMTs 20vPnC to PPSV23) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Table 23: Pneumococcal OPA GMTs and GMRs for the 13vPnC Serotypes 1 Month After Vaccination by Risk Status – Linear Regression Model – Cohort 2

Serotype	Risk Status[a]	Vaccine Group (as Randomised) 20vPnC n[b]	20vPnC GMT[c]	20vPnC (95% CI[c])	13vPnC n[b]	13vPnC GMT[c]	13vPnC (95% CI[c])	Vaccine Comparison 20vPnC/13vPnC GMR[d]	GMR (95% CI[d])
1	Overall	320	163.2	(136.5, 195.1)	107	192.3	(141.4, 261.6)	0.85	(0.60, 1.21)
	With Risk Factors	104	117.2	(85.4, 161.0)	32	84.6	(47.7, 149.9)	1.39	(0.72, 2.67)
	Without Risk Factors	216	198.4	(160.5, 245.3)	75	277.1	(193.9, 395.8)	0.72	(0.48, 1.08)
3	Overall	318	48.1	(42.2, 54.9)	108	47.0	(37.5, 58.9)	1.03	(0.79, 1.33)
	With Risk Factors	102	44.6	(35.5, 56.2)	32	52.5	(34.7, 79.4)	0.85	(0.53, 1.37)
	Without Risk Factors	216	49.9	(42.3, 58.8)	76	45.2	(34.4, 59.5)	1.10	(0.81, 1.51)
4	Overall	318	693.5	(569.3, 844.9)	108	1102.5	(790.0, 1538.7)	0.63	(0.43, 0.92)
	With Risk Factors	103	589.3	(426.3, 814.6)	32	632.6	(352.4, 1135.4)	0.93	(0.48, 1.82)
	Without Risk Factors	215	760.2	(592.0, 976.2)	76	1381.1	(916.2, 2081.8)	0.55	(0.34, 0.88)
5	Overall	313	93.6	(78.7, 111.3)	108	171.4	(127.7, 229.9)	0.55	(0.39, 0.77)
	With Risk Factors	100	63.9	(48.5, 84.3)	32	111.4	(68.2, 181.9)	0.57	(0.33, 1.01)
	Without Risk Factors	213	113.7	(91.4, 141.3)	76	217.2	(151.6, 311.2)	0.52	(0.35, 0.79)
6A	Overall	318	1410.9	(1156.4, 1721.3)	107	1644.9	(1167.5, 2317.6)	0.86	(0.58, 1.27)
	With Risk Factors	103	1305.7	(924.1, 1845.0)	32	2113.8	(1123.6, 3976.7)	0.62	(0.30, 1.27)
	Without Risk Factors	215	1480.2	(1155.9, 1895.5)	75	1530.3	(1012.6, 2312.6)	0.97	(0.60, 1.55)
6B	Overall	318	1780.2	(1495.9, 2118.7)	105	2227.4	(1658.0, 2992.4)	0.80	(0.57, 1.12)
	With Risk Factors	104	1601.7	(1182.8, 2168.8)	30	2071.5	(1190.5, 3604.3)	0.77	(0.41, 1.45)
	Without Risk Factors	214	1882.7	(1515.6, 2338.8)	75	2330.9	(1635.5, 3322.1)	0.81	(0.54, 1.22)
7F	Overall	313	1086.8	(932.1, 1267.2)	108	1888.9	(1458.4, 2446.5)	0.58	(0.43, 0.78)
	With Risk Factors	101	1028.8	(779.3, 1358.2)	32	1989.7	(1228.9, 3221.7)	0.52	(0.30, 0.90)
	Without Risk Factors	212	1136.9	(942.9, 1370.8)	76	1906.9	(1399.1, 2599.1)	0.60	(0.42, 0.85)
9V	Overall	312	1906.0	(1586.5, 2289.7)	105	3369.0	(2458.4, 4616.8)	0.57	(0.39, 0.81)
	With Risk Factors	100	1531.9	(1120.1, 2095.1)	30	2254.7	(1265.4, 4017.5)	0.68	(0.35, 1.31)
	Without Risk Factors	212	2146.2	(1709.7, 2694.2)	75	4109.8	(2815.3, 5999.6)	0.52	(0.34, 0.81)
14	Overall	313	1090.5	(915.8, 1298.6)	108	1306.9	(970.1, 1760.7)	0.83	(0.59, 1.18)
	With Risk Factors	103	948.2	(706.5, 1272.7)	32	1296.6	(763.3, 2202.5)	0.73	(0.40, 1.34)
	Without Risk Factors	210	1185.6	(952.7, 1475.5)	76	1362.4	(946.9, 1960.2)	0.87	(0.57, 1.32)
18C	Overall	315	2008.6	(1667.8, 2419.1)	107	2616.4	(1909.2, 3585.6)	0.77	(0.53, 1.10)
	With Risk Factors	102	1822.2	(1296.2, 2561.6)	32	1501.6	(814.2, 2769.2)	1.21	(0.60, 2.45)
	Without Risk Factors	213	2151.8	(1720.3, 2691.6)	75	3391.0	(2346.5, 4900.3)	0.63	(0.42, 0.97)
19A	Overall	318	682.9	(588.7, 792.3)	108	1165.1	(903.5, 1502.2)	0.59	(0.44, 0.78)

	With Risk Factors	104	600.2	(463.5, 777.2)	32	997.3	(629.4, 1580.2)	0.60	(0.35, 1.02)
	Without Risk Factors	214	741.2	(616.6, 890.9)	76	1286.2	(945.0, 1750.6)	0.58	(0.41, 0.82)
19F	Overall	320	311.4	(256.7, 377.7)	107	584.1	(418.9, 814.3)	0.53	(0.36, 0.78)
	With Risk Factors	104	251.5	(178.8, 353.7)	32	537.8	(289.5, 999.0)	0.47	(0.23, 0.95)
	Without Risk Factors	216	352.1	(277.4, 447.0)	75	614.5	(411.1, 918.4)	0.57	(0.36, 0.91)
23F	Overall	319	563.3	(447.6, 708.9)	107	901.1	(607.7, 1336.0)	0.63	(0.40, 0.98)
	With Risk Factors	104	557.3	(376.2, 825.5)	32	721.4	(359.5, 1447.3)	0.77	(0.35, 1.72)
	Without Risk Factors	215	586.3	(439.9, 781.4)	75	1018.7	(627.7, 1653.4)	0.58	(0.33, 1.00)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. n = Number of subjects with valid and determinate OPA titres for the specified serotype.

c. GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, age at vaccination in years (continuous), and baseline log transformed OPA titres.

d. GMRs (ratio of GMTs 20vPnC to 13vPnC) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Table 24: Pneumococcal OPA GMTs and GMRs for the 13vPnC Serotypes 1 Month After Vaccination by Risk Status – Linear Regression Model – B7471008 and 18-49 Years of Age in B7471007

Serotype	Risk Status[a]	Vaccine Group (as Randomised)						Vaccine Comparison 20vPnC/13vPnC	
		20vPnC			13vPnC				
		n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d]	(95% CI[d])
1	Overall	1702	201.4	(184.6, 219.6)	337	286.7	(245.0, 335.5)	0.70	(0.59, 0.83)
	With Risk Factors	474	146.7	(123.0, 175.1)	90	214.6	(155.8, 295.6)	0.68	(0.48, 0.97)
	Without Risk Factors	1228	228.1	(206.9, 251.6)	247	317.1	(265.8, 378.3)	0.72	(0.60, 0.87)
3	Overall	1694	47.1	(44.2, 50.1)	337	52.8	(47.1, 59.2)	0.89	(0.79, 1.01)
	With Risk Factors	472	44.0	(38.9, 49.8)	91	56.9	(45.5, 71.0)	0.77	(0.61, 0.99)
	Without Risk Factors	1222	48.4	(45.0, 52.1)	246	51.2	(44.8, 58.5)	0.95	(0.82, 1.09)
4	Overall	1689	1893.0	(1728.7, 2072.9)	333	2397.2	(2033.3, 2826.3)	0.79	(0.66, 0.94)
	With Risk Factors	465	1791.1	(1498.3, 2141.2)	88	2498.3	(1802.6, 3462.6)	0.72	(0.50, 1.02)
	Without Risk Factors	1224	1923.5	(1731.0, 2137.4)	245	2340.2	(1934.9, 2830.5)	0.82	(0.67, 1.01)
5	Overall	1690	129.8	(118.7, 142.0)	337	183.9	(156.4, 216.3)	0.71	(0.59, 0.84)
	With Risk Factors	471	115.0	(97.1, 136.2)	90	162.3	(119.5, 220.4)	0.71	(0.51, 0.99)
	Without Risk Factors	1219	136.5	(122.8, 151.6)	247	191.3	(158.1, 231.3)	0.71	(0.58, 0.88)
6A	Overall	1683	4277.2	(3922.1, 4664.4)	338	4675.5	(4000.1, 5465.0)	0.91	(0.77, 1.08)
	With Risk Factors	468	3913.6	(3269.6, 4684.3)	91	3884.3	(2796.2, 5395.9)	1.01	(0.70, 1.44)
	Without Risk Factors	1215	4444.8	(4029.1, 4903.5)	247	4953.1	(4156.7, 5902.1)	0.90	(0.74, 1.08)
6B	Overall	1694	4812.7	(4420.4, 5239.7)	331	5502.8	(4721.5, 6413.3)	0.87	(0.74, 1.03)
	With Risk Factors	472	4651.4	(3923.1, 5514.8)	89	5522.8	(4060.9, 7510.8)	0.84	(0.60, 1.18)
	Without Risk Factors	1222	4875.9	(4422.0, 5376.3)	242	5443.7	(4568.4, 6486.7)	0.90	(0.74, 1.08)
7F	Overall	1668	2040.1	(1876.4, 2218.1)	329	2709.3	(2329.3, 3151.1)	0.75	(0.64, 0.89)
	With Risk Factors	464	1669.2	(1416.2, 1967.4)	89	3044.3	(2271.1, 4080.5)	0.55	(0.40, 0.76)
	Without Risk Factors	1204	2197.1	(1994.5, 2420.3)	240	2592.1	(2175.7, 3088.1)	0.85	(0.70, 1.02)
9V	Overall	1682	6005.0	(5520.3, 6532.3)	335	6679.3	(5748.7, 7760.5)	0.90	(0.76, 1.06)
	With Risk Factors	468	5775.8	(4949.2, 6740.5)	89	7874.4	(5974.5, 10378.4)	0.73	(0.54, 0.99)
	Without Risk Factors	1214	6077.7	(5497.2, 6719.6)	246	6259.9	(5238.3, 7480.6)	0.97	(0.80, 1.18)
14	Overall	1688	2161.9	(1996.6, 2340.9)	334	2314.0	(2005.9, 2669.5)	0.93	(0.80, 1.09)
	With Risk Factors	468	2034.0	(1738.8, 2379.5)	91	2292.7	(1729.0, 3040.1)	0.89	(0.65, 1.21)
	Without Risk Factors	1220	2221.1	(2025.2, 2436.0)	243	2312.6	(1960.2, 2728.5)	0.96	(0.80, 1.15)
18C	Overall	1681	4781.5	(4352.0, 5253.5)	329	5398.0	(4551.0, 6402.6)	0.89	(0.74, 1.06)
	With Risk Factors	467	4499.8	(3776.5, 5361.6)	88	5550.4	(4034.6, 7635.8)	0.81	(0.57, 1.15)
	Without Risk Factors	1214	4915.3	(4394.4, 5497.9)	241	5330.7	(4355.3, 6524.5)	0.92	(0.74, 1.14)
19A	Overall	1678	1577.2	(1462.8, 1700.6)	334	1831.1	(1599.4, 2096.3)	0.86	(0.74, 1.00)
	With Risk Factors	464	1624.9	(1409.4, 1873.3)	90	1582.5	(1230.7, 2034.9)	1.03	(0.78, 1.35)
	Without Risk Factors	1214	1557.2	(1424.3, 1702.5)	244	1930.8	(1644.4, 2267.1)	0.81	(0.68, 0.96)
19F	Overall	1688	620.8	(566.3, 680.5)	336	847.7	(718.5, 1000.3)	0.73	(0.61, 0.88)
	With Risk Factors	468	560.6	(469.7, 669.1)	91	737.2	(536.0, 1014.0)	0.76	(0.54, 1.08)
	Without Risk Factors	1220	642.4	(576.9, 715.4)	245	887.5	(731.5, 1076.7)	0.72	(0.59, 0.89)
23F	Overall	1699	1652.7	(1483.3, 1841.4)	337	1917.7	(1577.5, 2331.3)	0.86	(0.70, 1.06)
	With Risk Factors	474	1312.5	(1060.3, 1624.7)	90	1465.0	(995.6, 2155.6)	0.90	(0.59, 1.36)
	Without Risk Factors	1225	1801.9	(1591.8, 2039.8)	247	2106.1	(1684.6, 2632.9)	0.86	(0.67, 1.09)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least squares; OPA = opsonophagocytic activity. Notes: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Evaluable Immunogenicity Population: Evaluable 13-Matched Immunogenicity Population for Cohort 1, Evaluable-20 Immunogenicity Population for Cohort 2 and 3 for B7471007 and Evaluable Immunogenicity Population for B7471008.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. n = Number of subjects with valid and determinate OPA titres for the specified serotype.

c. GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with study, vaccine group, sex, age at vaccination in years (continuous), and baseline log transformed OPA titres.

d. GMRs (ratio of GMTs 20vPnC to 13vPnC) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

Table 25: Proportion of Subjects Achieving a ≥4-Fold Rise in OPA Titres From Before Vaccination to 1 Month After Vaccination for the 13vPnC Serotypes by Risk Status – Cohort 1

Sero type	Risk Status[a]	Vaccine Group (as Randomised)							
		20vPnC				13vPnC			
		N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
1	Overall	1425	1027	72.1	(69.7, 74.4)	1418	1060	74.8	(72.4, 77.0)
	With Risk Factors	463	293	63.3	(58.7, 67.7)	516	344	66.7	(62.4, 70.7)
	Without Risk Factors	962	734	76.3	(73.5, 79.0)	902	716	79.4	(76.6, 82.0)
3	Overall	1404	787	56.1	(53.4, 58.7)	1401	864	61.7	(59.1, 64.2)
	With Risk Factors	453	237	52.3	(47.6, 57.0)	510	301	59.0	(54.6, 63.3)
	Without Risk Factors	951	550	57.8	(54.6, 61.0)	891	563	63.2	(59.9, 66.4)
4	Overall	1370	1035	75.5	(73.2, 77.8)	1374	1094	79.6	(77.4, 81.7)
	With Risk Factors	443	304	68.6	(64.1, 72.9)	500	376	75.2	(71.2, 78.9)
	Without Risk Factors	927	731	78.9	(76.1, 81.4)	874	718	82.2	(79.4, 84.6)
5	Overall	1411	784	55.6	(52.9, 58.2)	1394	845	60.6	(58.0, 63.2)
	With Risk Factors	456	231	50.7	(46.0, 55.3)	506	302	59.7	(55.3, 64.0)
	Without Risk Factors	955	553	57.9	(54.7, 61.1)	888	543	61.1	(57.9, 64.4)
6A	Overall	1382	1112	80.5	(78.3, 82.5)	1371	1152	84.0	(82.0, 85.9)
	With Risk Factors	448	351	78.3	(74.2, 82.1)	505	408	80.8	(77.1, 84.1)
	Without Risk Factors	934	761	81.5	(78.8, 83.9)	866	744	85.9	(83.4, 88.2)
6B	Overall	1360	1029	75.7	(73.3, 77.9)	1360	1055	77.6	(75.3, 79.8)
	With Risk Factors	439	308	70.2	(65.6, 74.4)	494	372	75.3	(71.3, 79.0)
	Without Risk Factors	921	721	78.3	(75.5, 80.9)	866	683	78.9	(76.0, 81.5)
7F	Overall	1367	981	71.8	(69.3, 74.1)	1355	979	72.3	(69.8, 74.6)
	With Risk Factors	445	294	66.1	(61.5, 70.5)	491	323	65.8	(61.4, 70.0)
	Without Risk Factors	922	687	74.5	(71.6, 77.3)	864	656	75.9	(72.9, 78.7)
9V	Overall	1317	892	67.7	(65.1, 70.3)	1294	897	69.3	(66.7, 71.8)
	With Risk Factors	430	260	60.5	(55.7, 65.1)	475	309	65.1	(60.6, 69.3)
	Without Risk Factors	887	632	71.3	(68.1, 74.2)	819	588	71.8	(68.6, 74.9)
14	Overall	1370	797	58.2	(55.5, 60.8)	1366	737	54.0	(51.3, 56.6)
	With Risk Factors	453	252	55.6	(50.9, 60.3)	495	240	48.5	(44.0, 53.0)
	Without Risk Factors	917	545	59.4	(56.2, 62.6)	871	497	57.1	(53.7, 60.4)
18C	Overall	1407	1093	77.7	(75.4, 79.8)	1396	1111	79.6	(77.4, 81.7)
	With Risk Factors	455	322	70.8	(66.4, 74.9)	508	387	76.2	(72.2, 79.8)
	Without Risk Factors	952	771	81.0	(78.3, 83.4)	888	724	81.5	(78.8, 84.0)
19A	Overall	1400	1031	73.6	(71.3, 75.9)	1379	1069	77.5	(75.2, 79.7)
	With Risk Factors	456	312	68.4	(63.9, 72.7)	501	364	72.7	(68.5, 76.5)
	Without Risk Factors	944	719	76.2	(73.3, 78.9)	878	705	80.3	(77.5, 82.9)
19F	Overall	1405	894	63.6	(61.1, 66.2)	1397	935	66.9	(64.4, 69.4)
	With Risk Factors	454	259	57.0	(52.4, 61.7)	507	321	63.3	(59.0, 67.5)
	Without Risk Factors	951	635	66.8	(63.7, 69.8)	890	614	69.0	(65.8, 72.0)
23F	Overall	1409	995	70.6	(68.2, 73.0)	1402	1043	74.4	(72.0, 76.7)
	With Risk Factors	458	314	68.6	(64.1, 72.8)	508	361	71.1	(66.9, 75.0)
	Without Risk Factors	951	681	71.6	(68.6, 74.5)	894	682	76.3	(73.4, 79.0)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.

c. n = Number of subjects with a ≥4-fold rise in titers from before vaccination to 1 month after vaccination for the specified serotype.

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

Table 26: Proportion of Subjects Achieving a ≥4-Fold Rise in OPA Titres From Before Vaccination to 1 Month After Vaccination for the 13vPnC Serotypes by Risk Status - Cohort 2

Sero type	Risk Status[a]	Vaccine Group (as Randomised)							
		20vPnC				13vPnC			
		N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
1	Overall	319	239	74.9	(69.8, 79.6)	107	84	78.5	(69.5, 85.9)
	With Risk Factors	104	69	66.3	(56.4, 75.3)	32	21	65.6	(46.8, 81.4)
	Without Risk Factors	215	170	79.1	(73.0, 84.3)	75	63	84.0	(73.7, 91.4)
3	Overall	317	187	59.0	(53.4, 64.5)	108	65	60.2	(50.3, 69.5)
	With Risk Factors	102	55	53.9	(43.8, 63.8)	32	20	62.5	(43.7, 78.9)
	Without Risk Factors	215	132	61.4	(54.5, 67.9)	76	45	59.2	(47.3, 70.4)
4	Overall	304	256	84.2	(79.6, 88.1)	106	90	84.9	(76.6, 91.1)
	With Risk Factors	100	82	82.0	(73.1, 89.0)	31	23	74.2	(55.4, 88.1)
	Without Risk Factors	204	174	85.3	(79.7, 89.9)	75	67	89.3	(80.1, 95.3)
5	Overall	312	171	54.8	(49.1, 60.4)	108	78	72.2	(62.8, 80.4)
	With Risk Factors	100	43	43.0	(33.1, 53.3)	32	20	62.5	(43.7, 78.9)
	Without Risk Factors	212	128	60.4	(53.5, 67.0)	76	58	76.3	(65.2, 85.3)

6A	Overall	312	268	85.9	(81.5, 89.6)	104	92	88.5	(80.7, 93.9)
	With Risk Factors	103	84	81.6	(72.7, 88.5)	31	27	87.1	(70.2, 96.4)
	Without Risk Factors	209	184	88.0	(82.9, 92.1)	73	65	89.0	(79.5, 95.1)
6B	Overall	299	236	78.9	(73.9, 83.4)	103	85	82.5	(73.8, 89.3)
	With Risk Factors	100	75	75.0	(65.3, 83.1)	30	25	83.3	(65.3, 94.4)
	Without Risk Factors	199	161	80.9	(74.7, 86.1)	73	60	82.2	(71.5, 90.2)
7F	Overall	300	219	73.0	(67.6, 77.9)	106	91	85.8	(77.7, 91.9)
	With Risk Factors	96	67	69.8	(59.6, 78.7)	32	27	84.4	(67.2, 94.7)
	Without Risk Factors	204	152	74.5	(68.0, 80.3)	74	64	86.5	(76.5, 93.3)
9V	Overall	288	212	73.6	(68.1, 78.6)	97	74	76.3	(66.6, 84.3)
	With Risk Factors	95	66	69.5	(59.2, 78.5)	28	22	78.6	(59.0, 91.7)
	Without Risk Factors	193	146	75.6	(69.0, 81.5)	69	52	75.4	(63.5, 84.9)
14	Overall	300	187	62.3	(56.6, 67.8)	103	62	60.2	(50.1, 69.7)
	With Risk Factors	96	57	59.4	(48.9, 69.3)	30	18	60.0	(40.6, 77.3)
	Without Risk Factors	204	130	63.7	(56.7, 70.3)	73	44	60.3	(48.1, 71.5)
18C	Overall	308	254	82.5	(77.8, 86.5)	106	88	83.0	(74.5, 89.6)
	With Risk Factors	100	79	79.0	(69.7, 86.5)	31	25	80.6	(62.5, 92.5)
	Without Risk Factors	208	175	84.1	(78.4, 88.8)	75	63	84.0	(73.7, 91.4)
19A	Overall	310	248	80.0	(75.1, 84.3)	105	91	86.7	(78.6, 92.5)
	With Risk Factors	101	78	77.2	(67.8, 85.0)	32	25	78.1	(60.0, 90.7)
	Without Risk Factors	209	170	81.3	(75.4, 86.4)	73	66	90.4	(81.2, 96.1)
19F	Overall	316	203	64.2	(58.7, 69.5)	106	83	78.3	(69.2, 85.7)
	With Risk Factors	104	62	59.6	(49.5, 69.1)	32	23	71.9	(53.3, 86.3)
	Without Risk Factors	212	141	66.5	(59.7, 72.8)	74	60	81.1	(70.3, 89.3)
23F	Overall	313	254	81.2	(76.4, 85.3)	106	93	87.7	(79.9, 93.3)
	With Risk Factors	100	82	82.0	(73.1, 89.0)	32	28	87.5	(71.0, 96.5)
	Without Risk Factors	213	172	80.8	(74.8, 85.8)	74	65	87.8	(78.2, 94.3)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.

b. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.

c. n = Number of subjects with a ≥4-fold rise in titres from before vaccination to 1 month after vaccination for the specified serotype.

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

Table 27: Proportion of Subjects Achieving a ≥4-Fold Rise in OPA Titres From Before Vaccination to 1 Month After Vaccination for the 13vPnC Serotypes by Risk Status - B7471008 and 18-49 years of age in B7471007

Serotype	Risk Status[a]	Vaccine Group (as Randomised)							
		20vPnC				13vPnC			
		N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])
1	Overall	315	271	86.0	(81.7, 89.7)	105	92	87.6	(79.8, 93.2)
	With Risk Factors	79	61	77.2	(66.4, 85.9)	30	26	86.7	(69.3, 96.2)
	Without Risk Factors	236	210	89.0	(84.3, 92.7)	75	66	88.0	(78.4, 94.4)
3	Overall	312	177	56.7	(51.0, 62.3)	105	66	62.9	(52.9, 72.1)
	With Risk Factors	79	44	55.7	(44.1, 66.9)	30	20	66.7	(47.2, 82.7)
	Without Risk Factors	233	133	57.1	(50.5, 63.5)	75	46	61.3	(49.4, 72.4)
4	Overall	302	276	91.4	(87.6, 94.3)	103	94	91.3	(84.1, 95.9)
	With Risk Factors	77	73	94.8	(87.2, 98.6)	30	26	86.7	(69.3, 96.2)
	Without Risk Factors	225	203	90.2	(85.6, 93.8)	73	68	93.2	(84.7, 97.7)
5	Overall	315	204	64.8	(59.2, 70.0)	106	79	74.5	(65.1, 82.5)
	With Risk Factors	79	48	60.8	(49.1, 71.6)	31	23	74.2	(55.4, 88.1)
	Without Risk Factors	236	156	66.1	(59.7, 72.1)	75	56	74.7	(63.3, 84.0)
6A	Overall	305	295	96.7	(94.1, 98.4)	103	98	95.1	(89.0, 98.4)
	With Risk Factors	77	75	97.4	(90.9, 99.7)	30	27	90.0	(73.5, 97.9)
	Without Risk Factors	228	220	96.5	(93.2, 98.5)	73	71	97.3	(90.5, 99.7)
6B	Overall	286	255	89.2	(85.0, 92.5)	97	84	86.6	(78.2, 92.7)
	With Risk Factors	71	62	87.3	(77.3, 94.0)	30	28	93.3	(77.9, 99.2)
	Without Risk Factors	215	193	89.8	(84.9, 93.5)	67	56	83.6	(72.5, 91.5)
7F	Overall	284	216	76.1	(70.7, 80.9)	97	82	84.5	(75.8, 91.1)
	With Risk Factors	70	49	70.0	(57.9, 80.4)	29	24	82.8	(64.2, 94.2)
	Without Risk Factors	214	167	78.0	(71.9, 83.4)	68	58	85.3	(74.6, 92.7)
9V	Overall	281	236	84.0	(79.2, 88.1)	99	80	80.8	(71.7, 88.0)
	With Risk Factors	74	62	83.8	(73.4, 91.3)	30	22	73.3	(54.1, 87.7)
	Without Risk Factors	207	174	84.1	(78.3, 88.8)	69	58	84.1	(73.3, 91.8)
14	Overall	291	181	62.2	(56.4, 67.8)	100	62	62.0	(51.7, 71.5)
	With Risk Factors	74	42	56.8	(44.7, 68.2)	29	17	58.6	(38.9, 76.5)
	Without Risk Factors	217	139	64.1	(57.3, 70.4)	71	45	63.4	(51.1, 74.5)
18C	Overall	299	261	87.3	(83.0, 90.8)	96	83	86.5	(78.0, 92.6)
	With Risk Factors	76	64	84.2	(74.0, 91.6)	29	24	82.8	(64.2, 94.2)
	Without Risk Factors	223	197	88.3	(83.4, 92.2)	67	59	88.1	(77.8, 94.7)
19A	Overall	299	247	82.6	(77.8, 86.7)	105	85	81.0	(72.1, 88.0)
	With Risk Factors	74	64	86.5	(76.5, 93.3)	31	23	74.2	(55.4, 88.1)

	Without Risk Factors	225	183	81.3	(75.6, 86.2)	74	62	83.8	(73.4, 91.3)
19F	Overall	310	243	78.4	(73.4, 82.8)	105	81	77.1	(67.9, 84.8)
	With Risk Factors	77	63	81.8	(71.4, 89.7)	30	23	76.7	(57.7, 90.1)
	Without Risk Factors	233	180	77.3	(71.3, 82.5)	75	58	77.3	(66.2, 86.2)
23F	Overall	309	271	87.7	(83.5, 91.1)	104	95	91.3	(84.2, 96.0)
	With Risk Factors	79	65	82.3	(72.1, 90.0)	31	26	83.9	(66.3, 94.5)
	Without Risk Factors	230	206	89.6	(84.9, 93.2)	73	69	94.5	(86.6, 98.5)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. Group with risk factors includes subjects with one or more medical history conditions or other factors (smoker) that puts them with an increased risk for serious pneumococcal disease; group with no risk factors includes subjects without an identified medical condition or other factors that would put them with an increased risk for serious pneumococcal disease.
b. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.
c. n = Number of subjects with a ≥4-fold rise in titres from before vaccination to 1 month after vaccination for the specified serotype.
d. Exact 2-sided CI based on the Clopper and Pearson method.

Study B7471006

Participants were enrolled into different cohorts based on pneumococcal vaccination history:

- Cohort A: Approximately 375 participants who had received PPSV23 ≥1 to ≤5 years previously but had not been vaccinated with 13vPnC were to be randomised (2:1) to receive either 20vPnC or 13vPnC (control for safety only).
- Cohort B: Approximately 375 participants who had received 13vPnC ≥6 months previously, but had not been vaccinated with PPSV23, were to be randomised (2:1) to receive either 20vPnC or PPSV23 (control for safety only).
- Cohort C: Approximately 125 participants who had previously received 13vPnC followed by PPSV23 (PPSV23 vaccination must have been given ≥1 year prior to vaccination in this study) were to receive 20vPnC.

Primary Immunogenicity Endpoint

Pneumococcal serotype specific OPA GMTs:

• At 1 month after 20vPnC, OPA GMTs for most of the 20 vaccine serotypes tended to be numerically highest in participants with prior 13vPnC only, ranging from 54.3 (serotype 3) to 4156.5 (serotype 22F) and lowest in participants with prior PPSV23 only, ranging from 31.1 (serotype 3) to 2026.2 (serotype 33F). OPA GMTs in participants with prior 13vPnC and PPSV23 generally fell in between, ranging from 39.3 (serotype 3) to 2717.8 (serotype 22F).

Table 28: Pneumococcal OPA GMTs – Evaluable Immunogenicity Population

Sero type	Sampling Time Point	Cohort A 20vPnC			Cohort B 20vPnC			Cohort C 20vPnC		
		n	GMT	(95% CI)	n	GMT	(95% CI)	n	GMT	(95% CI)
13vPnC										
1	Before vaccination	246	23.7	(19.9, 28.2)	243	33.5	(27.6, 40.7)	121	42.2	(31.9, 55.8)
	1 Month after vaccination	246	50.8	(41.6, 62.0)	243	115.3	(96.3, 137.9)	120	82.1	(61.2, 110.1)
3	Before vaccination	247	12.8	(11.2, 14.6)	241	15.4	(13.4, 17.7)	121	20.5	(16.8, 25.0)
	1 Month after vaccination	243	31.1	(26.7, 36.1)	242	54.3	(46.9, 62.8)	119	39.3	(32.0, 48.2)
4	Before vaccination	242	28.5	(23.3, 34.9)	235	66.6	(52.5, 84.3)	120	73.1	(53.1, 100.7)
	1 Month after vaccination	236	149.9	(118.2, 190.1)	241	334.9	(273.8, 409.5)	116	193.7	(143.2, 262.0)
5	Before vaccination	244	27.3	(23.8, 31.3)	243	37.8	(32.2, 44.4)	121	46.6	(36.9, 58.9)
	1 Month after vaccination	244	62.8	(52.7, 74.9)	243	87.3	(73.2, 104.2)	120	83.5	(64.8, 107.6)
6A	Before vaccination	244	56.6	(45.8, 69.9)	236	125.1	(98.8, 158.3)	118	161.0	(115.7, 224.1)
	1 Month after vaccination	242	748.7	(576.7, 972.0)	241	1080.9	(880.2, 1327.4)	121	1085.3	(796.9, 1478.1)
6B	Before vaccination	242	107.0	(86.3, 132.6)	240	173.9	(137.9, 219.4)	119	258.9	(190.7, 351.6)
	1 Month after vaccination	243	727.3	(573.6, 922.1)	241	1159.4	(950.7, 1413.8)	121	1033.3	(754.6, 1414.8)
7F	Before vaccination	240	155.7	(132.1, 183.7)	241	209.9	(175.3, 251.2)	120	205.8	(163.9, 258.5)
	1 Month after vaccination	240	378.1	(316.4, 451.9)	243	555.4	(466.8, 660.9)	120	345.8	(277.0, 431.7)
9V	Before vaccination	231	203.0	(171.0, 241.0)	234	339.2	(281.8, 408.2)	118	352.4	(270.2, 459.4)
	1 Month after vaccination	241	550.3	(454.0, 666.9)	237	1085.0	(893.5, 1317.5)	117	723.4	(558.1, 937.6)
14	Before vaccination	242	212.1	(166.4, 270.3)	238	282.2	(223.7, 355.9)	121	335.5	(237.9, 473.1)
	1 Month after vaccination	240	391.2	(314.6, 486.3)	242	664.9	(554.1, 797.9)	119	580.5	(433.7, 777.0)
18C	Before vaccination	247	172.8	(137.3, 217.5)	242	219.3	(176.8, 272.0)	120	277.8	(209.1, 369.2)
	1 Month after vaccination	245	551.9	(445.1, 684.4)	240	845.9	(692.5, 1033.1)	120	621.2	(469.9, 821.3)
19A	Before vaccination	244	81.6	(66.4, 100.3)	240	123.6	(100.0, 152.8)	118	182.1	(140.9, 235.4)
	1 Month after vaccination	242	238.6	(197.5, 288.4)	242	365.1	(303.0, 440.0)	120	340.6	(264.1, 439.2)

19F	Before vaccination	246	60.9	(51.9, 71.3)	242	88.9	(74.0, 106.8)	121	120.2	(93.7, 154.2)
	1 Month after vaccination	244	159.0	(131.4, 192.3)	242	242.3	(199.4, 294.3)	118	217.7	(168.1, 281.8)
23F	Before vaccination	244	22.8	(18.3, 28.3)	242	47.9	(37.2, 61.8)	120	65.9	(46.1, 94.1)
	1 Month after vaccination	245	151.6	(115.3, 199.3)	243	450.2	(357.8, 566.4)	120	292.6	(203.6, 420.5)
Additional serotypes										
8	Before vaccination	239	55.4	(45.4, 67.5)	236	27.9	(23.6, 33.0)	113	138.8	(98.6, 195.4)
	1 Month after vaccination	230	211.9	(172.0, 261.0)	226	602.9	(482.9, 752.8)	109	293.8	(220.0, 392.4)
10A	Before vaccination	221	211.6	(166.2, 269.5)	231	141.2	(112.9, 176.6)	119	399.6	(280.8, 568.5)
	1 Month after vaccination	219	1012.1	(806.7, 1269.8)	210	2005.4	(1586.0, 2535.7)	110	1580.3	(1175.9, 2123.8)
11A	Before vaccination	208	510.0	(396.2, 656.4)	210	269.0	(211.0, 343.0)	106	550.4	(385.7, 785.3)
	1 Month after vaccination	216	1473.2	(1192.4, 1820.2)	206	1908.2	(1541.5, 2362.2)	102	1566.6	(1140.7, 2151.4)
12F	Before vaccination	230	147.0	(112.1, 192.9)	227	53.2	(43.3, 65.4)	113	367.8	(236.3, 572.5)
	1 Month after vaccination	224	1054.5	(822.0, 1352.7)	214	1763.4	(1371.8, 2266.7)	110	1401.2	(1001.8, 1959.7)
15B	Before vaccination	231	140.2	(104.3, 188.6)	215	74.1	(55.9, 98.3)	110	190.0	(124.0, 291.0)
	1 Month after vaccination	225	647.1	(490.8, 853.1)	201	1479.5	(1093.0, 2002.8)	110	1066.9	(721.3, 1578.1)
22F	Before vaccination	236	167.5	(122.0, 229.9)	223	60.4	(44.6, 81.7)	116	286.4	(179.7, 456.4)
	1 Month after vaccination	218	1772.8	(1354.7, 2319.8)	206	4156.5	(3243.8, 5326.2)	108	2717.8	(1978.4, 3733.4)
33F	Before vaccination	231	1128.8	(935.8, 1361.7)	226	605.8	(507.3, 723.4)	115	1352.8	(1036.9, 1764.9)
	1 Month after vaccination	216	2026.2	(1684.3, 2437.4)	208	3174.9	(2579.1, 3908.3)	103	2182.9	(1638.6, 2907.8)

Abbreviations: GMT = geometric mean titre; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution).

Secondary Immunogenicity Endpoints

Serotype-specific pneumococcal OPA GMFRs From Before to 1 Month After Vaccination:

Increases in OPA titres for all 20 vaccine serotypes were observed based on OPA GMFRs from before to 1 month after 20vPnC in all 3 cohorts, regardless of prior pneumococcal vaccination. Immune responses to the 7 additional serotypes 1 month after 20vPnC from participants with prior 13vPnC only (Cohort B) were substantially higher than before vaccination with 20vPnC.

For the 13vPnC serotypes, the GMFRs appeared to be generally highest in Cohort B (prior 13vPnC only), ranging from 2.3 (serotypes 5 and 14) to 9.3 (serotype 23F), followed by Cohort A (prior PPSV23 only), ranging from 1.8 (serotype 14) to 12.6 (serotype 6A) and lowest in Cohort C (prior 13vPnC and PPSV23), ranging from 1.6 (serotype 7F) to 6.5 (serotype 6A); however, differences were small, and as noted above, baseline titres to these serotypes were also higher in participants with prior 13vPnC and PPSV23 relative to participants with prior PPSV23 only. As PPSV23 does not contain the polysaccharide for serotype 6A, participants previously vaccinated with PPSV23 only were naïve to vaccination for that serotype.

For the 7 additional serotypes, GMFRs were higher in participants with prior 13vPnC only, who were naïve to these vaccine serotypes prior to receiving 20vPnC, ranging from 5.4 (serotype 33F) to 66.9 (serotype 22F), than in participants with prior PPSV23 only, ranging from 1.8 (serotype 33F) to 11.1 (serotype 22F), and in participants with prior 13vPnC and PPSV23, ranging from 1.8 (serotype 33F) to 9.8 (serotype 22F).

Table 29: Pneumococcal OPA GMFRs From Before Vaccination to 1 Month After Vaccination – Evaluable Immunogenicity Population

Serotype	Vaccine Group	n	Before Vaccination		1 Month After Vaccination		1 Month After Vaccination/ Before Vaccination	
			GMT	(95% CI)	GMT	(95% CI)	GMFR	(95% CI)
13vPnC								
1	Cohort A 20vPnC	245	23.8	(20.0, 28.3)	51.2	(41.9, 62.5)	2.2	(1.9, 2.5)
	Cohort B 20vPnC	243	33.5	(27.6, 40.7)	115.3	(96.3, 137.9)	3.4	(2.9, 4.1)
	Cohort C 20vPnC	120	40.9	(31.0, 53.8)	82.1	(61.2, 110.1)	2.0	(1.7, 2.4)
3	Cohort A 20vPnC	243	12.7	(11.1, 14.6)	31.1	(26.7, 36.1)	2.4	(2.1, 2.8)
	Cohort B 20vPnC	240	15.3	(13.4, 17.6)	54.3	(46.9, 63.0)	3.5	(3.1, 4.1)
	Cohort C 20vPnC	119	20.3	(16.6, 24.8)	39.3	(32.0, 48.2)	1.9	(1.6, 2.3)
4	Cohort A 20vPnC	231	29.9	(24.2, 36.9)	145.8	(114.6, 185.5)	4.9	(3.9, 6.1)
	Cohort C 20vPnC	115	78.2	(56.4, 108.3)	191.4	(141.2, 259.2)	2.4	(1.9, 3.1)
5	Cohort A 20vPnC	241	27.4	(23.8, 31.4)	62.2	(52.2, 74.1)	2.3	(2.0, 2.6)
	Cohort B 20vPnC	243	37.8	(32.2, 44.4)	87.3	(73.2, 104.2)	2.3	(2.0, 2.6)
	Cohort C 20vPnC	120	47.1	(37.3, 59.5)	83.5	(64.8, 107.6)	1.8	(1.5, 2.0)
6A	Cohort A 20vPnC	239	57.9	(46.7, 71.8)	731.3	(562.9, 950.0)	12.6	(9.5, 16.7)
	Cohort B 20vPnC	234	127.2	(100.4, 161.1)	1051.2	(852.2, 1296.8)	8.3	(6.6, 10.4)

	Cohort C 20vPnC	118	161.0	(115.7, 224.1)	1048.1	(765.8, 1434.5)	6.5	(4.7, 9.1)
6B	Cohort A 20vPnC	238	108.9	(87.6, 135.2)	720.3	(565.6, 917.3)	6.6	(5.2, 8.4)
	Cohort B 20vPnC	238	175.5	(138.9, 221.6)	1178.8	(967.0, 1436.9)	6.7	(5.4, 8.3)
	Cohort C 20vPnC	119	258.9	(190.7, 351.6)	1030.3	(753.0, 1409.6)	4.0	(3.0, 5.2)
7F	Cohort A 20vPnC	233	160.6	(135.7, 190.0)	366.5	(306.2, 438.7)	2.3	(1.9, 2.7)
	Cohort B 20vPnC	241	209.9	(175.3, 251.2)	545.0	(458.8, 647.5)	2.6	(2.2, 3.0)
	Cohort C 20vPnC	119	204.5	(162.6, 257.3)	337.1	(271.1, 419.2)	1.6	(1.4, 2.0)
9V	Cohort A 20vPnC	226	206.1	(173.1, 245.4)	503.3	(413.4, 612.7)	2.4	(2.1, 2.9)
	Cohort B 20vPnC	228	346.6	(287.8, 417.5)	1058.3	(867.7, 1290.9)	3.1	(2.6, 3.6)
	Cohort C 20vPnC	114	345.4	(263.9, 452.1)	720.5	(552.2, 940.0)	2.1	(1.7, 2.6)
14	Cohort A 20vPnC	236	213.3	(167.3, 272.0)	386.3	(309.8, 481.8)	1.8	(1.5, 2.1)
	Cohort B 20vPnC	237	285.5	(226.4, 360.0)	659.7	(548.1, 794.1)	2.3	(1.9, 2.8)
	Cohort C 20vPnC	119	341.6	(241.8, 482.8)	580.5	(433.7, 777.0)	1.7	(1.4, 2.1)
18C	Cohort A 20vPnC	245	175.1	(139.0, 220.7)	551.9	(445.1, 684.4)	3.2	(2.5, 3.9)
	Cohort B 20vPnC	240	217.2	(174.9, 269.8)	845.9	(692.5, 1033.1)	3.9	(3.2, 4.8)
	Cohort C 20vPnC	119	272.5	(205.1, 362.0)	611.3	(462.2, 808.5)	2.2	(1.8, 2.7)
19A	Cohort A 20vPnC	239	83.8	(68.1, 103.2)	240.6	(198.8, 291.2)	2.9	(2.4, 3.4)
	Cohort B 20vPnC	239	124.4	(100.6, 153.9)	356.0	(295.7, 428.7)	2.9	(2.4, 3.4)
	Cohort C 20vPnC	117	183.5	(141.7, 237.6)	344.9	(266.3, 446.8)	1.9	(1.6, 2.2)
19F	Cohort A 20vPnC	243	61.0	(52.0, 71.5)	160.2	(132.4, 193.8)	2.6	(2.2, 3.1)
	Cohort B 20vPnC	241	89.4	(74.4, 107.4)	242.2	(199.2, 294.5)	2.7	(2.3, 3.2)
	Cohort C 20vPnC	118	117.5	(91.1, 151.5)	217.7	(168.1, 281.8)	1.9	(1.5, 2.3)
23F	Cohort A 20vPnC	242	23.0	(18.5, 28.6)	151.3	(114.8, 199.5)	6.6	(5.1, 8.5)
	Cohort B 20vPnC	242	47.9	(37.2, 61.8)	446.6	(354.8, 562.1)	9.3	(7.4, 11.8)
	Cohort C 20vPnC	119	64.3	(45.0, 91.8)	287.7	(199.9, 414.1)	4.5	(3.4, 6.0)
Additional								
8	Cohort A 20vPnC	223	57.6	(46.8, 71.0)	207.3	(168.6, 254.9)	3.6	(2.9, 4.4)
	Cohort B 20vPnC	219	27.1	(22.8, 32.2)	608.7	(485.2, 763.6)	22.5	(17.2, 29.4)
	Cohort C 20vPnC	101	137.1	(95.2, 197.4)	291.7	(214.4, 396.9)	2.1	(1.6, 2.8)
10A	Cohort A 20vPnC	198	212.4	(164.5, 274.3)	956.2	(752.5, 1215.0)	4.5	(3.5, 5.7)
	Cohort B 20vPnC	199	133.5	(105.3, 169.3)	1923.2	(1513.8, 2443.4)	14.4	(10.9, 19.0)
	Cohort C 20vPnC	109	359.6	(250.7, 515.8)	1595.1	(1184.4, 2148.3)	4.4	(3.3, 6.0)
11A	Cohort A 20vPnC	184	532.0	(406.6, 696.0)	1348.1	(1076.8, 1687.9)	2.5	(2.0, 3.2)
	Cohort B 20vPnC	183	270.3	(209.5, 348.8)	1806.6	(1435.1, 2274.2)	6.7	(5.0, 9.0)
	Cohort C 20vPnC	91	491.1	(332.6, 725.2)	1514.1	(1074.7, 2133.2)	3.1	(2.2, 4.4)
12F	Cohort A 20vPnC	208	139.2	(104.5, 185.3)	1000.2	(772.2, 1295.4)	7.2	(5.5, 9.5)
	Cohort B 20vPnC	200	53.2	(42.6, 66.3)	1684.2	(1290.3, 2198.3)	31.7	(23.1, 43.4)
	Cohort C 20vPnC	103	358.0	(225.3, 568.9)	1367.0	(964.3, 1937.8)	3.8	(2.7, 5.5)
15B	Cohort A 20vPnC	211	145.3	(106.5, 198.2)	625.0	(470.7, 830.0)	4.3	(3.3, 5.7)
	Cohort B 20vPnC	184	74.3	(54.9, 100.5)	1401.7	(1016.7, 1932.4)	18.9	(13.0, 27.4)
	Cohort C 20vPnC	99	198.6	(126.8, 311.0)	955.9	(637.1, 1434.3)	4.8	(3.1, 7.5)
22F	Cohort A 20vPnC	207	160.6	(114.2, 225.8)	1779.1	(1347.2, 2349.5)	11.1	(8.0, 15.3)
	Cohort B 20vPnC	191	61.2	(44.4, 84.4)	4099.3	(3156.5, 5323.6)	66.9	(46.5, 96.4)
	Cohort C 20vPnC	104	266.0	(163.5, 432.8)	2616.0	(1900.2, 3601.5)	9.8	(6.2, 15.6)
33F	Cohort A 20vPnC	203	1136.7	(932.3, 1386.0)	2058.6	(1703.0, 2488.4)	1.8	(1.5, 2.2)
	Cohort B 20vPnC	196	564.3	(470.3, 677.2)	3041.1	(2453.8, 3768.8)	5.4	(4.2, 6.8)
	Cohort C 20vPnC	99	1268.8	(949.7, 1695.1)	2233.7	(1665.8, 2995.2)	1.8	(1.4, 2.2)

GMFR = geometric mean fold rise; GMT = geometric mean titre; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. n = Number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. GMTs, GMFRs, and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titres or fold rises and the corresponding CIs based on the Student t distribution

Proportion of Participants Achieving a ≥4-Fold Rise in serotype-specific Pneumococcal OPA Titres From Before to 1 Month After Vaccination:

For most of the 13vPnC serotypes, the proportions of participants who achieved a ≥4-fold rise in OPA titres from before to 1 month after 20vPnC were generally numerically highest in Cohort B (prior 13vPnC only), ranging from 24.9% (serotype 14) to 58.7% (serotype 23F), followed by Cohort A (prior PPSV23 only), ranging from 15.7% (serotype 14) to 61.5% (serotype 6A). The proportions of participants who achieved a ≥4-fold rise in OPA titres from before to 1 month after 20vPnC were lowest in Cohort C (prior 13vPnC and PPSV23), ranging from 14.3% (serotype 7F) to 44.9% (serotype 6A).

For the 7 additional serotypes, the proportions of participants with a ≥4-fold rise in OPA titres from before to 1 month after 20vPnC were higher in participants with prior 13vPnC only, who were naïve to these vaccine serotypes prior to receiving 20vPnC, ranging from 53.6% (serotype 33F) to 83.2% (serotype 22F), than in participants with prior PPSV23 only, ranging from 18.7% (serotype 33F) to 57.0% (serotype 22F) and participants with prior 13vPnC and PPSV23, ranging from 19.2% (serotype 33F) to 54.8% (serotype 22F).

Table 30: Proportion of Subjects Achieving a ≥4-Fold Rise in Pneumococcal OPA Titres From Before Vaccination to 1 Month After Vaccination – Evaluable Immunogenicity Population

Serotype	Cohort A 20vPnC				Cohort B 20vPnC				Cohort C 20vPnC			
	N	n	%	(95% CI)	N	n	%	(95% CI)	N	n	%	(95% CI)
13vPnC												
1	245	56	22.9	(17.8, 28.6)	243	98	40.3	(34.1, 46.8)	120	25	20.8	(14.0, 29.2)
3	243	72	29.6	(24.0, 35.8)	240	99	41.3	(35.0, 47.8)	119	22	18.5	(12.0, 26.6)
4	231	95	41.1	(34.7, 47.8)	235	97	41.3	(34.9, 47.9)	115	29	25.2	(17.6, 34.2)
5	241	62	25.7	(20.3, 31.7)	243	66	27.2	(21.7, 33.2)	120	19	15.8	(9.8, 23.6)
6A	239	147	61.5	(55.0, 67.7)	234	132	56.4	(49.8, 62.9)	118	53	44.9	(35.7, 54.3)
6B	238	127	53.4	(46.8, 59.8)	238	131	55.0	(48.5, 61.5)	119	42	35.3	(26.8, 44.6)
7F	233	61	26.2	(20.7, 32.3)	241	73	30.3	(24.6, 36.5)	119	17	14.3	(8.5, 21.9)
9V	226	64	28.3	(22.5, 34.7)	228	82	36.0	(29.7, 42.6)	114	23	20.2	(13.2, 28.7)
14	236	37	15.7	(11.3, 21.0)	237	59	24.9	(19.5, 30.9)	119	19	16.0	(9.9, 23.8)
18C	245	72	29.4	(23.8, 35.5)	240	92	38.3	(32.2, 44.8)	119	21	17.6	(11.3, 25.7)
19A	239	71	29.7	(24.0, 35.9)	239	70	29.3	(23.6, 35.5)	117	18	15.4	(9.4, 23.2)
19F	243	71	29.2	(23.6, 35.4)	241	79	32.8	(26.9, 39.1)	118	20	16.9	(10.7, 25.0)
23F	242	120	49.6	(43.1, 56.1)	242	142	58.7	(52.2, 64.9)	119	51	42.9	(33.8, 52.3)
Additional												
8	223	89	39.9	(33.4, 46.7)	219	159	72.6	(66.2, 78.4)	101	31	30.7	(21.9, 40.7)
10A	198	90	45.5	(38.4, 52.7)	199	141	70.9	(64.0, 77.1)	109	48	44.0	(34.5, 53.9)
11A	184	56	30.4	(23.9, 37.6)	183	100	54.6	(47.1, 62.0)	91	32	35.2	(25.4, 45.9)
12F	208	107	51.4	(44.4, 58.4)	200	153	76.5	(70.0, 82.2)	103	42	40.8	(31.2, 50.9)
15B	211	79	37.4	(30.9, 44.3)	184	122	66.3	(59.0, 73.1)	99	38	38.4	(28.8, 48.7)
22F	207	118	57.0	(50.0, 63.8)	191	159	83.2	(77.2, 88.2)	104	57	54.8	(44.7, 64.6)
33F	203	38	18.7	(13.6, 24.8)	196	105	53.6	(46.3, 60.7)	99	19	19.2	(12.0, 28.3)

LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations. n = Number of subjects with a ≥4-fold rise in titres from before vaccination to 1 month after vaccination for the specified serotype.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. 95% CI: Exact 2-sided CI based on the Clopper and Pearson method.

- **Summary of main efficacy results**

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 31: Summary of Efficacy for Trial B7471007 (for detailed results please refer to the tables above)

Title: B7471007 A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Pneumococcal Vaccine–Naïve Adults 18 Years of Age and Older		
Study identifier	Protocol Number: B7471007 EudraCT Number: 2018-004279-11 ClinicalTrials.gov Identifier: NCT03760146	
Design	Parallel, randomised, double blind, multi-centre three cohorts based on age	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First Subject First Visit: 12 December 2018 Last Subject Last Visit: 16 December 2019 Not applicable Not applicable

Hypothesis	Cohort 1: Non-inferiority of OPA GMTs between 20vPnC and two comparator vaccines Cohort 2: Non-inferiority of OPA GMTs to subgroup of Cohort 1 Cohort 3: Non-inferiority of OPA GMTs to subgroup of Cohort 1 Non-inferior immune response is assumed if the lower bound of the 2-sided 95% CI for the ratio of OPA GMTs between the respective comparator arms is >0.5 [2-fold NI margin].		
Treatments groups	Cohort 1: adults ≥ 60 yoa		20vPnC/saline, n= 1514 13vPnC/PPSV23, n= 1495 Vaccinations were administered as single dose one month apart
	Cohort 2: adults 50-59 yoa		20vPnC, n= 334 13vPnC, n= 111
	Cohort 3: adults 18-49 yoa		20vPnC, n= 336 13vPnC, n= 112
Endpoints and definitions (only immunogenicity)	Co-Primary endpoint	NI Cohort 1 13vPnC	To demonstrate non-inferiority of the immune responses to 20vPnC compared with 13vPnC for each of the 13 matched serotypes. For all cohorts: Main parameter: OPA GMTs Additional parameter: GMFR, proportion of subjects achieving a ≥4-fold rise in OPA titres from before to one month after vaccination and proportion of subjects achieving OPA titres ≥ LLOQ one month after vaccination
	Co-Primary endpoint	NI Cohort 1 PPSV23	To demonstrate non-inferiority of the immune responses to 20vPnC compared with PPSV23 for each of the 7 additional serotypes.
	Secondary endpoint	NI Cohort 2	To demonstrate non-inferiority of the immune response in subjects receiving 20vPnC in Cohort 2 compared to subjects 60 through 64 years of age (subset of Cohort 1).
	Secondary endpoint	NI Cohort 3	To demonstrate non-inferiority of the immune response in subjects receiving 20vPnC in Cohort 3 compared to subjects 60 through 64 years of age (subset of Cohort 1).
	Exploratory endpoint	Risk factors	Descriptive; Immune responses in persons at increased risk for pneumococcal disease compared with persons without risk factors
Database lock	20 Feb 2020: initial database release. 10 Apr 2020: database was re-released.		
Results and Analysis			
Analysis description	**Primary Analysis – Cohort 1 - 13vPnC**		

Analysis population and time point description	Evaluable 13-Matched Immunogenicity Population This population generally included any participant who: 1. received the assigned Vaccination 1 (20vPnC or 13vPnC) as randomised, 2. was enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 years of age or older in Cohort 1), 3. had the Visit 2 blood collection within 27 to 49 days after Vaccination 1, 4. had at least 1 valid OPA titre for any of the 13 matched serotypes at Visit 2, 5. had no other major PDs as determined by the clinician. Time point: OPA GMTs one month after vaccination with 20vPnC or 13vPnC
Results	The immune responses to the 13-matched vaccine serotypes induced by 20vPnC were non-inferior to those induced by 13vPnC.
Note	OPA GMT ratios [20vPnC/13vPnC] were consistently around 0.8. The clinical relevance of this reduction in most serotypes is unknown as well as the clinical relevance of the applied NI margin.
Analysis description	**Primary Analysis – Cohort 1 – PPSV23**
Analysis population and time point description	Evaluable 7-Additional Immunogenicity Population This population generally included any participant who: 1. received Vaccination 1 (20vPnC) if randomised to the 20vPnC/saline group or received both vaccinations as randomised if randomised to the 13vPnC/PPSV23 group, 2. was enrolled in the appropriate cohort based on age on the day Evaluable-20 Immunogenicity Population of first vaccination (ie, 60 years of age and older in Cohort 1), 3. had either Visit 2 blood collection within 27 to 49 days after Vaccination 1 for the 20vPnC/saline group or Visit 3 blood collection within 27 to 49 days after Vaccination 2 (PPSV23) for the 13vPnC/PPSV23 group, 4. had at least 1 valid and determinate OPA titre for any of the 7 additional serotypes at either Visit 2 for the 20vPnC/saline group or Visit 3 for the 13vPnC/PPSV23 group, 5. had no other major PDs as determined by the clinician. Time point: OPA GMTs one month after vaccination with 20vPnC or PPSV23
Results	The immune responses to 6 of the 7 additional vaccine serotypes induced by 20vPnC were non-inferior to those induced by PPSV23.
Note	Reduced response to serotype 8 was observed compared to PPSV23. Serotype 8 is still one of the most prevalent serotypes causing IPD and pneumonia in the EU. Based on additional analyses that further characterize the immune responses to serotype 8, the immune response is expected to provide protection similar to the other 19 vaccine serotypes in 20vPnC that met non-inferiority.
Analysis description	**Secondary Analysis – Cohort 2 vs 60-64-year-old subjects**
Analysis population and time point description	Evaluable-20 Immunogenicity Population This population generally included any participant who: 1. received the assigned vaccination at Visit 1 as randomised, 2. was enrolled in the appropriate cohort based on age on the day of first vaccination (i.e., adults 60 through 64 years of age for Cohort 1, 50 through 59 years of age for Cohort 2, and 18 through 49 years of age for Cohort 3), 3. had the Visit 2 blood collection within 27 to 49 days after vaccination, 4. had at least 1 valid and determinate OPA titre for any of the 20 serotypes for Visit 2, 5. had no other major PDs as determined by the clinician. Time point: OPA GMTs one month after vaccination with 20vPnC
Results	The immune responses to the 20 vaccine serotypes induced by 20vPnC in adults 50 - 59 years of age were non-inferior to those in adults 60 - 64 years of age.

Note	It is known also from 13vPnC that immune response declines with age. A comparison to 13vPnC was not intended but the post-hoc analysis performed by the applicant showed numerically lower immune response to 20vPnC compared to 13vPnC overall similar to cohort 1. OPA titres for this cohort are above the titres induced by 13vPnC in cohort 1, which is assumed to provide a protective effect.
Analysis description	**Secondary Analysis – Cohort 3 vs 60-64-year-old subjects**
Analysis population and time point description	Evaluable-20 Immunogenicity Population See analysis population definition for cohort 2 Time point: OPA GMTs one month after vaccination with 20vPnC
Results	The immune responses to the 20 vaccine serotypes induced by 20vPnC in adults 18 - 49 years of age were non-inferior to those in adults 60 - 64 years of age.
Note	See Note to cohort 2. The same aspects also apply to cohort 3.
Analysis description	**Exploratory Analysis – Risk Factors**
Analysis population and time point description	Evaluable-20 Immunogenicity Population See analysis population definition for cohort 2 Time point: OPA GMTs one month after vaccination with 20vPnC
Results	Immune responses to all 20 vaccine serotypes 1 month after 20vPnC were observed in adults ≥18 years of age with and without increased risk for serious pneumococcal disease based on OPA GMTs, GMFRs, proportions of participants achieving a ≥4-fold rise in OPA titres, and proportions of participants with OPA titres ≥ LLOQ.
Note	OPA GMTs for patients with risk factors were approx. 20% lower compared to subjects without risk factors. An analysis combining subjects from all cohorts was performed, as well as a post-hoc comparative analysis by age cohorts. It is not known whether induced titres for patients with risk factors are representative for protection.

Table 32: Summary of Efficacy for Trial B7471006 (for detailed results please refer to the tables above)

Title: B7471006 A phase 3, randomized, multicentre (33 sites in the US and 8 sites in Sweden), controlled, open-label trial to evaluate the safety and immunogenicity of 20vPnC in adults ≥65 yoa with prior pneumococcal vaccination.		
Study identifier	Protocol Number: B7471006 EudraCT: 2018-004278-91 ClinicalTrials.gov Identifier: NCT03835975	
Design	randomised, multicentre, controlled, open-label trial to evaluate the safety and immunogenicity of 20vPnC in adults ≥65 yoa with prior pneumococcal vaccination	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase	First Subject First Visit: 12 February 2019 Last Subject Last Visit: 12 February 2020 12 Months not applicable not applicable
Hypothesis	not applicable	

Treatments groups	Cohort A (had received PPSV23 1-5 years previously)		Single dose 20vPnC or 13vPnC IM at visit 1 (Day 1) n= 375 (2:1, 20vPnC vs 13vPnC)
	Cohort B (had received 13vPnC ≥6 months previously)		Single dose 20vPnC or PPSV23 13vPnC IM at visit 1 (Day 1) n= 375 (2:1, 20vPnC vs PPSV23)
	Cohort C (had received 13vPnC followed by PPSV23; PPSV23 ≥1 year previously)		Single dose 20vPnC IM at visit 1 (Day 1) n= 125 (20vPnC only)
Endpoints and definitions	Primary endpoint	Immunogenicity	In all three cohort: Pneumococcal serotype specific OPA titres 1 month after vaccination
	Secondary endpoints	Immunogenicity	In all three cohorts. - Fold rise in serotype-specific OPA titres from before to 1 month after vaccination. - Proportion of subjects who reached ≥4-Fold rise in serotype-specific OPA titres from before to 1 month after vaccination. - Proportion of subjects who reached serotype-specific OPA titres ≥ LLOQ 1 month after vaccination
Database lock	13 May 2020: excluding OPA immunogenicity data 04 Jun 2020: The database was re-released to include the serology data		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Evaluable Immunogenicity Population includes any participant who: • received 20vPnC, • was enrolled in the appropriate cohort based on prior pneumococcal vaccination history, • had Visit 2 blood collection within 27 to 49 days after vaccination, • had at least 1 valid and determinate OPA titre for any serotype for Visit 2, and • did not have any other major protocol deviations as determined by the clinician Participants were included in the vaccine group as randomised in the analyses Time points: Day 1 before vaccination and 1 Month after vaccination
Results	At 1 month after 20vPnC, OPA GMTs for most of the 20 vaccine serotypes tended to be numerically highest in participants with prior 13vPnC only, ranging from 54.3 (serotype 3) to 4156.5 (serotype 22F) and lowest in participants with prior PPSV23 only, ranging from 31.1 (serotype 3) to 2026.2 (33F). OPA GMTs in participants with prior 13vPnC and PPSV23 generally fell in between ranging from 39.3 (serotype 3) to 2717.8 (22F).
Analysis description	**Secondary analysis**
Analysis population and time point description	All-Available Immunogenicity Population includes all participants who: • received 20vPnC and • had at least 1 valid and determinate OPA titre 1 month after vaccination Analysis of immunogenicity data based on the all-available immunogenicity population was to be performed only if there was 10% or more difference in sample size between the all-available and evaluable populations. Time points: Day 1 before vaccination and 1 Month after vaccination

Results	For the 13vPnC serotypes, higher OPA GMFRs and higher proportions of participants with ≥4-fold rise in OPA titres were noted in cohort B compared to cohort A and C. For the additional 7 serotypes, GMFRs were larger and proportions of participants with a ≥4-fold rise in OPA titres were higher in cohort B compared to cohort A and C.
Notes	Immune responses differed considerably between cohorts. No comparison to 13vPnC or PPSV23 is possible.

2.6.5.3. Clinical studies in special populations

Children: No data has been submitted for children < 18 yoa, as the target population for this MAA are adults ≥18 yoa. Studies in children with 20vPnC are currently ongoing. A PIP was discussed with the PDCO and a deferral was agreed.

Elderly: This population is generally considered as one of the most vulnerable for pneumococcal disease and is included in the studied population. Compared to younger populations studied (18-49 yoa and 50-59 yoa), a generally lower humoral immune response (based on OPA GMTs) was induced by 20vPnC (and 13vPnC). This is not unexpected and in line with other (pneumococcal) vaccines.

Table 33: Number of Participants in the 20vPnC and Control Groups (Combined) From the Two Phase 3 Trials That Included Enrollment of Adults ≥65 Years of Age, by Age Group - Safety Population

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	1547/4763	317/4762	21/4762
Non Controlled Trials	N/A	N/A	N/A

Abbreviation: N/A = not applicable.
a. Includes participants in Phase 3 trials B7471007 and B7471006 who received study vaccine.
b. 7471006 was a randomised, active-controlled, open-label trial with a 3-cohort design. A matched control group was present for Cohorts A and B, but not for Cohort C. This trial was controlled for safety assessments but not for the immunogenicity analyses.

Renal and hepatic impairment: No explicit studies in patients with renal or hepatic impairment were performed. However, subjects with general risk factors for pneumococcal disease were enrolled in the main studies, potentially including respective patients. Respectively, the number of subjects with renal or hepatic impairment who received 20vPnC was very low.

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

None

2.6.5.5. Supportive studies

Study B7471008 (Phase 3), lot-to-lot consistency

This was a Phase 3, multicentre, randomised, double-blind study with a 4-arm parallel design conducted in the US in approximately 1610 adults 18- 49 years of age with no history of pneumococcal vaccination. Participants were randomised into 1 of 4 groups in a 2:2:2:1 ratio (20vPnC Lot 1; 20vPnC Lot 2; 20vPnC Lot 3; 13vPnC) by site-based randomisation.

The primary safety objective was to describe the safety profile of 20vPnC in the study population. The 13vPnC arm was included as a control for safety assessments.

The pre-specified equivalence criteria were met for all comparisons between 20vPnC lots. The 2-sided 95% CIs for the model-based estimate of serotype-specific OPA GMRs 1 month after vaccination for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) are contained in the pre-specified interval (0.5, 2.0) for each of the 20 serotypes (Figure below).

OPA GMFRs, proportion of participants with ≥ 4-fold rise in OPA Pneumococcal Titres, and proportion of participants with OPA titres ≥ LLOQ were generally similar across all three lots supporting lot equivalence.. These results are discussed with the results of the main studies under "ancillary analyses".

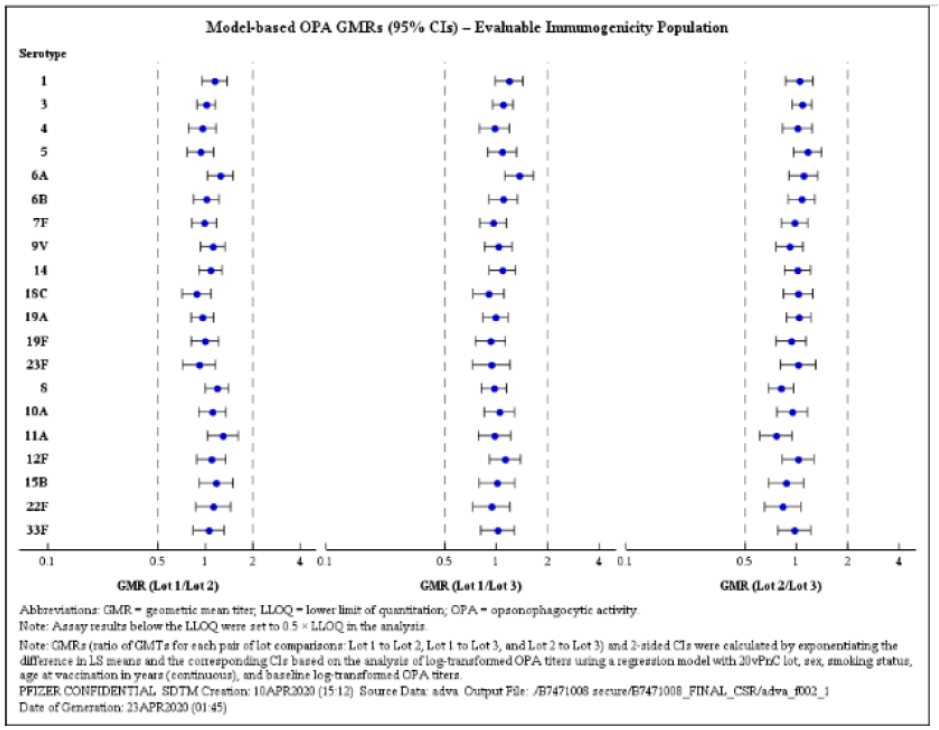

Figure 6: Model-Based OPA GMRs With 95% CIs- Evaluable Immunogenicity Population

Study B7471002 (Phase 2)

This was a phase 2, multicentre, randomised, active-controlled, double-blind study (2-arm parallel design conducted in the US) to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in 444 healthy, pneumococcal vaccine naïve adults 60 through 64 years of age (randomised 1:1 to receive either 20vPnC/saline or 13vPnC/PPSV23 one month apart).

Study results

For each of the 13vPnC serotypes, the 95% confidence intervals (CIs) for OPA GMTs 1 month after Vaccination 1 overlapped in the vaccine groups, although this was marginal for 19F.

For the seven additional serotypes, the 95% CIs for the OPA GMTs 1 month after Vaccination 1 for the 20vPnC/saline group and 1 month after Vaccination 2 for the 13vPnC/PPSV23 group did not overlap for serotypes 10A, 15B, 22F, and 8. The OPA GMTs 1 month after vaccination with 20vPnC from the 20vPnC/saline group were higher than the OPA GMTs 1 month after vaccination with PPSV23 from the 13vPnC/PPSV23 group for serotypes 10A, 15B, and 22F, but the OPA GMT from the 20vPnC/saline group was lower than the OPA GMT from the 13vPnC/PPSV23 group for serotype 8.

A 6-fold or higher OPA GMFR was observed for all 20 serotypes 1 month after vaccination with 20vPnC. Overall, a similar tendency between treatment groups was seen as for the GMT analysis.

Pneumococcal OPA GMTs for all serotypes increased substantially after vaccination and then declined but remained elevated above baseline levels (before vaccination) at 12 months after Vaccination 1.

Examples of patterns of OPA GMTs across the time points for the 13 serotypes matched to 13vPnC are denoted by serotype 1 and 19F and for the seven additional serotypes are denoted by serotype 8 and 10A.

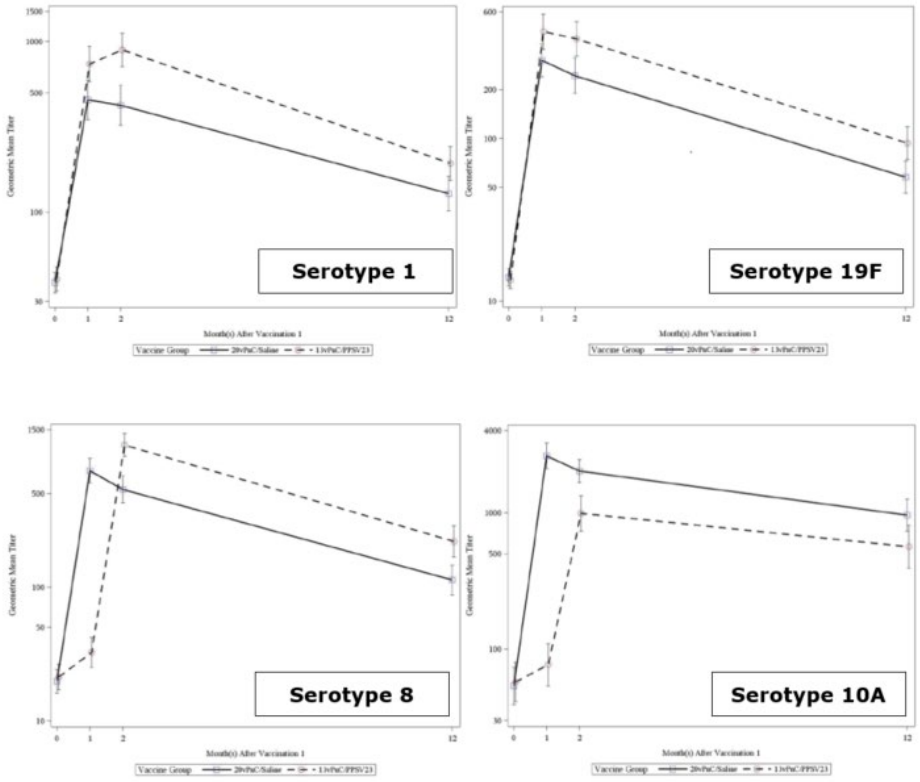

Figure 7: Antibody Response Curve 12 months after vaccination, OPA GMTs – Evaluable Immunogenicity Population; representative examples

Table 34: Summary of Pneumococcal OPA GMTs 1 and 12 Months After Vaccination with 20vPnV/saline or 13vPnC/PPSV23

		Baseline			1 Month after Vaccination 1				1 Month after Vaccination 2				12 Months after Vaccination 1			%vacc
ST		**n**	**GMT**	**95% CI**	**n**	**GMT**	**95% CI**	**GMFR**	**n**	**GMT**	**95% CI**	**GMFR**	**n**	**GMT**	**95% CI**	
1	20vPnC/saline	209	14	(12.4, 15.8)	205	302	(239.6, 381.4)	21.2	204	243	(189.0, 311.8)		200	58	(45.9, 72.7)	19
	13vPnC/PPSV23	208	13	(11.9, 15.2)	205	454	(352.6, 584.5)	33.5	203	410	(321.2, 522.5)		199	94	(74.0, 118.4)	21
3	20vPnC/saline	210	9	(7.6, 9.5)	208	51	(43.2, 61.2)	6.0	204	51	(43.0, 60.1)		198	16	(13.9, 18.7)	31
	13vPnC/PPSV23	208	9	(8.0, 10.2)	204	64	(54.1, 76.7)	7.1	203	103	(89.4, 118.7)		199	22	(18.7, 25.4)	34
4	20vPnC/saline	200	22	(17.2, 27.3)	202	876	(676.8, 1134.7)	37.8	195	859	(652.5, 1131.0)		189	245	(178.8, 334.4)	28
	13vPnC/PPSV23	201	22	(17.7, 27.8)	200	1153	(883.3, 1504.1)	51.0	200	1519	(1188.4, 1941.5)		192	334	(242.6, 459.0)	29
5	20vPnC/saline	210	17	(16.0, 18.6)	204	144	(113.3, 183.2)	8.3	201	152	(118.4, 195.5)		200	41	(34.0, 48.8)	28
	13vPnC/PPSV23	208	18	(16.5, 20.5)	202	215	(168.7, 274.4)	11.6	196	231	(184.3, 290.6)		199	50	(40.9, 61.3)	23
6A	20vPnC/saline	201	32	(26.5, 37.6)	205	1907	(1492.7, 2436.2)	58.6	201	1995	(1553.9, 2560.6)		195	492	(379.3, 638.3)	26
	13vPnC/PPSV23	200	34	(27.7, 40.8)	199	2440	(1848.9, 3219.9)	68.6	199	2913	(2276.1, 3728.0)		193	634	(490.3, 819.7)	26
6B	20vPnC/saline	201	64	(50.5, 80.0)	201	2006	(1591.4, 2527.5)	29.6	198	1873	(1465.7, 2392.3)		195	652	(499.9, 850.4)	33
	13vPnC/PPSV23	194	53	(42.0, 66.9)	202	2218	(1716.9, 2865.1)	38.8	201	2570	(2019.3, 3271.5)		191	798	(612.7,1038.4)	36
7F	20vPnC/saline	198	124	(104.9, 147.0)	207	1581	(1361.6, 1836.0)	12.2.	204	1620	(1387.8, 1892.0)		198	412	(344.1, 494.3)	26
	13vPnC/PPSV23	197	120	(102.0, 140.7	204	1936	(1651.1, 2269.6)	15.8	203	2285	(1986.7, 2628.7)		198	497	(419.0, 589.0)	26
9V	20vPnC/saline	205	147	(123.2, 176.0)	201	2447	(2013.0, 2975.6)	7.7	202	1148	(944.3, 1396.6)		195	663	(546.5, 805.4)	27
	13vPnC/PPSV23	201	157	(131.5, 187.5)	199	3016	(2469.5, 3684.4)	10.1	196	1842	(1510.2, 2246.8)		194	726	(588.0, 897.1)	24
14	20vPnC/saline	202	125	(96.5, 161.0)	206	1114	(905.0, 1371.4)	8.5	202	1119	(898.1, 1393.7)		199	527	(423.9, 655.1)	47
	13vPnC/PPSV23	202	131	(101.2, 170.2)	204	1282	(1017.4, 1614.9)	9.6	201	1823	(1465.9, 2267.0)		196	682	(544.0, 855.4)	53
18C	20vPnC/saline	206	47	(37.0, 59.2)	204	1322	(1053.2, 1658.9)	26.8	201	1205	(951.5, 1527.0)		194	416	(319.5, 542.7)	31
	13vPnC/PPSV23	200	45	(35.8, 57.0)	203	1660	(1335.1, 2064.5)	35.2	202	2101	(1717.5, 2569.5)		192	540	(418.8, 696.1)	33
19A	20vPnC/saline	207	40	(32.1, 49.2)	207	943	(783.5, 1136.1)	23.3	204	904	(741.5, 1101.4)		196	257	(210.9, 314.2)	27
	13vPnC/PPSV23	207	37	(29.4, 46.4)	203	1137	(936.5, 1379.4)	30.9	202	1457	(1219.5, 1739.9)		198	376	(309.2, 456.6)	33
19F	20vPnC/saline	207	39	(33.6, 44.3)	204	455	(349.2, 592.2)	11.8	198	423	(323.4, 552.8)		198	128	(101.7, 162.2)	28
	13vPnC/PPSV23	207	40	(34.4, 47.7)	205	738	(582.1, 936.5)	18.4	198	893	(713.1, 1117.8)		197	193	(153.7, 242.6)	26
23F	20vPnC/saline	209	12	(10.0, 14.4)	206	408	(293.0, 568.0)	33.6	203	427	(309.6, 589.4)		200	129	(93.9, 177.6)	32
	13vPnC/PPSV23	206	13	(10.4, 15.3)	205	509	(377.3, 687.1)	39.8	200	558	(416.1, 748.9)		194	158	(116.6, 213.3)	31
8	20vPnC/saline	206	20	(16.1, 24.2)	207	740	(598.0, 915.7)	37.1	201	536	(425.4, 674.4)		192	113	(87.4, 145.8)	15
	13vPnC/PPSV23	204	21	(17.0, 26.5)	203	32	(25.0, 42.0)		200	1150	(944.4, 1401.6)	56.9	194	219	(167.5, 286.6)	19
10A	20vPnC/saline	198	54	(39.1, 73.4)	201	2604	(2096.4, 3234.4)	49.3	202	2020	(1664.6, 2452.2)		191	960	(732.2,1257.5)	37
	13vPnC/PPSV23	198	57	(41.2, 79.9)	197	77	(53.7, 109.5)		197	988	(731.2, 1335.5)	17.1	192	563	(389.6, 813.2)	57
11A	20vPnC/saline	202	288	(219.2, 378.9)	197	3210	(2613.2, 3943.8)	11.2	200	3389	(2873.0, 3997.4)		194	1752	(1400.8,2191.4)	55
	13vPnC/PPSV23	183	292	(216.3, 393.2)	186	336	(248.5, 454.1)		200	3007	(2443.0, 3700.3)	9.8	189	1504	(1188.7,1902.1)	50
12F	20vPnC/saline	193	52	(42.0, 64.3)	200	6571	(5022.2, 8597.3)	113.4	191	4046	(3236.5, 5057.8)		192	748	(566.0, 987.1)	11
	13vPnC/PPSV23	200	60	(47.3, 75.1)	190	79	(59.9, 103.7)		191	4290	(3190.8, 5769.1)	77.0	189	621	(442.2, 871.7)	14
15B	20vPnC/saline	205	32	(27.0, 38.8)	205	1889	(1434.7, 2488.3)	57.1	199	1385	(1082.2, 1773.6)		197	316	(236.8, 422.2)	17
	13vPnC/PPSV23	203	33	(28.0, 39.8)	203	47	(37.7, 59.0)		200	720	(530.8, 975.9)	21.3	195	185	(137.5, 248.4)	26
22F	20vPnC/saline	192	110	(80.5, 149.2)	201	6286	(5025.0, 7863.2)	55.4	191	4093	(3383.7, 4950.3)		188	1214	(919.8, 1602.7)	19
	13vPnC/PPSV23	196	164	(121.6, 221.6)	184	182	(129.3, 257.0)		189	3513	(2824.8, 4367.7)	20.3	192	976	(724.4, 1314.9)	28
33F	20vPnC/saline	190	379	(287.9, 500.2)	185	5584	(4374.1, 7128.0)	14.0	185	2929	(2385.5, 3595.7)		185	2288	(1825.1,2867.3)	41
	13vPnC/PPSV23	194	430	(333.1, 555.9	189	480	(366.0, 629.8)		181	3940	(3136.2, 4950.9)	8.9	181	2072	(1589.9,2700.8)	53

n = Number of subjects with valid results for the serotype at the time point. GMT = Geometric Mean Titre, CI = confidence interval, GMFR = GMT ratio (only reported for the relevant comparisons), %vacc = ratio of the GMT 12 months after Vaccination 1 to the GMT 1 month after Vaccination 1 for all 20vPnC results and the 13 shared serotypes for the comparator or compared to Vaccination 2 for the seven additional serotypes for the comparator. 1 Month after Vaccination 2 (saline or PPSV23) = 2 months after Vaccination 1 (20vPnC or 13vPnC)

Subjects with ≥4-fold change in OPA titres 1 year after vaccination (all 20 serotypes)

Table 35: Proportion of Subjects Achieving a ≥4-fold Rise in OPA Titres From Before Vaccination 1 to 12 Months After Vaccination 1- Evaluable Immunogenicity Population

serotype	20vPnC/Saline				13vPnC/PPSV23			
	N	n	%	(95 CI)	N	n	%	(95 CI)
13vPnC								
1	197	96	48.7	(41.6, 55.9)	195	116	59.5	(52.2, 66.4)
3	196	49	25.0	(19.1, 31.7)	195	66	33.8	(27.2, 41.0)
4	178	96	53.9	(46.3, 61.4)	181	105	58.0	(50.5, 65.3)
5	198	61	30.8	(24.5, 37.7)	195	65	33.3	(26.8, 40.4)
6A	186	131	70.4	(63.3, 76.9)	183	131	71.6	(64.5, 78.0)
6B	188	120	63.8	(56.5, 70.7)	175	114	65.1	(57.6, 72.2)
7F	184	81	44.0	(36.7, 51.5)	183	88	48.1	(40.7, 55.6)
9V	189	92	48.7	(41.4, 56.0)	184	89	48.4	(41.0, 55.8)
14	189	77	40.7	(33.7, 48.1)	186	77	41.4	(34.2, 48.8)
18C	188	104	55.3	(47.9, 62.6)	181	118	65.2	(57.8, 72.1)
19A	192	105	54.7	(47.4, 61.9)	193	128	66.3	(59.2, 72.9)
19F	193	72	37.3	(30.5, 44.5)	192	97	50.5	(43.2, 57.8)
23F	197	117	59.4	(52.2, 66.3)	188	114	60.6	(53.3, 67.7)
Additional								
8	186	96	51.6	(44.2, 59.0)	186	118	63.4	(56.1, 70.4)
10A	181	125	69.1	(61.8, 75.7)	181	109	60.2	(52.7, 67.4)
11A	187	100	53.5	(46.1, 60.8)	162	84	51.9	(43.9, 59.8)
12F	176	120	68.2	(60.8, 75.0)	177	107	60.5	(52.8, 67.7)
15B	190	121	63.7	(56.4, 70.5)	186	88	47.3	(40.0, 54.7)
22F	170	110	64.7	(57.0, 71.9)	176	91	51.7	(44.1, 59.3)
33F	165	94	57.0	(49.0, 64.6)	168	93	55.4	(47.5, 63.0)

Abbreviations: OPA = opsonophagocytic activity; LLOQ = lower limit of quantitation. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. N = number of subjects with valid and determinate assay results for the specified serotype. These values are used as the denominators for the percentage calculations. n = Number of subjects with a ≥4-fold rise in antibody titre for the specified serotype.

Note: The 9V serotype data at 1 month after Vaccination 1 is retest data.

Exact 2-sided CI based upon the observed proportion of subjects, calculated using the Clopper and Pearson method.

Study B7471005 (Phase 1b)

Study B7471005 was a phase 1b, randomised, controlled (3-arm parallel design), double-blind trial, conducted at 3 sites in the US, to evaluate the safety and immunogenicity of multivalent pneumococcal conjugate vaccines in approximately 99 healthy pneumococcal vaccine naïve Japanese adults 18-49 yoa. Subjects were randomised equally 1:1:1 to receive a single dose of 20vPnC, c7vPnC (an unauthorised investigational vaccine including the 7 serotypes not included in 13vPnC) or 13vPnC as control group.

Immunogenicity results

One month after vaccination, increased OPA GMTs were observed for all serotypes in the respective groups. OPA GMFRs for all 20 serotypes with 20vPnC ranged between 6.1-fold (serotypes 3 and 11A) to 150.7-fold (serotype 8).

The majority of participants vaccinated with 20vPnC achieved a ≥4-fold rise in OPA titres from before to 1 month after vaccination for all 20 serotypes (range: 54.8% (serotype 7F) to 97.0% (serotype 23F)).

2.6.6. Discussion on clinical efficacy

The applied indication for 20vPnC/Apexxnar, a 20-valent protein conjugated pneumococcal vaccine, is "active immunisation for the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by *Streptococcus pneumoniae* in adults ≥ 18 years of age". Currently other vaccines are licensed for this indication in adults in the EU: e.g. Prevenar13 (13vPnC) and PNEUMOVAX23 (PPSV23). Another pneumococcal vaccine is licensed but not for the intended adult population (Synflorix). The applicant is also the marketing authorisation holder of 13vPnC and 20vPnC is based on the same manufacturing process as Prevenar 13 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) with 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F and 33F). PPSV23 is an unconjugated polysaccharide vaccine containing 23 serotypes, including the serotypes of 20vPnC, except 6A, which is only included in 20vPnC and 13vPnC. The additional serotypes of PPSV23 are 2, 9N, 17F, 20. Both vaccines are routinely used in European vaccination programmes. Both vaccines are used as comparators for this MAA. The choice of the comparator vaccines is considered acceptable and has been agreed in the scientific advice.

Currently, no correlate of protection has been established in the adult population for pneumococcal vaccines. Consequently, efficacy has to be inferred via immunobridging between 20vPnC and vaccines with proven protective efficacy: 13vPnC (for the 13 shared serotypes) and PPSV23 (for the 7 additional serotypes). This immunobridging approach is in accordance with the respective EMA guidance (EMEA/CHMP/VWP/164653/2005) and scientific advice.

The clinical programme for 20vPnC consists of six randomised controlled trials to study safety and immunogenicity of 20vPnC. Studies B7471007 (pivotal, pneumococcal vaccine naïve subjects) and B7471006 (primed subjects) are considered as main evidence for this application as separate important aspects of the target population are covered (including relevant age groups, risk factors and pneumococcal vaccination history). Supportive data derives from two Phase 1 studies (B7471001 (FIH), B7471005 (Japanese subjects)), a Phase 2 study (B7471002) and a Phase 3 lot consistency study (B7471008).

No dedicated dose-finding studies were conducted for 20vPnC, since prior experience with its predecessor 13vPnC exists. Both 13vPnC and 20vPnC contain 2.2 µg pneumococcal polysaccharide per serotype (4.4 µg for serotype 6B) per single dose of 0.5 mL IM.

No studies with 20vPnC have been performed to evaluate the ability to induce memory, the longevity of protection or boosting. Respective information should be extrapolated from 13vPnC given a robust bridge has been established.

Design and conduct of main clinical studies

The **main evidence for the immunological bridge** is generated in the **pivotal study B7471007** in different steps represented by the primary and secondary objectives. The primary comparison between 20vPnC and 13vPnC is performed in pneumococcal vaccine naïve adults ≥60 years of age (cohort 1) to establish non-inferiority of 20vPnC to 13vPnC in this age group. Subsequently, non-inferiority of the immune response elicited by 20vPnC should be established in 60-64-year-old subjects (a subset of cohort 1) and the younger cohorts 2 and 3 (50 - 59 and 18 - 49 years of age). No additional comparison between vaccines (20vPnC and 13vPnC or PPSV23) was intended for these cohorts. This approach to bridge to younger cohorts was previously discussed during the scientific advice procedure (EMEA/H/SA/3940/1/2018/III CORRIGENDUM). Since it is in line with the previous development programme of 13vPnC, it was considered appropriate, if it is confirmed that the vaccine is essentially

the same medicinal product as 13vPnC, plus seven additional serotypes. According to the assessment of the quality part of the provided dossier, no differences are expected. However, the planned non-inferiority margin (0.5) was seen critical in this advice as meeting this margin was not considered to ensure that adults 18 through 49 and 50 through 59 years of age will have non-inferior immune responses to 20vPnC compared to 13vPnC. The clinical (ir)relevance of the employed non-inferiority margins is currently not known. Additionally, it is known, also from 13vPnC, that immune response declines with age and it is to be expected that the immune response in younger subjects will be higher than in older subjects. Consequently, non-inferior immune response in the younger compared to the oldest cohort could be expected regardless of whether the immune response is comparable between 20vPnC and 13vPnC or PPSV23 in younger subjects. The immunological bridge is further discussed with the respective results below.

Study B7471006 enrolled subjects with prior vaccination history. This is considered a relevant part of the intended target population, since pneumococcal vaccines are already available for the adult population since several years or even decades in the case of PPSV23. Consequently, it is very likely that especially the older target population will have received at least one prior vaccination with either or both vaccines. Study B7471006 enrolled subjects ≥ 65 years of age into different cohorts based on their previously received different pneumococcal vaccination (13vPnC, PPSV23 or both sequentially (13vPnC/PPSV23), representing all common prior pneumococcal vaccinations. Unfortunately, the study was not designed to generate confirmatory evidence which would have been preferred and has several shortcomings, including the open label design, the descriptive reporting of results and the lack of immunogenicity data from a control arm to further substantiate the immunological bridge required for this MAA. Nevertheless, the presented data are considered informative for this subset of the target population.

The inclusion and exclusion criteria are generally comparable for both main studies. Differences relate to definition of relevant subject groups mainly based on age (B7471007) and prior pneumococcal vaccination status (B7471006) in line with the study objectives. The majority of subjects who received 20vPnC were 60-69 years old (in total 1661; naïve: 1312; primed: 349). In addition, a total of 470 subjects older than 70 years (naïve: 195; primed: 275) received 20vPnC. Overall, the included population is considered to adequately reflect the population ≥ 60 yoa, most vulnerable to pneumococcal disease. In addition, 334 subjects 50-59 yoa and 335 subjects 18-49 yoa received 20vPnC in study B7471007. Supportive data for the youngest cohort (18-49 year) is also generated in the lot-to-lot consistency study (n=1463). The main evidence for the intended immunobridge was generated in pneumococcal vaccine naïve subjects ≥ 60 yoa. This population is considered an adequate and sensitive population to establish the intended immunobridge since potential interactions with prior pneumococcal vaccinations can be excluded.

The clinical development programme did not specifically aim to recruit subjects at specific risk for pneumococcal disease, e.g. with chronic comorbidities (e.g. diabetes, chronic heart or lung disease), behavioural habits (e.g. smoking) or subjects living in a community/environment with increased risk of disease transmission. Nevertheless, about 1/3 of all subjects enrolled in study B7471007 had risk factors for pneumococcal disease and a respective analysis comparing subjects with and without risk factors has been performed. No studies were performed in immunocompromised patients and the applicant argues that respective efficacy can be extrapolated from 13vPnC based on the characteristics of a conjugate vaccine. This can currently not fully be agreed on (see below).

The submitted studies were mainly conducted in the US and at some study sites in Sweden. Consequently, the experience with 20vPnC in the European population is limited but prior global experience with 13vPnC and PPSV23 do not give rise to concerns regarding potential differences relevant for the European population.

The applicant used opsonophagocytic activity (OPA) titres for the evaluation of immune response, which is endorsed and was agreed on during the scientific advice procedure. OPA titres are commonly used as surrogate markers for a protective effect as they reflect the in vivo scenario of antibody-mediated protection. However, no correlate of protection has been established. Comparisons across serotypes are also not possible due to different capsule compositions, potentially resulting in different titres required for protection for each serotype. The complementary immunogenicity parameter of IgG concentrations was only used in the Phase 1 and 2 studies but not in the main studies. This is considered acceptable since OPA GMTs are considered a more relevant parameter.

In all studies participants received a single dose of either vaccine (20vPnC, 13vPnC or PPSV23), which is in line with the approved regimen for 13vPnC and PPSV23. Immune responses were evaluated before and one month after vaccination. Serotype-specific OPA geometric mean titres (GMTs) at 1 month after the respective vaccination were used as variables for the primary endpoints.

Secondary endpoints to further assess the immune response included differences in geometric mean fold rises (GMFRs) in serotype-specific OPA titres, the proportion of subjects with a ≥4-fold OPA GMT rise from baseline and the proportion of subjects with titres above LLOQ. Immunogenicity objectives and endpoints are generally supported and are in line with the vaccine guideline (EMA/CHMP/VWP/164653/05 Rev.1).

In order to be able to evaluate the immune response of both comparator vaccines, 13vPnC and PPSV23 were given to the same subjects one month apart and the respective evaluation was performed separately for the respective serotypes one month after the respective vaccination. This dosing regimen is not representative for the commonly recommended sequential vaccination of 13vPnC and PPSV23. No data concerning a sequential vaccination, as commonly recommended in the EU (with an interval between vaccinations of several weeks up to 1 year, depending on the subject's risk factors and age) was submitted neither with 20vPnC nor as comparison thereof. Respective information collected with 13vPnC could be extrapolated given a robust immunobridge.

Efficacy data and additional analyses

Overall, 20vPnC was immunogenic in all studies and subgroups tested, based on consistently elevated OPA GMTs 1 month after vaccination compared to baseline.

The main evidence for the immunological bridge to the comparator vaccines with proven efficacy was generated in study B7471007, in several steps:

(1) Establishing non-inferiority to 13vPnC for the 13 shared serotypes in Cohort 1 (subjects ≥ 60 yoa),

(2) Establishing non-inferiority to PPSV23 for the seven additional serotypes in Cohort 1 and

(3) Establishing non-inferiority in a subset of cohort 1 (60-64 yoa) and younger subjects in Cohorts 2 (50-59 yoa) and 3 (18-49 yoa), respectively.

Non-inferior immune response is assumed if the lower bound of 2-sided 95% CI for the ratio of OPA GMTs between the respective comparator arms is >0.5 [2-fold NI margin].

(1) **13 shared serotypes**: The defined non-inferiority criteria were met for all 13 serotypes included in 20vPnC and 13vPnC. Nevertheless, lower immune response was observed for 11 serotypes. The ratio of OPA GMTs between 20vPnC and 13vPnC was consistently around 0.8 and the GMR 95%-CI did not include 1. In addition, the 95%-CI of the vaccine specific GMTs were non-overlapping between both vaccines for five serotypes and hardly overlapping for another five. Although meeting the non-inferiority criteria, these differences are noteworthy, especially since both vaccines are essentially the same product (with the additional serotypes

for 20vPnC). The clinical relevance of this difference is unclear, especially since no correlate of protection exists. However, the protective effect for serotype 3 is unclear given the reduced response although the NI criterion was met. Although both vaccines 13vPnC and PPSV23 contain serotype 3, it is still the most prevalent serotype causing IPD in Europe (14.7% of all reported IPD cases; ECDC "Invasive Pneumococcal Disease, Annual Epidemiological Report for 2018"). Consequently, these findings have been reflected in the PI in order to provide relevant information to the prescriber. Further, the applicant outlined that the clinical relevance of these findings will be further investigated in the post-marketing setting to confirm 20vPnC effectiveness (see section on post-marketing below).

(2) **7 additional serotypes**: The defined non-inferiority criteria were met for six of the seven additional serotypes. The GMRs for these serotypes were clearly above 1, indicating higher immune response with 20vPnC compared to PPSV23. Only serotype 8 missed the non-inferiority margin. The clinical relevance of this finding and the impact on vaccine efficacy and protection against serotype 8 is not known. The applicant argued that protection similar to the other serotypes could be assumed, based on only narrowly missing the criteria (GMR 0.55 (0.49, 0.62)) and other immunogenicity endpoints in the range of other serotypes, but this is not endorsed. In Europe, serotype 8 is the most common serotype causing IPD in subjects 18-65 yoa (approx. 22-32% of reported IPD cases) and after serotype 3 (14.7%) the second most common IPD causing serotype in adults ≥65 yoa (14.0%) (IPD Annual Epidemiological Report for 2018; ECDC). The additional benefit for six of the seven additional serotypes can be agreed upon. As regards serotype 8, while acknowledging the potential benefits of conjugate-induced immunity by 20vPnC as opposed to PPSV23, the considerably reduced response to this serotype is of concern. The potential reasons for the pronounced difference observed for serotype 8 compared to the other six new serotypes are unknown. The clinical relevance of this finding will be further investigated to infer vaccine effectiveness against serotype 8 in the post-marketing (see section on post-marketing below). Breakthrough disease due to reduced vaccine effectiveness (or potential vaccine failure) as well as serotype replacement will be followed up via routine pharmacovigilance in the post marketing (see section on post-marketing below).

(3) **Bridge to younger cohorts**: After establishing the initial immunological bridge to 13vPnC in cohort 1, a bridge to the younger cohorts should be established via demonstrating non-inferiority of immune responses of all 20 serotypes elicited by 20vPnC in a subgroup of cohort 1 (60-64 years) and Cohorts 2 and 3, respectively. The comparison of Cohort 2 (50-59 years) to Cohort 1 (60-64 years) showed GMT ratios around 1 for all serotypes, meeting the NI criteria. The comparison of Cohort 3 to Cohort 1 (60-64 years) showed overall ratios clearly above 1, except for serotype 3 (GMT ratio: 1.00), meeting all NI criteria.

Although all endpoints were met, concerns about the intended bridge to younger cohorts remain. While this approach to compare the immune response across age groups has been accepted in the Scientific Advice, it was also specifically mentioned that the chosen margin does not allow any conclusions about whether the immune response between 20vPnC and 13vPnC would be comparable. Further, it is known also from 13vPnC that higher immune responses are elicited in younger subjects, which was also stated by the applicant. Therefore, higher and consequently non-inferior immune response in younger subjects were to be expected. Information about the comparability of immune response between both vaccines can only be provided with comparative data between 20vPnC and 13vPnC in Cohorts 2 and 3. Although data for 13vPnC was collected, no pre-specified comparative analysis was performed by the applicant. The respective data has been compiled by the assessors and shows that immune response elicited by 20vPnC is consistently lower in all cohorts compared to 13vPnC.

These observations should be reflected in the SmPC. In Cohort 2, including 50-59-year-old subjects, the difference seems even more pronounced compared to Cohort 1, although the conclusions are somewhat hampered by the small number of subjects receiving 13vPnC. The observations of reduced response are further supported by overall reduced proportion of subjects with a ≥4-fold rise. The results raise doubts whether the approach to compare immune response between age groups instead of against the comparator vaccine directly is appropriate to establish an immunological bridge between a new vaccine and a vaccine with proven efficacy. Similar reductions have also been observed in other studies were respective data is available: the lot consistency study B7471008 and a paediatric study, submitted by the applicant (B7471003), although this population is not part of the current indication.

Despite the concerns raised regarding the consistently lower immune response compared to 13vPnC in each cohort, it has to be acknowledged that almost all GMTs for 20vPnC in Cohorts 2 and 3 were higher than the GMTs observed for 13vPnC in subjects ≥60 yoa (cohort 1), which are assumed to provide protection against IPD and pneumonia. Consequently, a protective effect of 20vPnC for those two cohorts can be assumed. Nevertheless, the clinical relevance of the observed reduced immune response is currently unknown. Especially, it is not apparent whether the reduced GMTs observed in the most vulnerable age group, subjects ≥60 years, are still predictive for a (long-term) protective effect.

Further, several populations exist in which a reduced immune response was already observed during the development of 13vPnC. These include amongst others primed subjects and subjects with risk factors, who have also been part of this development programme. For both populations reduced GMTs compared to pneumococcal vaccine naïve subjects or subjects without risk factors have been observed (see below). It is not apparent whether the further reduced immune response to 20vPnC would elicit protective titres in these populations or at least in parts of these populations depending potentially on age or prior pneumococcal vaccine (see below). The need of another vaccination schedule (e.g. additional dose), especially for risk groups was not discussed by the applicant and so far, also no plans have been outlined how this could be investigated in the post-marketing (see section on post-marketing below).

Even if the observed titres would be representative for protection against IPD and pneumonia, it is not apparent how long this protection would last. It has to be assumed that the duration of the provided protection would also be reduced. Only limited data with 20vPnC for 12 months are available in about 200 pneumococcal vaccine naïve adults 60-64 years of age from the Phase 2 study B7471002. The data can, however, not be compared to 13vPnC due to the applied dosing regimen and does not provide further information for the populations with reduced immune response. The applicant assumes that immune persistence for 20vPnC can be extrapolated from experience with 13vPnC since both are similar conjugate vaccines. Whether this is the case is, however, currently unclear considering the reduced immune response. No further discussion was provided to substantiate the claim of a protective effect similar to 13vPnC in adults ≥60 yoa, primed subjects and patients with decreased immune response. Therefore, upon request the applicant provided plans for the post-marketing to monitor breakthrough disease and potential other indications for lack of efficacy (see section on post-marketing below).

Risk factors

Adult subjects with risk factors for IPD regardless of age are an important target population for pneumococcal vaccines. Although such subjects were not explicitly recruited, about 1/3 of the enrolled subjects of the pivotal study had at least one risk factor. While such an analysis is considered important for this MAA, the initially performed analysis has several shortcomings: (1) The data analysis only compares subjects with risk factor to subjects without risk factor, regardless of type and amount

of risk factors. (2) the presented analysis combined data from all three cohorts, which is not considered appropriate, since the GMTs differ substantially between cohorts. Upon request, the applicant provided respective analyses for each cohort.

In general, the immune response in patients with risk factors was clearly detectable and supported by other parameters, e.g. a substantial proportion of subjects reached ≥4-fold GMT rise. However, the observed immune responses (OPA GMTs) were lower in subjects with risk factors compared to those without in all cohorts (GMT ratio ~ 0.6-0.8, ≥ 4-fold rise ~5-10% difference). The effect of reduced immune response is also known for 13vPnC. In the requested analyses, the applicant also compared the results between 20vPnC and the respective comparator, 13vPnC for all cohorts and PPSV23 in cohort 1. While the reduction observed between subjects with and without risk factors is similar between 20vPnC and 13vPnC, the reduced immune response of 20vPnC compared to 13vPnC seen in the naïve population of the pivotal study is also seen in this population. This further reduction of immune response raises concerns regarding a protective effect in patients with risk factors. The achieved titres in younger patients (cohort 2 and 3) with risk factors are comparable or above the titres achieved with 13vPnC in cohort 1, which are assumed to elicit a protective effect. However, whether the observed reduction in patients with risk factors of at least 60 years of age has clinical relevance, it is currently unknown. Since the initial titres are reduced, it is likely that the reduced titres also affect the long-term protection. The applicant was invited to further substantiate the claim, that these titres provide a protective effect, discuss respective implications on long term protection and present suitable post-marketing plans. Upon request, the applicant outlined how the clinical impact of these findings can be further investigated in the post-marketing in the general target population. However, some aspects of 20vPnC vaccine effectiveness are not especially addressed including (younger) subjects at risk for pneumococcal disease, primed subjects or immunocompromised patients.

Consequently, it is currently still questioned whether data from 13vPnC can be extrapolated for patients at high risk for pneumococcal disease, e.g. immunocompromised subjects, which were not included in the development programme of 20vPnC. In order to provide supportive information to the prescriber, data derived with 13vPnC are included in the SmPC together with a clear statement that no data with 20vPnC are available and that lower titres have been observed. If vaccine effectiveness is shown in the respective post marketing studies, this will also be reassuring concerning those populations.

The currently approved vaccines for the adult population in the EU include Prevenar13 (13vPnC) and Pneumovax23 (PPSV23, polysaccharide). Since the MAH of 13vPnC is also the applicant for 20vPnC, it is a reasonable assumption that 20vPnC is intended to replace 13vPnC in the applicant's portfolio and will be removed from the European market, creating a lack of alternative conjugate vaccines. Consequently, remaining uncertainties about the protective effect especially in at-risk populations have to be further minimised (see section on post marketing below).

Primed subjects

The applicant performed Study B7471006 in adults ≥65 years of age (yoa) with prior pneumococcal vaccination separated in three different cohorts based on prior pneumococcal vaccinations. Overall, 20vPnC elicited immune responses across all serotypes and cohorts but the immune responses differed considerably between the different cohorts. Overall, the data indicate that 20vPnC achieved higher immune responses after prior vaccination with the conjugate vaccine 13vPnC compared to prior vaccination with the unconjugated vaccine PPSV23, either alone or after prior vaccination with 13vPnC.

It is not known, whether the elicited immune response in any of the cohorts is comparable to 13vPnC or PPSV23. The design of the study does not allow for such a comparison, which is regarded as shortcoming for this MAA. For cohort A and B, a safety control arm exists with subjects receiving either

13vPnC (cohort A) or PPSV23 (cohort B) but no immunogenicity data exist for these arms. Alternatively, one general control arm with pneumococcal vaccine naïve subjects would have been suitable to establish a bridge to the pivotal data from study B7471007. Since any kind of bridging is missing, it is not apparent whether an extrapolation of efficacy from 13vPnC and PPSV23 in primed subjects is possible. The applicant did not discuss this issue and argues instead that showing elicited immune response in primed subjects in general, is enough to conclude a protective effect. Although comparing results across studies is not optimal, the assessors compiled respective data to compare results derived in all three cohorts to the GMTs observed in cohort 1 from study B7471007 with a similar age group (≥60 yoa, pneumococcal naïve subjects). While similar immune response can be concluded for most serotypes between naïve subjects and subjects who received only 13vPnC, a reduced response has been observed in both cohorts including subjects who received PPSV23, especially as single vaccination. The applicant confirmed upon request that an effect to a similar degree was also observed with 13vPnC. However, the clinical relevance of this observation in unknown. While it is assumed that the apparent reduced immunity with 20vPnC in subjects previously vaccinated with PPSV23 could be induced by a hypo-response phenomenon, this has not been scientifically proven yet. In addition, the applicant clarified that the role of the interval between the last dose of PPSV23 (in Cohort A and C) and 20vPnC cannot be evaluated since respective data was not collected in the study.

No data about a potential booster vaccination have been submitted. The applicant argues that persistence of immune response can be extrapolated from 13vPnC based on the established immunological bridge and nature of the pneumococcal conjugate response. While this might be possible for the 13 shared serotypes, given a robust immunological bridge, an extrapolation for the seven additional serotypes from 13vPnC is not possible. Although the pivotal study intends to establish an immunological bridge to PPSV23 for these serotypes, extrapolation of immune persistence is questionable. The comparator PPSV23 is an unconjugated polysaccharide vaccine with known limited persistence. Supportive long-term data up to one year is generated in the phase 2 study (B7471002) as exploratory endpoint. For this time-point, control data of a sequential vaccination with 13vPnC followed one month later by PPSV23 are available. Data from 12 months after the first vaccination indicate that OPA GMTs declined similarly over time for both vaccination regimen and OPA titres remained above baseline levels. This allows for a comparison of the immune response between 20vPnC and PPSV23 against the seven additional (non-13vPnC) serotypes but only between 12 months data for 20vPnC and 11 months data for PPSV23. Nevertheless, the additional data are considered informative for the assessment of immune persistence of these seven serotypes. Unfortunately, no direct comparison between 20vPnC and 13vPnC is possible to confirm the extrapolated information for the 13 shared serotypes. The applicant does not intend to conduct a post-marketing study to assess the need for booster vaccination in adults and presented data from a study evaluating multiple doses of 13vPnC in HIV infected patients, showing moderately increased titres after 3 doses. Since it is currently not known whether the observed reduction in OPA GMTs for 20vPnC would result in a reduced protection or whether similar results would be obtained with 20vPnC for multiple doses as presented for 13vPnC and whether the gained increase would improve the protective effect, it is agreed that it is currently not necessary to perform respective multiple dose studies with 20vPnC. This, however, might change, if appropriate post-marketing studies would detect a reduced protection with 20vPnC.

Lot-to-lot consistency (Study B7471008): The pre-defined equivalence criteria were met for all serotypes for all three 20vPnC lots. Each of the pairwise 2-sided 95% confidence intervals (CIs) for the geometric mean ratio (GMR) of OPA titres 1 month after vaccination were contained in the interval (0.5, 2.0). Although the clinical relevance of the defined margins is not established, it is acknowledged that all CI included 1. Lot-to-lot consistency studies are not routinely required based on the EMA guideline on clinical evaluation of vaccines.

No data on concomitant vaccination with other vaccines relevant to the target population (e.g. Influenza vaccines) are currently available. A respective trial evaluating 20vPnC co-administered with seasonal inactivated influenza vaccine is currently ongoing (variation intended for post marketing).

Post-marketing assessments to monitor vaccine effectiveness:

The applicant provided an outline of their post-marketing plans to assess effectiveness of 20vPnC. These are considered important to address the remaining uncertainties regarding the lower titres induced by 20vPnC vaccination compared to 13vPnC and the considerable low titre against serotype 8 (compared to PPSV23). The applicant's plans are as follows:

1. A vaccine effectiveness study against vaccine-type community-acquired pneumonia (CAP)

As a post-marketing requirement with the US FDA (condition of accelerated approval), the applicant will conduct a vaccine effectiveness (VE) study against vaccine-type (VT) community-acquired pneumonia (CAP) in the USA (B7471015) in adults ≥65 years of age. 20vPnC VE against all 20 serotypes, VE against the 13vPnC matched and 7 additional serotypes (including serotype 8) will be evaluated employing a test-negative design. Study results are expected by 30 November 2027. The study protocol has been provided with the applicant's response. As serotype distribution differs across continents, the applicant is expected to provide a detailed discussion on the applicability of study results to the European situation together with the study results. With test-negative design, the study will also include subjects with risk factors as well as subjects with pneumococcal vaccination history (≥65 years of age) and has the potential to also provide further information on VE (against CAP) in this population. However, no additional data on subjects at higher risk for pneumococcal disease and/or generally lower immune response to pneumococcal vaccination (e.g. with prior PPSV23 vaccination) < 65 years of age will be generated.

As this study is considered relevant to further address remaining uncertainties, it is added as a post-authorisation obligation (see Product information- Annex II D and Risk Management Plan [RMP]).

2. Two Phase 4 Observational, Real-World Studies of 20vPnC Effectiveness. One against VT CAP in Europe and one against VT IPD in Europe

Two additional studies to evaluate the impact of 20vPnC vaccination on vaccine type (VT) CAP and IPD in Europe (are currently undergoing feasibility evaluation. The applicant is expected to further investigate VE in these populations as part of the post-marketing assessment.

Completion of the feasibility assessment is ongoing, with submission of both protocols in likelihood by end Q1 2024 (date added to RMP). Since the data generated in these studies will be important for the future assessment of the remaining uncertainties, the commitment is included as post-authorisation measure in Annex II D. Tentative timeline for CSRs submission has been set.

3. Monitoring of Pneumococcal Serotype Epidemiology and Vaccine Failures in Europe

Ultimately, European national IPD surveillance systems as well as the ECDC European IPD surveillance system will be employed to monitor serotype epidemiology and breakthrough infections. Annual reports will be submitted. This is considered part of the routine pharmacovigilance measures and therefore expected regardless of other post marketing studies.

Taken together, the presented post-marketing plans are expected to provide valuable information on 20vPnC effectiveness, and the remaining uncertainties related to the clinical impact of reduced immune responses elicited by 20vPnC compared to the majority of serotypes shared with 13vPnC and serotype 8 shared with PPSV23. However, some aspects of 20vPnC vaccine effectiveness are not especially addressed including (younger) subjects at risk for pneumococcal disease, primed subjects or immunocompromised patients. Nevertheless, if vaccine effectiveness is shown in the respective

studies, this will also be reassuring concerning those populations (Post-authorisation measures stated in Annex II D and RMP).

2.6.7. Conclusions on the clinical efficacy

Overall, the results indicate that 20vPnC was immunogenic in all subgroups tested. However, several uncertainties were identified concerning numerically lower immune response compared to 13vPnC (for most shared serotypes) and compared to PPSV23 (for serotype 8). The SmPC appropriately reflects these findings. The applicant will further address these findings in the post-marketing setting and evaluate their impact on 20vPnC effectiveness. The RMP and SmPC Annex II were updated accordingly to include the respective post-marketing commitments.

The CHMP considers the following measures necessary to address issues related to efficacy:

a. In order to further investigate the long-term effectiveness of Apexxnar for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*, the MAH should conduct and submit the results of US study B7471015, a Phase 4 study using a test-negative design to evaluate the effectiveness of Apexxnar against Vaccine-Type Community-Acquired Pneumonia in adults ≥ 65 years of age.

b. In order to further investigate the long-term effectiveness of Apexxnar for active immunisation for the prevention of pneumonia 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 Apexxnar against Vaccine-Type Community-Acquired Pneumonia in Europe according to an agreed protocol.

c. In order to further investigate the long-term effectiveness of Apexxnar 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 Apexxnar against Vaccine-Type Invasive Pneumococcal Disease in Europe according to an agreed protocol.

2.6.8. Clinical safety

The 20vPnC adult clinical development programme was designed to characterize the safety, tolerability, and immunogenicity of 20vPnC in adults ≥18 years of age. The adult clinical development programme for 20vPnC is generally modelled after the 13vPnC adult programme and takes into consideration the favourable safety profile established for 13vPnC in the adult clinical development programme and the adult post-marketing experience since initial licensure in 2011.

The safety of 20vPnC was assessed in three early stage (two Phase 1 trials and one Phase 2 trial) and three Phase 3 clinical trials. Early phase trials enrolled adults who were naïve to pneumococcal vaccine 18 through 49 years of age (B7471001 and B7471005) and 60 through 64 years of age (B7471002). The Phase 3 safety data are summarised and discussed separately for individuals who were naïve to pneumococcal vaccine at trial enrolment (B7471007 and B7471008) and for individuals ≥65 years of age who had previously been vaccinated with 13vPnC, PPSV23, or both (B7471006). In all three Phase 3 trials, the safety of 20vPnC was mainly evaluated in comparison to 13vPnC.

Data pooling:

Each Phase 3 trial has distinct study objectives and design, including different subject populations with regard to age and prior pneumococcal vaccination status. The only overlapping subject populations across studies are pneumococcal vaccine naïve subjects 18-49 years of age from B7471007 Cohort 3

and B7471008. Age and prior pneumococcal vaccination status are important factors when interpreting safety and tolerability results. As these factors differ by study, safety data are presented mainly by study in side-by-side displays, except that data are pooled for subjects 18-49 years of age

2.6.8.1. Patient exposure

The 6 studies contributing to the evaluation of safety enrolled 7048 adult subjects. In total, 4552 subjects received 20vPnC and 2496 received control vaccine. The extent of exposure in the different studies is presented in Table 38. 20vPnC is given as a single IM dose.

Table 36: Number (%) of Subjects who Received at Least 1 Study Vaccination in all Adult Clinical Studies

Study [20vPnC Group vs Control Group]	20vPnC n (%)	Control n (%)	Total n (%)
Total Exposure[a]	4552 (100.0)	2496 (100.0)	7048 (100.0)
Phase 1	68 (1.5)	67 (2.7)	135 (1.9)
B7471001 [20vPnC vs Tdap]	33 (0.7)	33 (1.3)	66 (0.9)
B7471005 [20vPnC vs 13vPnC]	35 (0.8)	34 (1.4)	69 (1.0)
Phase 2	221 (4.9)	222 (8.9)	443 (6.3)
B7471002 [20vPnC/saline vs 13vPnC/PPSV23]	221 (4.9)	222 (8.9)	443 (6.3)
Phase 3	4263 (93.7)	2207 (88.4)	6470 (91.8)
B7471006 [20vPnC vs 13vPnC or PPSV23]	624 (13.7)	249 (10.0)	873 (12.4)
B7471007 [Cohort 1: 20vPnC/saline vs 13vPnC/PPSV23; Cohorts 2 and 3: 20vPnC vs 13vPnC]	2176 (47.8)	1713 (68.6)	3889 (55.2)
B7471008 [20vPnC Lot 1, 2, and 3 combined vs 13vPnC]	1463 (32.1)	245 (9.8)	1708 (24.2)

a. The values in this row are used as the denominators for percentage calculations.

Because adults ≥65 years of age are at increased risk of pneumococcal disease, this is the population most often targeted by national recommendations for adult pneumococcal vaccination. For this reason, safety data are summarised separately for this age group, including both pneumococcal vaccine naïve subjects (in B7471007) and subjects with prior pneumococcal vaccination (in B7471006). The Phase 3 studies enrolled 1885 subjects ≥65 years of age; among these, 1138 received 20vPnC and 747 received control vaccine (**Table 37**).

Table 37: Number (%) of Subjects who Received at Least 1 Study Vaccination in the Phase 3 Studies – Subjects ≥65 Years of Age by Study and Pneumococcal vaccination status

Study Prior Vaccination Status [20vPnC Group vs Control Group]	20vPnC n (%)	Control n (%)	Total n (%)
Total Exposure[a]	1138 (100.0)	747 (100.0)	1885 (100.0)
B7471006			
Prior PPSV23 (Cohort A) [20vPnC vs 13vPnC]	253 (22.2)	122 (16.3)	375 (19.9)
Prior 13vPnC (Cohort B) [20vPnC vs PPSV23]	246 (21.6)	127 (17.0)	373 (19.8)
Prior 13vPnC and PPSV23 (Cohort C) [20vPnC]	125 (11.0)		125 (6.6)
B7471007			
Naïve (Cohort 1) [20vPnC/saline vs 13vPnC/PPSV23]	514 (45.2)	498 (66.7)	1012 (53.7)

Across the three Phase 3 trials, subjects were predominantly female (52.0% to 65.9% across groups defined by age and prior pneumococcal vaccination status within the 20vPnC and control vaccine groups). With regard to age, 59.8% of subjects were ≥60 years of age, 6.9% were 50 through 59 years of age, and 33.3% were 18 through 49 years of age. The Phase 3 trials were conducted in the United States and Sweden; subjects in Sweden were enrolled in B7471007 (Cohort 1 only) and B7471006 (Cohort A only). Overall, the safety populations in B7471007 and B7471008 reflected a diverse racial and ethnic distribution (80.7% white, 14.2% black, 2.1% Asian; and 10.3% Hispanic).

In B7471006, subjects were predominantly white (92.4%). Entrance criteria for this study required that subjects had previously received pneumococcal vaccination, which may have affected the racial distribution. In addition, approximately 15% of subjects in the study were enrolled at sites in Sweden.

2.6.8.2. Adverse events

Data collection and analysis strategy

The methods for safety data collection and analysis were the same in all three Phase 3 trials.

Immediate reactions within the first 30 minutes after vaccination were assessed and documented as an AE or SAE, as appropriate, in the case report form (CRF).

Postvaccination safety evaluations were reported by the subject in an electronic diary as follows:

- Specific reactions and events and use of antipyretic or pain medications were reported by subjects in response to specific prompts using an electronic diary (e-diary):
    - local reactions (redness, swelling, and pain at the injection site) occurring within 10 days after vaccination
    - systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination
    - use of antipyretic or pain medications within 7 days after vaccination
- AEs occurring within 1 month after vaccination
- SAEs occurring within 6 months after vaccination
- NDCMCs occurring within 6 months after vaccination

Immediate adverse events

After each vaccination, subjects were observed for at least 30 minutes by site staff, who recorded AEs occurring during that time.

The proportion of subjects who reported immediate AEs after vaccination was low, both among subjects naïve to pneumococcal vaccine (≤0.2% after 20vPnC; ≤0.9% after 13vPnC) and among subjects ≥65 years of age by prior pneumococcal vaccination status (≤0.4% after 20vPnC; ≤0.8% after control vaccines).

Subjects naïve to pneumococcal vaccine (B7471007 and B7471008)

Table 38: Immediate Adverse Events Reported After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group – Safety Population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=1507)	13vPnC/PPSV23 (N[a]=1490)	20vPnC (N[a]=334)	13vPnC (N[a]=111)	20vPnC (N[a]=1798)	13vPnC (N[a]=357)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	3 (0.2)	3 (0.2)	0	1 (0.9)	2 (0.1)	1 (0.3)
GASTROINTESTINAL DISORDERS	0	0	0	0	2 (0.1)	0
Nausea	0	0	0	0	2 (0.1)	0
Vomiting	0	0	0	0	2 (0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.1)	2 (0.1)	0	0	0	0
Injection site pain	1 (0.1)	1 (0.1)	0	0	0	0
Injection site swelling	0	1 (0.1)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.1)	0	0	0	0	0
Joint swelling	1 (0.1)	0	0	0	0	0
Musculoskeletal stiffness	1 (0.1)	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	1 (0.1)	0	1 (0.9)	0	1 (0.3)
Dizziness	0	0	0	0	0	1 (0.3)
Headache	0	0	0	1 (0.9)	0	0
Somnolence	0	1 (0.1)	0	0	0	0

Subjects ≥65 years of age by prior pneumococcal vaccination status (B7471006 and B7471007)

Table 39: Immediate Adverse Events Reported After Vaccination – Subjects ≥65 Years of Age by Study and Prior Pneumococcal Vaccination Status – Safety Population

Study	B7471007		B7471006		B7471006		B7471006
Prior Pneumococcal Vaccination Status	Naïve		Prior PPSV23		Prior 13vPnC		Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514)	13vPnC/PPSV23 (N[a]=498)	20vPnC (N[a]=253)	13vPnC (N[a]=122)	20vPnC (N[a]=246)	PPSV23 (N[a]=127)	20vPnC (N[a]=125)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	0	1 (0.2)	1 (0.4)	0	0	1 (0.8)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.2)	0	0	0	0	0
Injection site swelling	0	1 (0.2)	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	1 (0.4)	0	0	0	0
Dehydration	0	0	1 (0.4)	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	1 (0.4)	0	0	1 (0.8)	0
Dizziness	0	0	1 (0.4)	0	0	1 (0.8)	0
Paraesthesia	0	0	1 (0.4)	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	1 (0.4)	0	0	0	0
Anxiety	0	0	1 (0.4)	0	0	0	0
VASCULAR DISORDERS	0	0	1 (0.4)	0	0	0	0
Hypotension	0	0	1 (0.4)	0	0	0	0

Notes:
MedDRA (v22.1) coding dictionary applied.
For B7471007 Naïve (subset of Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.
Immediate AE refers to an AE reported in the 30-minute observation period after vaccination (after Vaccination 1 for B7471007 Naïve).
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any immediate adverse event.

Solicited adverse events

Subjects naïve to pneumococcal vaccine (B7471007 and B7471008)

Most local reactions were mild or moderate in severity. Across age groups and in both vaccine groups, the most frequently reported local reaction was pain at the injection site (55% to 79% after 20vPnC; 54% to 78% after 13vPnC), with a trend toward decreasing frequency with increasing age. Other local reactions were reported at lower frequencies (redness: 7.3% to 8.2% after 20vPnC, 5.4% to 7.3% after 13vPnC, and swelling: 7.5% to 9.1% after 20vPnC, 8.0% to 10.8% after 13vPnC). Across age groups and after either 20vPnC or 13vPnC, the median onset day for local reactions was generally between Day 1 to Day 2.5 and reactions generally resolved with a median duration between 1 to 2 days.

Table 40: Local reactions, by Maximum Severity, within 10 Days after Vaccination – pneumococcal vaccine naïve Subjects by Study and Age Group – Safety population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N^a=1505) n^b (%)	13vPnC/PPSV23 (N^a=1483) n^b (%)	20vPnC (N^a=331) n^b (%)	13vPnC (N^a=111) n^b (%)	20vPnC (N^a=1791) n^b (%)	13vPnC (N^a=355) n^b (%)
Redness[c]						
Any	110 (7.3)	92 (6.2)	27 (8.2)	6 (5.4)	132 (7.4)	26 (7.3)
Mild	56 (3.7)	56 (3.8)	17 (5.1)	3 (2.7)	67 (3.7)	14 (3.9)
Moderate	42 (2.8)	33 (2.2)	9 (2.7)	3 (2.7)	56 (3.1)	12 (3.4)
Severe	12 (0.8)	3 (0.2)	1 (0.3)	0	9 (0.5)	0
Swelling[c]						
Any	113 (7.5)	118 (8.0)	29 (8.8)	12 (10.8)	163 (9.1)	35 (9.9)
Mild	72 (4.8)	72 (4.9)	19 (5.7)	8 (7.2)	103 (5.8)	23 (6.5)
Moderate	36 (2.4)	42 (2.8)	10 (3.0)	4 (3.6)	57 (3.2)	12 (3.4)
Severe	5 (0.3)	4 (0.3)	0	0	3 (0.2)	0
Pain at injection site[d]						
Any	834 (55.4)	803 (54.1)	240 (72.5)	77 (69.4)	1418 (79.2)	276 (77.7)
Mild	682 (45.3)	662 (44.6)	177 (53.5)	58 (52.3)	871 (48.6)	172 (48.5)
Moderate	149 (9.9)	136 (9.2)	59 (17.8)	18 (16.2)	529 (29.5)	99 (27.9)
Severe	3 (0.2)	5 (0.3)	4 (1.2)	1 (0.9)	18 (1.0)	5 (1.4)
Any local reaction[e]	864 (57.4)	830 (56.0)	241 (72.8)	78 (70.3)	1425 (79.6)	276 (77.7)

Note: The 20vPnC group from B7471008 is the pooled 20vPnC group, which includes subjects from the 20vPnC Lot 1, 2, and 3 groups.

a. N = number of subjects with any e-diary data reported after vaccination (after Vaccination 1 [20vPnC or 13vPnC] for B7471007 ≥60 years [Cohort 1]).
This value is the denominator for the percentage calculations.

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

c. Mild is >2.0 to 5.0 cm; moderate is >5.0 to 10.0 cm; severe is >10.0 cm.

d. Mild = does not interfere with activity; moderate = interferes with activity; severe = prevents daily activity.

e. Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after vaccination.

Most systemic events were mild or moderate in severity. Across age groups and in both vaccine groups, the most frequently reported systemic event was muscle pain (39% to 63% after 20vPnC; 37% to 65% after 13vPnC). Across the age groups, the frequency of most systemic events tended to decrease with increasing age. Fever ≥38°C was reported at low frequency (0.9% to 1.5% after 20vPnC; 0.8% to 1.1% after 13vPnC).

Across age groups and after either 20vPnC or 13vPnC, the median onset day for most systemic events was generally between Day 1 to Day 2, and systemic events generally resolved with a median duration of 1 to 2 days.

Table 41: Systemic events, by maximum severity, within 7 days after vaccination – pneumococcal vaccine naïve subjects by study and age group – safety population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=1505) n[b] (%)	13vPnC/PPSV23 (N[a]=1483) n[b] (%)	20vPnC (N[a]=331) n[b] (%)	13vPnC (N[a]=111) n[b] (%)	20vPnC (N[a]=1791) n[b] (%)	13vPnC (N[a]=355) n[b] (%)
Fever						
≥38.0°C	14 (0.9)	12 (0.8)	5 (1.5)	1 (0.9)	22 (1.2)	4 (1.1)
≥38.0°C to 38.4°C	4 (0.3)	6 (0.4)	2 (0.6)	1 (0.9)	13 (0.7)	1 (0.3)
>38.4°C to 38.9°C	4 (0.3)	3 (0.2)	1 (0.3)	0	5 (0.3)	1 (0.3)
>38.9°C to 40.0°C	1 (0.0)	0	1 (0.3)	0	4 (0.2)	2 (0.6)
>40.0°C	5 (0.3)	3 (0.2)	1 (0.3)	0	0	0
Fatigue[c]						
Any	454 (30.2)	455 (30.7)	130 (39.3)	40 (36.0)	836 (46.7)	155 (43.7)
Mild	243 (16.1)	260 (17.5)	70 (21.1)	20 (18.0)	422 (23.6)	82 (23.1)
Moderate	193 (12.8)	177 (11.9)	57 (17.2)	17 (15.3)	383 (21.4)	65 (18.3)
Severe	18 (1.2)	18 (1.2)	3 (0.9)	3 (2.7)	31 (1.7)	8 (2.3)
Headache[c]						
Any	324 (21.5)	345 (23.3)	107 (32.3)	40 (36.0)	657 (36.7)	130 (36.6)
Mild	233 (15.5)	252 (17.0)	68 (20.5)	24 (21.6)	401 (22.4)	84 (23.7)
Moderate	81 (5.4)	88 (5.9)	36 (10.9)	15 (13.5)	224 (12.5)	43 (12.1)
Severe	10 (0.7)	5 (0.3)	3 (0.9)	1 (0.9)	32 (1.8)	3 (0.8)
Muscle pain[c]						
Any	588 (39.1)	553 (37.3)	165 (49.8)	55 (49.5)	1127 (62.9)	230 (64.8)
Mild	435 (28.9)	398 (26.8)	112 (33.8)	35 (31.5)	682 (38.1)	141 (39.7)
Moderate	147 (9.8)	148 (10.0)	51 (15.4)	19 (17.1)	425 (23.7)	83 (23.4)
Severe	6 (0.4)	7 (0.5)	2 (0.6)	1 (0.9)	20 (1.1)	6 (1.7)
Joint pain[c]						
Any	190 (12.6)	203 (13.7)	51 (15.4)	23 (20.7)	290 (16.2)	54 (15.2)
Mild	104 (6.9)	106 (7.1)	35 (10.6)	14 (12.6)	166 (9.3)	29 (8.2)
Moderate	81 (5.4)	94 (6.3)	16 (4.8)	8 (7.2)	118 (6.6)	22 (6.2)
Severe	5 (0.3)	3 (0.2)	0	1 (0.9)	6 (0.3)	3 (0.8)
Any systemic event[d]	831 (55.2)	822 (55.4)	230 (69.5)	75 (67.6)	1377 (76.9)	269 (75.8)
Use of antipyretic or pain medication[e]	278 (18.5)	303 (20.4)	81 (24.5)	31 (27.9)	406 (22.7)	70 (19.7)

Note: The 20vPnC group from B7471008 is the pooled 20vPnC group, which includes subjects from the 20vPnC Lot 1, 2, and 3 groups.

a. N = number of subjects with any e-diary data reported after vaccination (after Vaccination 1 [20vPnC or 13vPnC] for B7471007 ≥60 years [Cohort 1]).
This value is the denominator for the percentage calculations.

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

c. Mild = does not interfere with activity; moderate = some interference with activity; severe = prevents daily activity.

d. Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.

e. Severity was not collected for use of antipyretic or pain medication. The numbers listed reflect yes responses (ie, number of events reported).

Subjects ≥65 years of age by prior pneumococcal vaccination status (B7471006 and B7471007)

Most local reactions were mild or moderate in severity. In all groups defined by prior pneumococcal vaccination status and after both 20vPnC and control vaccines, the most frequently reported local reaction was pain at the injection site (44% to 61% after 20vPnC; 43% to 56% after control vaccines). Other local reactions were reported at much lower frequencies (redness: 4.8% to 8.6% after 20vPnC; 2.5% to 13% after control vaccines; swelling: 4.0% to 9.9% after 20vPnC; 6.6% to 14% after control vaccines). In B7471006, after either 20vPnC or control vaccine, and across the cohorts, the median onset day for local reactions was Day 1 or Day 2, and reactions generally resolved with a median duration of 1 to 2 days.

Table 42: Local Reactions, by Maximum Severity, Within 10 Days After Vaccination – Subjects ≥65 Years of Age by Study and Prior Pneumococcal Vaccination Status – Safety Population

Study	B7471007		B7471006		B7471006		B7471006
Prior Pneumococcal Vaccination Status	Naïve		Prior PPSV23		Prior 13vPnC		Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514) n[b] (%)	13vPnC/PPSV23 (N[a]=493) n[b] (%)	20vPnC (N[a]=253) n[b] (%)	13vPnC (N[a]=121) n[b] (%)	20vPnC (N[a]=245) n[b] (%)	PPSV23 (N[a]=126) n[b] (%)	20vPnC (N[a]=125) n[b] (%)
Redness[c]							
Any	40 (7.8)	30 (6.1)	20 (7.9)	3 (2.5)	21 (8.6)	16 (12.7)	6 (4.8)
Mild	19 (3.7)	16 (3.2)	9 (3.6)	2 (1.7)	7 (2.9)	6 (4.8)	2 (1.6)
Moderate	14 (2.7)	13 (2.6)	8 (3.2)	1 (0.8)	13 (5.3)	9 (7.1)	4 (3.2)
Severe	7 (1.4)	1 (0.2)	3 (1.2)	0	1 (0.4)	1 (0.8)	0
Swelling[c]							
Any	34 (6.6)	36 (7.3)	25 (9.9)	8 (6.6)	23 (9.4)	18 (14.3)	5 (4.0)
Mild	20 (3.9)	24 (4.9)	13 (5.1)	8 (6.6)	14 (5.7)	8 (6.3)	2 (1.6)
Moderate	11 (2.1)	10 (2.0)	9 (3.6)	0	9 (3.7)	9 (7.1)	3 (2.4)
Severe	3 (0.6)	2 (0.4)	3 (1.2)	0	0	1 (0.8)	0
Pain at injection site[d]							
Any	224 (43.6)	217 (44.0)	127 (50.2)	52 (43.0)	150 (61.2)	71 (56.3)	66 (52.8)
Mild	184 (35.8)	178 (36.1)	116 (45.8)	47 (38.8)	134 (54.7)	51 (40.5)	59 (47.2)
Moderate	39 (7.6)	37 (7.5)	11 (4.3)	4 (3.3)	15 (6.1)	18 (14.3)	7 (5.6)
Severe	1 (0.2)	2 (0.4)	0	1 (0.8)	1 (0.4)	2 (1.6)	0
Any local reaction[e]	239 (46.5)	226 (45.8)	134 (53.0)	53 (43.8)	157 (64.1)	73 (57.9)	68 (54.4)

a. N = number of subjects with any e-diary data reported after vaccination (after Vaccination 1 [20vPnC or 13vPnC] for B7471007 Naïve [subset of Cohort 1]). This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Mild is >2.0 to 5.0 cm; moderate is >5.0 to 10.0 cm; severe is >10.0 cm.
d. Mild = does not interfere with activity; moderate = interferes with activity; severe = prevents daily activity.
e. Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after vaccination.

Most systemic events were mild or moderate in severity. In all groups defined by prior pneumococcal vaccination status and after both 20vPnC and control vaccines, the most frequently reported type of systemic event was muscle pain (32% to 38% after 20vPnC; 31% to 46% after control vaccines). Fever ≥38°C was reported at low frequency (0.0% to 1.2% after 20vPnC; 0.0% to 1.6% after control vaccines). In B7471006, in the 20vPnC and control vaccine groups, the median onset day for each type of systemic event was between Day 1 and Day 3.5. Systemic events generally resolved with a median duration of 1 to 2 days.

Table 43: Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – Subjects ≥65 Years of Age by Study and Prior Pneumococcal Vaccination Status – Safety Population

Study	B7471007		B7471006		B7471006		B7471006
Prior Pneumococcal Vaccination Status	Naïve		Prior PPSV23		Prior 13vPnC		Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514) n[b] (%)	13vPnC/PPSV23 (N[a]=493) n[b] (%)	20vPnC (N[a]=253) n[b] (%)	13vPnC (N[a]=121) n[b] (%)	20vPnC (N[a]=245) n[b] (%)	PPSV23 (N[a]=126) n[b] (%)	20vPnC (N[a]=125) n[b] (%)
Fever							
≥38.0°C	6 (1.2)	8 (1.6)	2 (0.8)	0	0	2 (1.6)	0
≥38.0°C to 38.4°C	1 (0.2)	3 (0.6)	2 (0.8)	0	0	1 (0.8)	0
>38.4°C to 38.9°C	1 (0.2)	2 (0.4)	0	0	0	1 (0.8)	0
>38.9°C to 40.0°C	1 (0.2)	0	0	0	0	0	0
>40.0°C	3 (0.6)	3 (0.6)	0	0	0	0	0
Fatigue[c]							
Any	130 (25.3)	134 (27.2)	73 (28.9)	27 (22.3)	76 (31.0)	42 (33.3)	41 (32.8)
Mild	64 (12.5)	77 (15.6)	45 (17.8)	12 (9.9)	48 (19.6)	25 (19.8)	24 (19.2)
Moderate	64 (12.5)	51 (10.3)	28 (11.1)	12 (9.9)	25 (10.2)	17 (13.5)	15 (12.0)
Severe	2 (0.4)	6 (1.2)	0	3 (2.5)	3 (1.2)	0	2 (1.6)
Headache[c]							
Any	81 (15.8)	95 (19.3)	45 (17.8)	22 (18.2)	33 (13.5)	27 (21.4)	24 (19.2)
Mild	59 (11.5)	67 (13.6)	32 (12.6)	15 (12.4)	24 (9.8)	26 (20.6)	16 (12.8)
Moderate	18 (3.5)	26 (5.3)	12 (4.7)	7 (5.8)	9 (3.7)	1 (0.8)	7 (5.6)
Severe	4 (0.8)	2 (0.4)	1 (0.4)	0	0	0	1 (0.8)
Muscle pain[c]							
Any	164 (31.9)	159 (32.3)	81 (32.0)	38 (31.4)	83 (33.9)	58 (46.0)	47 (37.6)
Mild	119 (23.2)	114 (23.1)	66 (26.1)	29 (24.0)	62 (25.3)	40 (31.7)	35 (28.0)
Moderate	44 (8.6)	41 (8.3)	14 (5.5)	6 (5.0)	21 (8.6)	15 (11.9)	11 (8.8)
Severe	1 (0.2)	4 (0.8)	1 (0.4)	3 (2.5)	0	3 (2.4)	1 (0.8)
Joint pain[c]							
Any	69 (13.4)	59 (12.0)	17 (6.7)	13 (10.7)	29 (11.8)	20 (15.9)	21 (16.8)
Mild	30 (5.8)	32 (6.5)	12 (4.7)	6 (5.0)	19 (7.8)	13 (10.3)	16 (12.8)
Moderate	37 (7.2)	26 (5.3)	5 (2.0)	6 (5.0)	10 (4.1)	7 (5.6)	5 (4.0)
Severe	2 (0.4)	1 (0.2)	0	1 (0.8)	0	0	0
Any systemic event[d]	245 (47.7)	247 (50.1)	131 (51.8)	53 (43.8)	123 (50.2)	75 (59.5)	66 (52.8)
Use of antipyretic or pain medication[e]	70 (13.6)	80 (16.2)	40 (15.8)	18 (14.9)	42 (17.1)	25 (19.8)	22 (17.6)

a. N = number of subjects with any e-diary data reported after vaccination (after Vaccination 1 [20vPnC or 13vPnC] for B7471007 Naïve [subset of Cohort 1]). This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Mild = does not interfere with activity; moderate = some interference with activity; severe = prevents daily activity.
d. Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.
e. Severity was not collected for use of antipyretic or pain medication. The numbers listed reflect yes responses (ie, number of events reported).

Supplementary data from phase 1/2 studies B7471001, B7471002 and B7471005

B7471001

Local reactions were reported by a similar proportion of subjects in the 20vPnC group and Tdap group with the majority being either mild or moderate in severity. One subject who was in the 20vPnC group reported severe pain at the injection site and severe limitation of arm movement. The most commonly reported local reaction in the 20vPnC and Tdap group was pain at the injection site (69.7% and 63.6%, respectively), followed by limitation of arm movement (36.4% and 18.2%, respectively). Redness and swelling were reported by 1 (3.0%) subject each in the 20vPnC group, and by no subjects in the Tdap group.

Systemic events were reported by a higher proportion of subjects in the 20vPnC group (72.7%) compared to the Tdap group (57.6%). The majority of systemic events were mild or moderate in severity. The most commonly reported systemic event in the 20vPnC and Tdap groups was new muscle pain (45.5% and 42.4%, respectively), followed by fatigue and headache (each reported by 39.4% and 30.3% of subjects in the 20vPnC and Tdap group, respectively). Fever was reported by 1 (3.0%) subject each in the 20vPnC group. One (1) subject who received 20vPnC reported a severe headache on Day 3 after vaccination and 1 subject who received Tdap report severe fatigue on Day 7 after vaccination.

A total of 21.2% of subjects in the 20vPnC group and 18.2% of subjects in the Tdap group reported the use of antipyretic or pain medication. The median day of onset for the use of medication to treat pain/fever was similar between subjects who received 20vPnC (Day 3) and Tdap (Day 4).

B7471002

The proportions of participants who reported prompted local reactions within 10 days after vaccination with 20vPnC or 13vPnC by maximum severity were similar in the 2 groups (60.9% in the 20vPnC/Saline group and 56.8 in the 13vPnC/PPSV23 group). The most frequent local reaction reported was pain at injection site, and most local reactions were mild or moderate in severity. Redness was observed slightly more often in 20vPnC higher (11.4%) compared to control (6.8%). The proportions and maximum severity of prompted systemic events reported within 7 days after Vaccination 1 were similar for the 2 groups (54.5% in the 20vPnC/Saline group and 55.9% in the 13vPnC/PPSV23 group). The most frequent systemic event reported was muscle pain, and most systemic events were mild or moderate in severity. Muscle pain was slightly higher in 20vPnC (43.2%) compared to control vaccine group (36.5%).

B7471005

The proportions of participants who reported prompted local reactions within 14 days after vaccination by maximum severity in the 20vPnC and c7vPnC groups were similar to the 13vPnC group. The most frequent local reaction reported was pain at injection site (77.1% in the 20vPnC group; 76.5% in the 20vPnC group; 79.4% in the 13vPnC group). Most local reactions were mild or moderate in severity. Swelling was reported by 2 subjects in each arm (<6%). Redness was reported by 2 subjects in 20vPnC and c7vPnC groups, whereas no events of redness were reported in 13vPnC group. The majority of local reactions had a median day of onset of between 1 to 3 days after vaccination. The majority of local reactions generally resolved with median durations between 1 to 3 days.

The proportions and maximum severity of prompted systemic events reported within 14 days after vaccination in the 20vPnC and c7vPnC groups were mostly similar to the 13vPnC group, except that a higher number of participants reported headache (mostly mild) in the 20vPnC group (13 out of 35 [37.1%] participants) compared to the c7vPnC group (8 out of 34 [23.5%] participants) and 13vPnC group (5 out of 34 [14.7%] participants). The most frequent systemic event reported was muscle pain (57.1% in the 20vPnC group; 35.3% in the c7vPnC group; 52.9% in the 13vPnC group). Most systemic events were mild or moderate in severity. The majority of systemic events had a median day of onset of between 1 to 2.5 days after vaccination, with the exception of headache (5 days in the 20vPnC groups, 7 days in the 13vPnC group) , and generally resolved with median durations between 1 to 4 days.

Unsolicited adverse events

Subjects naïve to pneumococcal vaccine (B7471007 and B7471008)

Only AEs (MedDRA Preferred Terms) reported for more than 1% of subjects in either vaccine group within each age group are presented here (**Table 44**).

The proportions of subjects reporting any AE within 1 month after vaccination were similar across age groups and were similar for subjects who received 20vPnC (8.4% to 10%) and 13vPnC (7.3% to 11%). Overall, the AEs reported were generally diseases and conditions often observed in adults in these age groups. The most frequently reported AEs were in the Infections and Infestations SOC (3.1% to 5.1% after 20vPnC; 3.2% to 5.4% after 13vPnC). Few AEs (MedDRA Preferred Terms) were reported for more than 1% of subjects in either vaccine group within each age group.

Table 44: Adverse Events Reported in ≥1% Subjects in At Least One Group From Vaccination to 1 Month After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group –Safety Population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=1507)	13vPnC/PPSV23 (N[a]=1490)	20vPnC (N[a]=334)	13vPnC (N[a]=111)	20vPnC (N[a]=1798)	13vPnC (N[a]=357)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	148 (9.8)	166 (11.1)	34 (10.2)	9 (8.1)	151 (8.4)	26 (7.3)
INFECTIONS AND INFESTATIONS	46 (3.1)	47 (3.2)	17 (5.1)	6 (5.4)	74 (4.1)	14 (3.9)
Upper respiratory tract infection	12 (0.8)	8 (0.5)	4 (1.2)	3 (2.7)	16 (0.9)	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	12 (0.8)	23 (1.5)	6 (1.8)	0	13 (0.7)	1 (0.3)
Fall	5 (0.3)	7 (0.5)	4 (1.2)	0	3 (0.2)	0

Notes:
MedDRA (v22.1) coding dictionary applied.
For B7471007 ≥60 years (Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.
The 20vPnC group from B7471008 is the pooled 20vPnC group, which includes subjects from the 20vPnC Lot 1, 2, and 3 groups.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any adverse event.

Subjects ≥65 years of age by prior pneumococcal vaccination status (B7471006 and B7471007)

The proportions of subjects reporting any AE within 1 month after vaccination were similar for subjects who received 20vPnC (4.9% to 10%) or control vaccines (9.0% to 12%). Overall, the AEs reported were generally the types of diseases and conditions often observed in adults ≥65 years of age. The most frequently reported AEs were in the Infections and Infestations SOC (1.2% to 3.2% after 20vPnC; 1.6% to 4.9% after control vaccines). Few AEs (MedDRA Preferred Terms) were reported for more than 1% of subjects in any vaccine group.

Table 45: Adverse Events Reported in ≥1% Subjects in At Least One Group From Vaccination to 1 Month After Vaccination – Subjects ≥65 years of age by study and prior pneumococcal vaccination status–Safety Population

Study	B7471007		B7471006		B7471006		B7471006
Prior Pneumococcal Vaccination Status	Naïve		Prior PPSV23		Prior 13vPnC		Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514)	13vPnC/PPSV23 (N[a]=498)	20vPnC (N[a]=253)	13vPnC (N[a]=122)	20vPnC (N[a]=246)	PPSV23 (N[a]=127)	20vPnC (N[a]=125)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	47 (9.1)	58 (11.6)	19 (7.5)	11 (9.0)	12 (4.9)	14 (11.0)	13 (10.4)
INFECTIONS AND INFESTATIONS	14 (2.7)	15 (3.0)	8 (3.2)	6 (4.9)	3 (1.2)	2 (1.6)	3 (2.4)
Nasopharyngitis	1 (0.2)	4 (0.8)	3 (1.2)	1 (0.8)	0	0	0
Urinary tract infection	1 (0.2)	1 (0.2)	0	2 (1.6)	1 (0.4)	0	1 (0.8)
NERVOUS SYSTEM DISORDERS	3 (0.6)	4 (0.8)	4 (1.6)	0	3 (1.2)	2 (1.6)	0
Dizziness	0	0	2 (0.8)	0	1 (0.4)	2 (1.6)	0

Notes:
MedDRA (v22.1) coding dictionary applied.
For B7471007 Naïve (subset of Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any adverse event.

Supplementary data from phase 1/2 studies B7471001, B7471002 and B7471005

B7471001: In the 20vPnC and the Tdap vaccine groups, 15 (45.5%) and 11 (33.3%) subjects reported AEs within 1 month after vaccination. The most frequently reported AEs in both the 20vPnC and Tdap groups were in the gastrointestinal disorders SOC (15.2% and 9.1% of subjects, respectively). The most frequently reported AEs in the 20vPnC group (reported by more than 1 subject) were dyspepsia, viral upper respiratory tract infection, headache, insomnia and dysmenorrhea (2 [6.1%] subjects each). All other AEs in both the 20vPnC and Tdap groups were reported in single subjects.

B7471002: At 1 month after Vaccination 1, the proportions of participants reporting any AEs were similar in the 2 groups (12.2% in the 20vPnC/Saline group and 13.1% in the 13vPnC/PPSV23 group). From Vaccination 2 to 1 month after Vaccination 2, the proportions of participants reporting any AEs were higher in the 13vPnC/PPSV23 group than in 20vPnC/saline group, particularly in system organ class (SOC) of general disorders and administration site conditions, which may be expected as one group received saline while the other received PPSV23 (7% in the 20vPnC/Saline group and 18.7 % in the 13vPnC/PPSV23 group). One month after participants received each vaccination, infections and infestations were the most frequently reported types of AEs by SOC in both groups. The most frequently reported AEs by preferred term within 1 month after each vaccination was upper respiratory tract infection in both groups, whereas injection site pain, and injection site swelling were also frequently reported in the 13vPnC/PPSV23 group 1 month after Vaccination 2.

B7471005: At 1 month after vaccination, the proportions of participants reporting any AEs were similar in the vaccine groups i.e. 2/35 (5.7%) in the 20vPnC group versus 3/34 (8.8%), with no more than 3 participants from each vaccine group reporting any AEs. No PT was reported in more than 1 participant. The most frequently reported AEs.

Related adverse events

Subjects naïve to pneumococcal vaccine (B7471007 and B7471008)

The proportions of subjects reporting any AE occurring within 1 month after vaccination and considered by the investigator to be related to study vaccine were low and were similar after 20vPnC (≤0.9%) or 13vPnC (≤1.5%) and across age groups (**Table 46**). The most frequently reported types of AEs considered by the investigator to be related to study vaccine were injection site reactions in the SOC of general disorders and administration site conditions.

Subjects ≥65 years of age by prior pneumococcal vaccination status (B7471006 and B7471007)

AEs considered related to study vaccine were reported for ≤1.6% of subjects after 20vPnC and for ≤2.4% after control vaccines (**Table 47**).

Table 46: Related Adverse Events Reported From Vaccination to 1 Month After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group –Safety Population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N^a=1507)	13vPnC/PPSV23 (N^a=1490)	20vPnC (N^a=334)	13vPnC (N^a=111)	20vPnC (N^a=1798)	13vPnC (N^a=357)
System Organ Class/ Preferred Term	n^b (%)	n^b (%)	n^b (%)	n^b (%)	n^b (%)	n^b (%)
Swelling	1 (0.1)	0	0	0	0	0
Vaccination site pruritus	1 (0.1)	0	0	0	0	0
Vaccination site swelling	1 (0.1)	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	1 (0.1)	0	0	0	0
Upper respiratory tract infection	0	1 (0.1)	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.1)	0	0	0	0
Contusion	0	1 (0.1)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.1)	1 (0.1)	0	0	2 (0.1)	1 (0.3)
Muscle oedema	1 (0.1)	0	0	0	0	0
Musculoskeletal pain	0	0	0	0	0	1 (0.3)
Musculoskeletal stiffness	1 (0.1)	0	0	0	0	0
Myalgia	0	1 (0.1)	0	0	1 (0.1)	0
Neck pain	0	0	0	0	0	1 (0.3)
Pain in extremity	0	0	0	0	1 (0.1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1)	0	0	0	0	0
Lipoma	1 (0.1)	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	1 (0.1)	4 (0.3)	0	0	2 (0.1)	1 (0.3)
Dizziness	0	0	0	0	0	1 (0.3)
Dysgeusia	1 (0.1)	0	0	0	0	0
Headache	0	3 (0.2)	0	0	1 (0.1)	0
Migraine	0	0	0	0	1 (0.1)	0
Somnolence	0	1 (0.1)	0	0	0	0
PSYCHIATRIC DISORDERS	1 (0.1)	0	0	0	1 (0.1)	0
Anxiety	1 (0.1)	0	0	0	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.1)	0	0	0	0
Bronchial hyperreactivity	0	1 (0.1)	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.2)	3 (0.2)	1 (0.3)	0	3 (0.2)	0
Dermatitis contact	0	1 (0.1)	0	0	0	0
Erythema	0	1 (0.1)	1 (0.3)	0	0	0
Hyperhidrosis	1 (0.1)	0	0	0	0	0
Pruritus	2 (0.1)	0	0	0	1 (0.1)	0
Rash	0	1 (0.1)	0	0	2 (0.1)	0
Urticaria	0	1 (0.1)	0	0	0	0

Notes:
MedDRA (v22.1) coding dictionary applied.
For B7471007 ≥60 years (Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.
The 20vPnC group from B7471008 is the pooled 20vPnC group, which includes subjects from the 20vPnC Lot 1, 2, and 3 groups.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any related adverse event.

Table 47: Related Adverse Events Reported From Vaccination to 1 Month After Vaccination – Subjects ≥65 years of age by study and prior pneumococcal vaccination status–Safety Population

Study Prior Pneumococcal Vaccination Status	B7471007 Naïve		B7471006 Prior PPSV23		B7471006 Prior 13vPnC		B7471006 Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514)	13vPnC/PPSV23 (N[a]=498)	20vPnC (N[a]=253)	13vPnC (N[a]=122)	20vPnC (N[a]=246)	PPSV23 (N[a]=127)	20vPnC (N[a]=125)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	5 (1.0)	9 (1.8)	1 (0.4)	0	4 (1.6)	3 (2.4)	0
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (0.4)	0	0
Diarrhoea	0	0	0	0	1 (0.4)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.8)	8 (1.6)	1 (0.4)	0	2 (0.8)	1 (0.8)	0
Fatigue	0	2 (0.4)	0	0	0	0	0
Feeling abnormal	1 (0.2)	0	0	0	0	0	0
Injection site bruising	0	1 (0.2)	0	0	0	0	0
Injection site erythema	0	0	0	0	1 (0.4)	1 (0.8)	0
Injection site pain	1 (0.2)	1 (0.2)	0	0	0	0	0
Injection site pruritus	0	2 (0.4)	1 (0.4)	0	1 (0.4)	0	0
Injection site reaction	0	1 (0.2)	0	0	0	0	0
Injection site swelling	0	1 (0.2)	0	0	0	0	0
Injection site warmth	0	1 (0.2)	1 (0.4)	0	0	0	0
Pain	1 (0.2)	0	0	0	0	0	0
Swelling	1 (0.2)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.2)	0	0	0	0	1 (0.8)	0
Muscle oedema	1 (0.2)	0	0	0	0	0	0
Pain in extremity	0	0	0	0	0	1 (0.8)	0
NERVOUS SYSTEM DISORDERS	0	0	0	0	1 (0.4)	1 (0.8)	0
Dizziness	0	0	0	0	0	1 (0.8)	0
Headache	0	0	0	0	1 (0.4)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.2)	0	0	0	0	0
Bronchial hyperreactivity	0	1 (0.2)	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.6)	0	0	0	0	0	0
Hyperhidrosis	1 (0.2)	0	0	0	0	0	0
Pruritus	2 (0.4)	0	0	0	0	0	0

Notes:
MedDRA (v22.1) coding dictionary applied.
For B7471007 Naïve (subset of Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any related adverse event.

Supplementary data from phase 1/2 studies B7471001, B7471002 and B7471005

B7471001

Within 1 month of vaccination there were 2 (6.1%) subjects each in the 20vPnC and Tdap groups who reported related AEs. Two (2) subjects in the 20vPnC group reported a total of 2 events and 2 subjects in the Tdap group reported a total of 4 events. No subjects reported related AEs after 1 month post-vaccination. Onset of related events ranged from the day of vaccination (Day 1) to 9 days after vaccination and the duration ranged from 1 to 31 days. Related AEs were reported by two subjects (decreased appetite [1] and limb discomfort [1]) in the 20vPnC group and by two subjects (limb discomfort [1] and photophobia, nausea, and dizziness [1]) in the Tdap group.

B7471002

Few participants reported AEs that were considered related to vaccination after receiving Vaccination 1 to 1 month after vaccination and after receiving Vaccination 2 to 1 month after vaccination in the 2

groups. The most frequent related AEs reported were in the SOC of general disorders and administration site conditions.

B7471005

Of the few AEs reported in the study, only 2 participants reported AEs that were considered related to vaccination. Following AEs were considered vaccine-related AEs: injection site erythema and swelling in the 20vPnC group; fatigue, vomiting and headache in the c7vPnC group. In the 13vPnC group no AE was considered as vaccine related.

Severe adverse events

The proportion of subjects who reported severe AEs after vaccination was low, both among subjects naïve to pneumococcal vaccine (≤0.8% after 20vPnC; ≤1.1% after 13vPnC) and among subjects ≥65 years of age by prior pneumococcal vaccination status (≤1.6% after 20vPnC; ≤2.4% after control vaccines).

Other Significant AEs/ Newly diagnosed medical conditions

The proportions of subjects reporting NDCMCs within 6 months after vaccination was low, both among subjects naïve to pneumococcal vaccine (≤2.3% after both 20vPnC and 13vPnC) and among subjects ≥65 years of age by prior pneumococcal vaccination status (≤4.0% after 20vPnC; ≤2.4% after control vaccines). The most frequently reported NDCMCs were in the SOCs of Musculoskeletal and connective tissue disorders, Metabolism and nutrition disorders (predominantly Type 2 diabetes mellitus), and Vascular disorders (predominantly hypertension). Overall, the NDCMCs reported were generally diseases and conditions often observed in adults in these age groups.

Of note that as of the cut-off date, two cases of autoimmune disorders (Basedow's disease [1] and rheumatoid arthritis [1]) were reported after 20nPvC.

2.6.8.3. Serious adverse event/deaths

Subjects naïve to pneumococcal vaccine (B7471007 and B7471008)

The proportions of subjects reporting one or more SAEs within 6 months after vaccination were low and similar after 20vPnC (≤2.4%) or 13vPnC (≤1.9%). SAEs were reported at a slightly higher frequency among subjects ≥60 years of age (2.4% after 20vPnC, 1.9% after 13vPnC) than in younger age groups (≤0.9% after either vaccine). None of the SAEs reported were considered by the investigator to be related to study vaccine. The most frequently reported SAEs were in the Infections and infestations SOC. (**Table 48**).

Table 48: Serious Adverse Events Reported Within 6 Months After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group – Safety Population

Study Age Group	B7471007 ≥60 Years		B7471007 50-59 Years		B7471007 and B7471008 18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=1507)	13vPnC/PPSV23 (N[a]=1490)	20vPnC (N[a]=334)	13vPnC (N[a]=111)	20vPnC (N[a]=1798)	13vPnC (N[a]=357)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	36 (2.4)	29 (1.9)	1 (0.3)	1 (0.9)	12 (0.7)	1 (0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)	0	0	1 (0.1)	0
Blood loss anaemia	0	1 (0.1)	0	0	0	0
Splenic cyst	0	0	0	0	1 (0.1)	0
CARDIAC DISORDERS	5 (0.3)	5 (0.3)	0	0	1 (0.1)	0
Acute myocardial infarction	0	1 (0.1)	0	0	1 (0.1)	0
Atrial fibrillation	1 (0.1)	1 (0.1)	0	0	0	0
Cardiac failure congestive	0	2 (0.1)	0	0	0	0
Coronary artery disease	3 (0.2)	1 (0.1)	0	0	0	0
Myocardial infarction	1 (0.1)	0	0	0	0	0
Silent myocardial infarction	0	1 (0.1)	0	0	0	0
GASTROINTESTINAL DISORDERS	0	3 (0.2)	0	0	3 (0.2)	0
Colitis	0	1 (0.1)	0	0	0	0
Gastritis	0	0	0	0	1 (0.1)	0
Gastrointestinal haemorrhage	0	1 (0.1)	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	1 (0.1)	0
Hiatus hernia	0	0	0	0	1 (0.1)	0
Upper gastrointestinal haemorrhage	0	1 (0.1)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.1)	2 (0.1)	0	0	0	0
Chest pain	0	1 (0.1)	0	0	0	0
Hernia	1 (0.1)	0	0	0	0	0
Non-cardiac chest pain	1 (0.1)	0	0	0	0	0
Systemic inflammatory response syndrome	0	1 (0.1)	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.1)	0	0	0	0	0
Biloma	1 (0.1)	0	0	0	0	0
INFECTIONS AND INFESTATIONS	7 (0.5)	3 (0.2)	0	1 (0.9)	2 (0.1)	1 (0.3)
Abdominal abscess	0	0	0	0	1 (0.1)	0
Appendicitis	2 (0.1)	0	0	0	0	0
Arthritis infective	1 (0.1)	0	0	0	0	0
Cellulitis	2 (0.1)	1 (0.1)	0	0	0	0
Clostridium difficile colitis	1 (0.1)	0	0	0	0	0
Diverticulitis	0	1 (0.1)	0	0	0	0
Erysipelas	1 (0.1)	0	0	0	0	0
Herpes simplex meningitis	0	0	0	0	0	1 (0.3)
Kidney infection	0	1 (0.1)	0	0	0	0
Osteomyelitis	0	0	0	0	1 (0.1)	0
Pneumonia mycoplasmal	0	0	0	0	1 (0.1)	0
Skin bacterial infection	0	0	0	1 (0.9)	0	0
Staphylococcal bacteraemia	0	0	0	0	1 (0.1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.3)	4 (0.3)	0	0	2 (0.1)	0
Femur fracture	1 (0.1)	0	0	0	0	0

Table 48 (cont.): Serious Adverse Events Reported Within 6 Months After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group – Safety Population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=1507)	13vPnC/PPSV23 (N[a]=1490)	20vPnC (N[a]=334)	13vPnC (N[a]=111)	20vPnC (N[a]=1798)	13vPnC (N[a]=357)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Gun shot wound	1 (0.1)	0	0	0	0	0
Head injury	1 (0.1)	0	0	0	0	0
Heat exhaustion	1 (0.1)	0	0	0	0	0
Humerus fracture	0	1 (0.1)	0	0	0	0
Meniscus injury	0	1 (0.1)	0	0	0	0
Muscle rupture	0	1 (0.1)	0	0	0	0
Post procedural haematuria	0	1 (0.1)	0	0	0	0
Procedural pneumothorax	0	0	0	0	1 (0.1)	0
Stress fracture	0	1 (0.1)	0	0	0	0
Subcutaneous haematoma	0	0	0	0	1 (0.1)	0
INVESTIGATIONS	0	1 (0.1)	0	0	0	0
Blood pressure increased	0	1 (0.1)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (0.1)	3 (0.2)	0	0	1 (0.1)	0
Dehydration	0	1 (0.1)	0	0	0	0
Diabetic ketoacidosis	0	0	0	0	1 (0.1)	0
Hyperglycaemia	0	1 (0.1)	0	0	0	0
Hyponatraemia	1 (0.1)	0	0	0	0	0
Type 2 diabetes mellitus	0	1 (0.1)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (0.3)	1 (0.1)	0	0	0	0
Arthralgia	1 (0.1)	0	0	0	0	0
Neck mass	0	1 (0.1)	0	0	0	0
Osteoarthritis	2 (0.1)	0	0	0	0	0
Rhabdomyolysis	1 (0.1)	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (0.3)	4 (0.3)	0	0	0	0
Colon cancer	0	1 (0.1)	0	0	0	0
Glioblastoma multiforme	0	1 (0.1)	0	0	0	0
Malignant melanoma	0	1 (0.1)	0	0	0	0
Metastases to peritoneum	1 (0.1)	0	0	0	0	0
Pancreatic carcinoma	0	1 (0.1)	0	0	0	0
Prostate cancer	2 (0.1)	0	0	0	0	0
Transitional cell carcinoma	1 (0.1)	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	5 (0.3)	1 (0.1)	0	0	0	0
Cerebrovascular accident	1 (0.1)	0	0	0	0	0
Hepatic encephalopathy	1 (0.1)	0	0	0	0	0
Ischaemic stroke	1 (0.1)	0	0	0	0	0
Syncope	1 (0.1)	1 (0.1)	0	0	0	0
Transient ischaemic attack	1 (0.1)	0	0	0	0	0
PRODUCT ISSUES	0	1 (0.1)	0	0	0	0
Device malfunction	0	1 (0.1)	0	0	0	0
PSYCHIATRIC DISORDERS	1 (0.1)	0	0	0	1 (0.1)	0
Completed suicide	1 (0.1)	0	0	0	0	0
Suicidal ideation	0	0	0	0	1 (0.1)	0
RENAL AND URINARY DISORDERS	4 (0.3)	1 (0.1)	1 (0.3)	0	0	0
Acute kidney injury	2 (0.1)	0	0	0	0	0

Table 48 (cont.): Serious Adverse Events Reported Within 6 Months After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group – Safety Population

Study	B7471007		B7471007		B7471007 and B7471008	
Age Group	≥60 Years		50-59 Years		18-49 Years	
Vaccine Group (as Administered)	20vPnC/Saline (N^a=1507)	13vPnC/PPSV23 (N^a=1490)	20vPnC (N^a=334)	13vPnC (N^a=111)	20vPnC (N^a=1798)	13vPnC (N^a=357)
System Organ Class/ Preferred Term	n^b (%)	n^b (%)	n^b (%)	n^b (%)	n^b (%)	n^b (%)
End stage renal disease	0	1 (0.1)	0	0	0	0
Haematuria	1 (0.1)	0	0	0	0	0
Nephrolithiasis	0	0	1 (0.3)	0	0	0
Renal failure	1 (0.1)	0	0	0	0	0
Ureteric obstruction	0	0	1 (0.3)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.2)	3 (0.2)	0	0	2 (0.1)	0
Acute respiratory failure	0	1 (0.1)	0	0	0	0
Chronic obstructive pulmonary disease	0	1 (0.1)	0	0	0	0
Dyspnoea	2 (0.1)	0	0	0	0	0
Hypoxia	0	1 (0.1)	0	0	0	0
Pleural effusion	0	0	0	0	1 (0.1)	0
Pulmonary embolism	1 (0.1)	0	0	0	1 (0.1)	0
Pulmonary oedema	0	1 (0.1)	0	0	0	0
Respiratory failure	0	1 (0.1)	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	0	1 (0.1)	0
Skin necrosis	0	0	0	0	1 (0.1)	0

Notes:
MedDRA (v22.1) coding dictionary applied.
The 20vPnC group from B7471008 is the pooled 20vPnC group, which includes subjects from the 20vPnC Lot 1, 2, and 3 groups.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any serious adverse event.

Subjects ≥65 years of age by prior pneumococcal vaccination status (B7471006 and B7471007)

The proportions of subjects reporting one or more SAEs within 6 months after vaccination were low and similar after 20vPnC (≤3.7% in naïve and 2.4% in previously vaccinated) or control vaccine (≤2.8% in naïve or 1.6% in previously vaccinated). None of the SAEs reported were considered related to study vaccine by the investigator (**Table 49**).

Table 49: Serious Adverse Events Reported Within 6 Months After Vaccination – Subjects ≥65 years of age by study and prior pneumococcal vaccination status–Safety Population

Study	B7471007		B7471006		B7471006		B7471006
Prior Pneumococcal Vaccination Status	Naïve		Prior PPSV23		Prior 13vPnC		Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N=514)	13vPnC/PPSV23 (N=498)	20vPnC (N=253)	13vPnC (N=122)	20vPnC (N=246)	PPSV23 (N=127)	20vPnC (N=125)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
Any Event	19 (3.7)	14 (2.8)	2 (0.8)	2 (1.6)	6 (2.4)	2 (1.6)	2 (1.6)
CARDIAC DISORDERS	4 (0.8)	3 (0.6)	1 (0.4)	0	1 (0.4)	0	0
Acute myocardial infarction	0	0	0	0	1 (0.4)	0	0
Atrial fibrillation	0	1 (0.2)	0	0	0	0	0
Cardiac failure congestive	0	0	1 (0.4)	0	0	0	0
Coronary artery disease	3 (0.6)	1 (0.2)	0	0	0	0	0
Myocardial infarction	1 (0.2)	0	0	0	0	0	0
Silent myocardial infarction	0	1 (0.2)	0	0	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (0.4)	1 (0.8)	0
Dysphagia	0	0	0	0	0	1 (0.8)	0
Gastrointestinal haemorrhage	0	0	0	0	1 (0.4)	0	0
HEPATOBILIARY DISORDERS	1 (0.2)	0	0	1 (0.8)	0	0	0
Biloma	1 (0.2)	0	0	0	0	0	0
Cholecystitis	0	0	0	1 (0.8)	0	0	0
INFECTIONS AND INFESTATIONS	3 (0.6)	1 (0.2)	0	0	0	2 (1.6)	1 (0.8)
Appendicitis	1 (0.2)	0	0	0	0	1 (0.8)	0
Cellulitis	0	1 (0.2)	0	0	0	0	0
Clostridium difficile colitis	1 (0.2)	0	0	0	0	1 (0.8)	0
Erysipelas	1 (0.2)	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (0.8)

Study Prior Pneumococcal Vaccination Status	B7471007 Naïve		B7471006 Prior PPSV23		B7471006 Prior 13vPnC		B7471006 Prior 13vPnC and PPSV23
Vaccine Group (as Administered)	20vPnC/Saline (N[a]=514)	13vPnC/PPSV23 (N[a]=498)	20vPnC (N[a]=253)	13vPnC (N[a]=122)	20vPnC (N[a]=246)	PPSV23 (N[a]=127)	20vPnC (N[a]=125)
System Organ Class/ Preferred Term	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)	n[b] (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.2)	4 (0.8)	0	0	0	0	0
Femur fracture	1 (0.2)	0	0	0	0	0	0
Humerus fracture	0	1 (0.2)	0	0	0	0	0
Meniscus injury	0	1 (0.2)	0	0	0	0	0
Muscle rupture	0	1 (0.2)	0	0	0	0	0
Post procedural haematuria	0	1 (0.2)	0	0	0	0	0
Stress fracture	0	1 (0.2)	0	0	0	0	0
INVESTIGATIONS	0	0	0	1 (0.8)	0	0	0
Blood pressure decreased	0	0	0	1 (0.8)	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (0.2)	1 (0.2)	0	0	0	1 (0.8)	0
Dehydration	0	0	0	0	0	1 (0.8)	0
Hyperglycaemia	0	1 (0.2)	0	0	0	0	0
Hyponatraemia	1 (0.2)	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.6)	1 (0.2)	0	0	0	0	1 (0.8)
Arthralgia	1 (0.2)	0	0	0	0	0	0
Neck mass	0	1 (0.2)	0	0	0	0	0
Osteoarthritis	2 (0.4)	0	0	0	0	0	1 (0.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.2)	2 (0.4)	0	0	1 (0.4)	0	0
Colon cancer	0	1 (0.2)	0	0	0	0	0
Malignant melanoma	0	1 (0.2)	0	0	0	0	0
Prostate cancer	1 (0.2)	0	0	0	1 (0.4)	0	0
NERVOUS SYSTEM DISORDERS	4 (0.8)	0	1 (0.4)	0	2 (0.8)	0	0
Carotid artery stenosis	0	0	1 (0.4)	0	0	0	0
Cerebrovascular accident	1 (0.2)	0	0	0	0	0	0
Ischaemic stroke	1 (0.2)	0	0	0	0	0	0
Syncope	1 (0.2)	0	0	0	2 (0.8)	0	0
Transient ischaemic attack	1 (0.2)	0	0	0	0	0	0
PRODUCT ISSUES	0	1 (0.2)	0	0	0	0	0
Device malfunction	0	1 (0.2)	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.4)	2 (0.4)	0	0	0	0	0
Acute respiratory failure	0	1 (0.2)	0	0	0	0	0
Chronic obstructive pulmonary disease	0	1 (0.2)	0	0	0	0	0
Dyspnoea	2 (0.4)	0	0	0	0	0	0
Hypoxia	0	1 (0.2)	0	0	0	0	0
Respiratory failure	0	1 (0.2)	0	0	0	0	0
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0	1 (0.4)	0	0
Cardiac pacemaker replacement	0	0	0	0	1 (0.4)	0	0

Notes:
MedDRA (v22.1) coding dictionary applied.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any serious adverse event.

Supplementary data from phase 1/2 studies B7471001, B7471002 and B7471005

B7471001: Two subjects (6.1%) who received 20vPnC reported SAEs from the visit 1 month after vaccination through the 6-month follow-up visit. One subject, who received 20vPnC, reported a SAE of loss of consciousness caused by exposure to carbon monoxide 30 days after vaccination. Another subject, who also received 20vPnC, reported a SAE of back pain 83 days after vaccination. None of the reported SAEs were considered related to vaccine.

B7471002: Few participants reported SAEs at 1 month after each vaccination. The majority of SAEs occurred 1 month after Vaccination 2 (5 events in the 20vPnC/saline group and 4 events in the 13vPnC/PPSV23 group). No SAEs reported were considered related to vaccine.

B7471005: No participants reported SAEs during the study.

Deaths

In B7471007 Cohort 1, a 60-year-old male who was naive to pneumococcal vaccine and received 20vPnC/saline, died 48 days after receiving Vaccination 2. The investigator considered the death not related to study vaccine.

In study B7471001, one subject died during the study due to a motor vehicle accident 75 days after vaccination. The cause of death was determined not to be related to the study vaccine by the investigator.

In B7471005, B7471006 and B7471008 no participants died during the studies.

2.6.8.4. Laboratory findings

Clinical laboratory evaluations were not performed systematically in any of the Phase 3 trials. Any clinical laboratory values of concern that came to the attention of the investigator were to be reported as AEs.

Supplementary data from phase 1 study B7471001

Standard laboratory testing for cardiac function, haematology, chemistry, and urinalysis were performed. Serial cardiac enzyme (cardiac troponin I) levels were assessed as a response to nonclinical observations of microscopic inflammation with degeneration/necrosis of cardiac myocytes or myocardial fibrosis in a small number of rabbits in the repeat-dose toxicity study. Nonclinical investigations supported that the rabbit cardiac findings were likely related to toxicity study procedures and handling, not directly related to 20vPnC, and unlikely to have any translational relevance to humans. No elevations in troponin I were observed, and no other cardiovascular concerns were identified in the Phase 1 trial. No cardiovascular signals have been identified in the Phase 2 and 3 trials. No other lab values were clinically significant. There were no clinically significant ECG results and no clinically significant ECG findings in the isolated number of subjects with ECGs conducted after vaccination for events of interest.

2.6.8.5. Safety in special populations

Sex, Race and Age

Within each Phase 3 trial, as appropriate based on population size and composition, the proportions of subjects with local reactions, systemic events, and AEs were summarised by sex (all 3 studies), race (B7471007 and B7471008 only), and age (B7471007 only).

Local Reactions: Within each of the sex, race, and age subgroups, the proportions of subjects reporting local reactions were similar after 20vPnC or control vaccine. There were trends toward a higher frequency of local reactions among females than among males in both vaccine groups, although this varied by study. In B7471007, the frequency of pain at the injection site decreased with increasing age across the age cohorts (see Section 2.7.4.2.1.1) and across age subgroups (60-64 years, 65-69 years, 70-79 years, and ≥80 years).

Systemic Events: Within each of the sex, race, and age subgroups, the proportions of subjects reporting systemic events were similar after 20vPnC or control vaccine. There were trends toward a higher frequency of systemic events among females than among males. In B7471007, the frequency of

systemic events decreased with increasing age across the age cohorts (see Section 2.7.4.2.1.2) and across age subgroups (60-64 years, 65-69 years, 70-79 years, and ≥80 years).

Adverse Events: Within each Phase 3 trial, as appropriate, AEs reported by ≥4 subjects in at least 1 vaccine group were summarised by sex, race, and age. In B7471007 and B7471008, within each of the sex, race, and age subgroups, the proportions of subjects reporting at least 1 AE were similar after 20vPnC or control vaccine. AEs were not summarised by sex for B7471006 because no AEs were reported for ≥4 subjects in that study. Overall, there were no consistent trends in the frequency of AEs by sex, race, or age.

Individuals at increased risk for pneumococcal disease

20vPnC had an acceptable safety profile in the B7471007 safety population, approximately 34% of whom were adults ≥18 years of age with risk factors that placed them at increased risk for serious pneumococcal disease, including smoking (13%), and medical conditions of chronic cardiovascular disease (5.5%), chronic pulmonary disease including asthma (8.7%), chronic liver disease (0.4%), and diabetes mellitus (14%).

Pregnancy and lactation

Women who were pregnant or lactating were not eligible for studies of 20vPnC. In total eight women became pregnant during participation in the Phase 3 trials; seven subjects who received 20vPnC and 1 subject who received 13vPnC in B7471007 and B7471008. These pregnancies were not associated with AEs but were communicated to the sponsor on an SAE form and AE case report form per sponsor guidance, and are included in the AE listings within each CSR.

Among the 7 subjects with reported events of pregnancy who had received 20vPnC, 6 events had an outcome of full-term live birth and 1 event had an unknown outcome. The subject who had received 13vPnC (in Study B7471008) reported being in a motor vehicle accident 187 days after vaccination and reported a spontaneous abortion 9 days later. This event occurred outside the safety reporting window and therefore was not included in the AE listing in the CSR. The investigator considered there was not a reasonable possibility that this event was related to study vaccine. The event was more likely triggered by the motor vehicle accident and associated with a foetal genetic anomaly (post-foetal demise test results showed "likely trisomy 21"). Further details about the events of pregnancy can be found in the CSRs (Module 5.3.5.1 B7471007 Report Body Section 12.5.5; Module 5.3.5.1 B7471008 Report Body Section 12.5.5).

It is not known whether 20vPnC is excreted in human milk. No vaccine-related effects on female fertility or the development of foetuses or offspring were observed in a fertility and developmental toxicity study of 20vPnC in rabbits (Module 4.2.3.5.1 20168231 [18GR287]).

Vaccination 2 in the Cohort 1 in the Study B7471007 (20vPnC/Saline vs. 13vPnC/PPSV23)

In B7471007, subjects in Cohort 1 received 2 vaccinations. At Vaccination 1, each subject received either 20vPnC or 13vPnC (control vaccine). Subjects in Cohort 1 who received 20vPnC at Vaccination 1, received saline at Vaccination 2. Subjects in Cohort 1 who received 13vPnC at Vaccination 1, received PPSV23 at Vaccination 2. Vaccination 2 took place 28-42 days after Vaccination 1.

Serious AEs as well as n diagnosed chronic medical conditions (NDCMC) reported from vaccination 2 to 1 month after vaccination 2 in Cohort 1 are already included in the tables presenting Serious AEs and NDCMC reported within 6 months from Vaccination 1 and thus not repeated here.

In Cohort 1, immediate AEs reported after vaccination 2 (saline or PPSV23) were low in frequency (<1%) for the 20vPnC/saline and 13vPnC/PPSV23 groups. Fewer immediate AEs were reported in the 20vPnC/saline group (0.1%) than in the 13vPnC/PPSV23 group (0.6%). Observed AEs were local

reactions, pain in extremity, dizziness and headache. In the 20vPnC arm, no PT was reported in more than 1 participant.

The proportion of participants with AEs related to study was lower in the 20vPnC/saline group (0.4%) than in the 13vPnC/PPSV23 group (6.4%). In the 20vPnC/saline group AEs that were considered to be related to the vaccine were diarrhoea, injection site erythema, pyrexia, bronchitis, headache and rash. No PT was reported in more than 1 participant in the 20vPnC/saline group.

2.6.8.6. Immunological events

Immunogenicity represents the PD effect of the vaccine and represents the main evidence for this application. Results are described and assessed in section 3.

Among pneumococcal vaccine naïve subjects, two cases of hypersensitivity considered unrelated to the study vaccine were reported.

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

No drug-drug interactions were investigated, and no data are available regarding concomitant use of 20vPnC with other vaccines in adults. A safety and immunogenicity trial of 20vPnC co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age is currently ongoing.

2.6.8.8. Discontinuation due to adverse events

AEs leading to discontinuation from the study were reported only for subjects in B7471007, Cohort 1 (subjects ≥60 years of age); these included 12 subjects (0.8%) who received 20vPnC and 8 (0.5%) who received 13vPnC. All of these subjects were withdrawn from the study after Vaccination 1 (20vPnC or 13vPnC) and before Vaccination 2 (saline or PPSV23), except for the subject in the 20vPnC/saline group who died (after Vaccination 2). The AEs leading to withdrawal were considered related to study vaccine for 5 of the subjects who received 20vPnC and 4 of the subjects who received 13vPnC; most of these AEs were injection site reactions.

Reasons for discontinuation in the 20vPnC arm considered to be related to the study vaccine were palpitations and anxiety (moderate/moderate); vaccination site pruritus and vaccination site swelling (moderate/moderate); feeling abnormal and pruritus (mild/moderate); swelling (severe); erythema (severe). Reasons for discontinuation which were considered not related to the study vaccine by the investigator were completed suicide, angioedema (due to concomitant medication, mild), presyncope, atopic dermatitis (pre-existing condition), hypersensitivity (seasonal allergens), coronary artery disease (cardiac disease), and arthritis (worsening of pre-existing condition).

Reasons for discontinuation in the 20vPnC arm considered to be related to the study vaccine were injection site pain and myalgia (mild/mild); headache (moderate), injection site reaction (mild), bronchial hyperreactivity (severe). Reasons for discontinuation which were considered not related to the study vaccine by the investigator were cystitis (primary cystitis), lower respiratory tract infection (community exposure); muscle rupture (old injury) and COPD (exacerbation).

A listing of AEs leading to discontinuation is available in Module 5.3.5.1 B7471007 Appendix 16.2.7.9.1.

No withdrawals due to AEs were reported in the other cohorts in B7471007 (18-49 and 50-59 years of age), nor in B7471006 or B7471008.

There were no withdrawals due to AEs in phase 1/2 studies B7471001, B7471002 or B7471005.

2.6.8.9. Post marketing experience

No post-marketing data are available as 20vPnC has not been marketed for adults in any country.

2.6.9. Discussion on clinical safety

The safety profile of 20vPnC was evaluated in 6 clinical trials in adults ≥18 years of age. The three Phase 1 and Phase 2 trials evaluated 20vPnC administered to adults 18 through 49 years of age (B7471001 and B7471005) and 60 through 64 years of age (B7471002). The Phase 3 trials included pneumococcal vaccine naïve adults≥18 years of age (B7471007 and B7471008) and adults ≥65 years previously vaccinated with a pneumococcal vaccine (B7471006). Age and prior pneumococcal vaccination status were considered as important factors resulting in a pooled analysis from pneumococcal vaccine naïve subjects 18-49 years of age from B7471007 Cohort 3 and B7471008. Safety data from other subjects were displayed side-by-side.

Methods to assess the reactogenicity and safety of 20vPnC are in principle considered appropriate. Local solicited reactions including redness, swelling, and pain at the injection site were followed for 7 days and systemic solicited events including fever, headache, fatigue, muscle pain, and joint pain were followed for 10 days. Although known to occur following vaccination with Prevenar 13, late onset local reactions were not observed following vaccination with 20vPnC in the early stage of development (Phase 1 and 2 studies). The choice of time for solicited local and systemic reactions in the phase 3 trials is therefore deemed acceptable. Subjects were followed for 6 months, which is considered a sufficient period of time to collect relevant adverse events. AEs were collected through 30 days post-vaccination, SAEs and NDCMCs were collected through 6-month post-vaccination.

Phase 1 and Phase 2 trials demonstrated that 20vPnC was well tolerated in this population, with a safety profile similar to that of 13vPnC, and supported the initiation of Phase 3 studies of 20vPnC in adults.

In all three Phase 3 trials, the safety of 20vPnC was mainly evaluated in comparison to 13vPnC. 20vPnC contains 13 serotypes already included in the licensed vaccine Prevenar 13 plus 7 additional serotypes that are included in the currently marketed unconjugated polysaccharide vaccine, Pneumovax 23 (PPSV23). PPSV23 was used as an additional comparator vaccine, although the direct comparison between 20vPnC and PPSV23 is based on a too small number of subjects (Study B7471006, Cohort B: 246 participants received 20vPnC and 127 participants received PPSV23) to draw definite conclusions.

Study B7471006 was conducted open label while studies B7471007 and B7471008 were double blinded. However, in the study B7471007 at Vaccination 2 (Cohort 1 only), saline and PPSV23 were prepared and administered by a third-party unblinded site staff member. The applicant clarified that in the Study B7471007 blinding of the site staff as well as the study participant was maintained.

Exposure

Overall, 4552 subjects received 20vPnC, while 2496 received control vaccine across all studies (majority of subjects received 13vPnC, while only a small number received PPSV23). The size of the safety database is considered sufficient for the assessment of the safety profile of 20vPnC, also taking into consideration that 20vPnC shares 13 serotypes with the licensed Prevenar 13, for which extensive safety data are available. Nonetheless, the size of the safety database limits the detection of more rare adverse events.

Immediate Adverse Events

The proportion of subjects who reported immediate AEs after vaccination was low, both among subjects naïve to pneumococcal vaccine (≤0.2% after 20vPnC; ≤0.9% after 13vPnC) and among subjects ≥65 years of age by prior pneumococcal vaccination status (20vPnC: ≤0.4; control vaccines: ≤0.8%).

Solicited Adverse Events

Across all age groups and independent of the previous pneumococcal status, observations about solicited AEs were consistent, with majority of participants experiencing 1 or more solicited AEs, and injection-site pain being the most frequently reported solicited AE, followed by myalgia and fatigue. In addition, most AEs were mild to moderate in intensity. Overall, the safety profile of 20vPnC was generally comparable to control vaccines 13vPnC/PPSV23.

The safety results from phase 1/2 studies B7471001, B7471002 and B7471005 resemble the adverse event profile evaluated in the phase 3 trials. Adverse events and use of antipyretic or pain medication were in general comparable between treatment groups. Limitation of arm movement was not explicitly solicited for in the phase 3 trials, however it was solicited for and observed with 20vPnC in the study B7471001 (36.4% in the 20vPnC group). The applicant complied with the request to add 'limitation of arm movement' to the section 4.8 of the SmPC.

In subjects naïve to pneumococcal vaccine, local and systemic reactions were reported with a similar frequency after 20vPnC and Prevenar13 across all age groups. Majority of both local and systemic solicited AEs were mild or moderate in severity and resolved within 1-3 days in both intervention groups. The most frequently reported local reaction across all age groups was pain at the injection site (55% to 79% after 20vPnC; 54% to 78% after 13vPnC), with a trend toward decreasing frequency with increasing age. Other local reactions were reported at much lower frequencies (redness: 7.3% to 8.2% after 20vPnC; 5.4% to 7.3% after 13vPnC and swelling: 7.5% to 9.1% after 20vPnC; 8.0% to 10.8% after 13vPnC). The most frequently reported systemic event across all age groups was myalgia (39% to 63% after 20vPnC; 37% to 65% after 13vPnC) followed by fatigue (20vPnC: 30% to 47%; 13vPnC: 30% to 44%), headache (21.5% to 36.7% following 20vPnC; 23.3% to 36.6% following 13vPnC) and arthralgia (12.6% to 16.2% following 20vPnC; 13.7% to 20.7% following 13vPnC).

In subjects ≥65 years of age with prior pneumococcal vaccination local and systemic reactions were reported with a similar frequency after 20vPnC or control vaccine (13vPnC or PPSV23). Solicited local as well as systemic reactions were primarily mild or moderate in intensity and resolved within 1-3 days. Most frequently reported local reaction was pain at the injection site (44% to 61% after 20vPnC; 43% to 56% after control vaccines), followed by redness (4.8% to 8.6% after 20vPnC; 2.5% to 13% after control vaccines) and swelling (4.0% to 9.9% after 20vPnC; 6.6% to 14% after control vaccines. The most frequently reported type of systemic event was muscle pain (32% to 38% after 20vPnC; 31% to 46% after control vaccines), followed by fatigue (28.9% to 32.8% after 20vPnC; 22.3% to 33.3% after control vaccines), headache (13.5% to 19.2% after 20vPnC; 18.2% to 21.4% after control vaccines) and joint pain (6.7% to 16.8% after 20vPnC; 10.7% to 15.9% after control vaccines).

In the 13vPnC arm in Cohort A (previously vaccinated with PPSV23) the frequency of solicited local and systemic events was in general slightly lower than in the PPSV23 arm in Cohort B (previously vaccinated with 13vPnC). Therefore, frequencies of AE were slightly higher in the 20vPnC arm compared to 13vPnC and slightly lower in 20vPnC when compared to PPSV23.

In subjects ≥65 years of age solicited local reaction were slightly more frequent in previously vaccinated (53 to 64,1% in 20vPnC vs 43.8 to 57.9% in control) compared to naïve subjects (46.5 % vs 45.8%) over 65 years, mostly due to higher numbers of swelling and pain at injection site. Solicited systemic events were comparable.

Unsolicited Adverse Events

In both groups (pneumococcal vaccine naïve and with prior pneumococcal vaccine) the proportions of subjects reporting any AE were comparable across age groups and were similar for subjects who received 20vPnC or control vaccine. The most frequently reported AEs were in the SOC Infections and Infestations (≤5.1% after 20vPnC; ≤5.4% after 13vPnC).

Among subjects naïve to pneumococcal vaccine, the proportions of those reporting any AE within 1 month after vaccination were 8.4% to 10% following vaccination with 20vPnC and 7.3% to 11% following vaccination with 13vPnC.

In subjects ≥65 years of age unsolicited local reaction were slightly less frequent in previously vaccinated (4.9% to 7.5% in 20vPnC vs 9% to 11% in control) compared to naïve subjects (9.1% in 20vPnC vs 11.6% in control) over 65 years.

In the Phase 1 trial (B7471001), serial cardiac enzyme (cardiac troponin I) levels were assessed as a response to nonclinical observations of microscopic inflammation with degeneration/necrosis of cardiac myocytes or myocardial fibrosis in a small number of rabbits in the repeat-dose toxicity study. No elevations in troponin I were observed in the Phase 1 trial and no other cardiovascular concerns were identified by the applicant in Phase 1 or subsequent phases of vaccine development. However, as several cardiac events were reported in phase 2 and 3 studies, the applicant was asked to provide reassurance that these were indeed not related to the vaccine. A comprehensive analysis of cardiac events was submitted and no apparent evidence of an increased risk of cardiac AEs with the use of 20vPnC could be observed.

Related Adverse Events

AEs considered related to study vaccine were reported with a similar frequency in subjects naïve to pneumococcal vaccine after 20vPnC (≤0.9%) and after 13vPnC (≤1.5%) vaccination. The most frequently reported types of AEs considered to be related to study vaccine were injection site reactions. AEs considered related to study vaccine were reported with a similar frequency in subjects ≥65 years of age with prior pneumococcal vaccination status after 20vPnC (≤1.6% of subjects) and after control vaccines (≤2.4% of subjects). None of the provided tables for related AEs included solicited adverse events, therefore tabular listings of all vaccine-related AEs including solicited injection-site and systemic AEs were requested for all studies and for the pooled analysis of studies B7471007 (Cohort 3) and B7471008 and respective data have been provided.

Newly diagnosed chronic medical conditions (NDCMCs)

The proportions of subjects reporting NDCMCs was low, both among subjects naïve to pneumococcal vaccine (≤2.3% after both 20vPnC and 13vPnC) and among subjects ≥65 years of age by prior pneumococcal vaccination status (≤4.0% after 20vPnC; ≤2.4% after control vaccines). Overall, the NDCMCs reported were generally diseases and conditions often observed in adults in these age groups.

As of the cut-off date, two cases of autoimmune disorders (Basedow's disease [1] and rheumatoid arthritis [1]) were reported after 20nPvC. Regarding the theoretical increased risk of autoimmune disorders after immunisation, the applicant was asked to provide additional information about these case-reports. Based on the reported information, it was agreed that there is no need to act for the time being.

Serious Adverse Events and Death

Overall, the proportion of patients with SAEs occurring 6 months after vaccination was low and comparable between study vaccine in both vaccine naïve (≤2.4%) as well as previously vaccinated subjects (20vPnC (≤2.4%) and control vaccine (≤1.6%). In pneumococcal naïve group SAEs were reported at a slightly higher frequency among subjects ≥60 years of age (2.4% after 20vPnC, 1.9% after 13vPnC) than in younger age groups (≤0.9% after either vaccine). In subjects ≥65 years of age serious AE were slightly less frequent in previously vaccinated (0.8% to 2.4% in 20vPnC vs 1.6% in control) compared to naïve subjects (3.7% in 20vPnC vs 2.8% in control) over 65 years. Since no subject narratives of serious adverse events were submitted, no assessment of SAEs can be made to confirm applicant's claims of unrelatedness. Upon request respective subject narratives for all serious adverse events reported in Phase 3 studies were provided. Majority of serious adverse events occurred in older participants with significant co-morbidities and investigator's conclusion that they are most likely attributable to underlying medical conditions and confounding factors, which was also concurred by the applicant, is agreed. Considering close temporal relationship with the vaccine administration and absence of pertinent medical history, the applicant was asked to provide a detailed discussion how the unrelatedness to 20vPnC was inferred for the events of pulmonary embolism and transient ischemic attack. Based in the provided information, the applicant's conclusion that there was no causal relationship between the 20vPnC and the events of pulmonary embolism and transient ischemic attack is agreed.

Over the course of the 6 studies, 2 participants died. One participant in B7471007 Cohort 1 who received 20vPnC and one participant in study B7471001 died 75 days after 20vPnC vaccination, both due to traumatic injuries. None were related to study interventions.

Safety in special populations

Age, sex, race

As expected, increasing age led to a decrease in reactogenicity. For the solicited AEs this decrease was seen for injection-site pain in study B7471007. Besides the lower frequency, the overall profile of AE remained similar.

Trends of higher frequency of both local and systemic reactions in females compared to males were seen, but do not impact the use of the vaccine.

Sex, race and age did not have a major impact on the overall safety profile of 20vPnC.

Prior pneumococcal vaccination

Prior pneumococcal vaccination has no major impact on the safety profile of 20vPnC, as the overall safety profile in participants with prior exposure to 13vPnC/PPSV23 was similar to the safety profile in the pneumococcal vaccine naïve population and no new safety signals are observed. In subjects ≥65 years of age solicited local reaction were slightly more frequent in previously vaccinated (53 to 64,1% in 20vPnC vs 43.8% to 57.9% in control) compared to naïve subjects (46.5 % vs 45.8%) over 65 years, mostly due to higher numbers of swelling and pain at injection site. In subjects ≥65 years of age unsolicited local reaction were slightly less frequent in previously vaccinated (4.9% to 7.5% in 20vPnC vs 9% to 11% in control) compared to naïve subjects (9.1% in 20vPnC vs 11.6% in control) over 65 years. Beside these slight differences in solicited local reactions and unsolicited reactions, the AEs were reported in similar proportions in both intervention groups and no concerns are raised.

Use in pregnancy/lactation

Currently there are no clinical data on the use of this vaccine in women who are pregnant/lactating and respective adaptions in the SmPC were requested. No vaccine-related effects on female fertility or the

development of foetus or offspring were observed in a fertility and developmental toxicity study of 20vPnC in rabbits. Eight reports of pregnancy had been received from clinical trials [B7471007 (2), B7471008 (6)]; none reported associated clinical adverse events (AEs). There were no cases reporting 20vPnC administration during breastfeeding.

However, as currently available data on 20vPnC vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy, 20vPnC should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Respective sections in the SmPC were adapted.

Individuals at increased risk for pneumococcal disease

In the B7471007 safety population, approximately 34% of participants had risk factors for serious pneumococcal disease at enrolment including smoking (13%), chronic cardiovascular disease (5.5%), chronic pulmonary disease including asthma (8.7%), chronic liver disease (0.4%), and diabetes mellitus (14%). The safety and immunogenicity of 7vPnC and 13vPnC in the high-risk populations generally reflected the same profile observed for 13vPnC in the general population, although responses were lower in immunocompromised individuals, as would be expected given the altered ability to respond to vaccines. Reduced immune response was observed with 20vPnC in comparison to 13vPnC (see OC in the efficacy part) which raises doubts about the protective effect of 20vPnC in patients with risk factors for IPD. Nonetheless, this is not expected to have negative effects on the safety in this group of patients.

Studies in human immunodeficiency virus (HIV) and bone marrow transplant participants have not been conducted with 20vPnC, which could be acceptable. Respective sections were included in the SmPC, also referring to data from Prevenar 13.

In general, the safety profile in the different subgroups was similar to the safety profile in the overall population and no new safety signals are observed.

No concerns arise from the review of reported AEs following Vaccination 2 in the 20vPnC/saline group in Cohort 1.

Immunological events

Among pneumococcal vaccine naïve subjects, two cases of hypersensitivity judged unrelated to the study vaccine were reported. Hypersensitivity is listed as an adverse reaction in the PI.

Concomitant administration

No data are available regarding concomitant use of 20vPnC with other vaccines in adults. However, a safety and immunogenicity trial of 20vPnC co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age is currently ongoing. No other studies have been conducted to examine the concomitant administration of 20vPnC with other vaccines licensed for use in adults 18 years of age and older.

Data from post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to 13vPnC suggest that administration of paracetamol concomitantly or within the same day of vaccination may reduce the immune response to 13vPnC after the infant series (infants and children aged 6 weeks to 5 years). The applicant was asked to discuss whether the same could also be extrapolated to adults receiving concomitantly 20vPnC and the same antipyretics. The applicant provided a reassuring discussion and confirmed that the effect observed in infants is not likely to replicate in adults.

Discontinuation due to AE

Only participants in the Cohort 1 of study B7471007 received a second vaccine (20vPnC/saline or 13vPnC/PPSV23) and could be discontinued from the study intervention. All subjects in this cohort were ≥60 years of age. The proportion of participants who discontinued the study were generally comparable across groups (12 subjects (0.8%) who received 20vPnC and 8 (0.5%) who received 13vPnC).

Out of AEs which led to discontinuation, 5/12 (20vPnC arm) and 4/8 (13vPnC arm) were vaccine related. These AEs were mostly injection site reactions. In both arms, the intensity (severity) of AEs ranged from mild to severe, with severe AEs being swelling and erythema (following 20vPnC) and bronchial hyperreactivity (following Prevenar 13).

All adverse reactions reported in clinical trials that were considered related to the IP have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of 20vPnC appears to be comparable to the safety profile of 13vPnC. Furthermore, no major safety differences between 20vPnC and PPSV23 were observed, although the number of subjects who received PPSV23 was too small to draw definite conclusions. A majority of participants reported 1 or more AEs, mostly mild or moderate in intensity and of short duration. The most frequently reported AEs by PT were solicited AEs including injection-site pain, myalgia, fatigue, headache, joint pain, swelling and redness. As expected, reactogenicity decreased with age, especially for solicited local and systemic reactions. The safety profile was also overall comparable between pneumococcal vaccine naïve adults ≥18 years of age and adults ≥65 years of age who have previously been vaccinated with 13vPnC/PPSV23. No deaths occurred that were considered possibly related.

All outstanding issues have been resolved. In conclusion, 20vPnC is well tolerated in adults ≥18 years and no major safety concerns were identified.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of the 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.

2.7.2. Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				

Ongoing and Planned Additional Pharmacovigilance Activities

Study/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
B7471004 A phase 3, randomised, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine (20vPnC) when coadministered with seasonal inactivated influenza vaccine (SIIV) in adults ≥65 years of age. Completed	Evaluate the safety and immunogenicity of 20vPnC when coadministered with quadrivalent inactivated influenza vaccine in adults ≥65 years of age.	Concomitant use of 20vPnC with other vaccine(s)	Submission of final study results by	30/04/2022
B7471026 A phase 3, randomised, double blind trial to describe the safety and immunogenicity of 20-valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older. Ongoing	Evaluate the safety and immunogenicity of 20vPnC when coadministered with a booster dose of COVID-19 mRNA vaccine in adults ≥65 years of age.	Concomitant use of 20vPnC with other vaccine(s)	Submission of final study results by	30/06/2022

2.7.3. Risk minimisation measures

Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine or COVID-19 mRNA vaccine	Routine risk minimisation measures: EU SmPC Section 4.5 *Interaction with other medicinal products and other forms of interaction*. PL Section 2 (*Other medicines/vaccines and Apexxnar*) *Medicine's legal status*: Medicinal product subject to medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Study B7471004 (quadrivalent inactivated influenza vaccine coadministration study) CSR due on 30/04/2022; • Study B7471026 (COVID-19 mRNA vaccine coadministration study) CSR due on 30/06/2022.

2.7.4. Conclusion

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

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08.06.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Labelling exemptions

None requested.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Apexxnar (pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)) is included in the additional monitoring list as it is a biological product and additionally contains five new serotypes, 8, 10A, 11A, 12F and 15B conjugated to CRM197 carrier protein which can be qualified as new active substances.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pneumococcal disease mainly presents as non-invasive disease, such as non-bacteraemic pneumonia, sinusitis or acute otitis media (the latter most commonly in young children). The less frequent albeit generally more severe invasive pneumococcal disease (IPD) occurs when *S. pneumoniae* gains access to more distal, normally sterile anatomical sites. IPD presents as meningitis, bacteraemic pneumonia, bacteraemia without focus and septic arthritis. In general, pneumococcal pneumonia is associated with complications and long-term sequelae in all age groups (e.g. respiratory failure requiring hospitalisation, exacerbations of chronic medical conditions, decline in quality of life, increased risk of death within 30 days (acute) and 1 year (long-term) after the event.)

Pneumococcal disease burden is highest in young children ≤5 yoa and older adults ≥65 yoa. Irrespective of age, certain comorbid conditions (e.g. chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma) and immunodeficiency (e.g. HIV, HSCT patients) and lifestyle factors (e.g. smoking) predispose to pneumococcal disease.

3.1.2. Available therapies and unmet medical need

Disease Treatment

S. pneumoniae infections are treated based on clinical presentation and susceptibility data to antimicrobials. Broad-spectrum antibiotics are the most commonly used antimicrobials against *S. pneumoniae*. Although *S.pneumoniae* is not considered as a "classical" multi-resistant pathogen, increasing resistance rates have been reported which may lead to treatment failures.

Disease Prevention

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

In the EU, prevention of pneumococcal disease in adults currently includes vaccination with two authorised vaccines - Prevenar 13 (13vPnC, protein-conjugated) and PNEUMOVAX23 (PPSV23, polysaccharide, unconjugated) - and the prophylactic use of antibiotics in special populations. Serotypes currently covered by vaccines are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (Prevenar 13) and 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F (PNEUMOVAX23).

20vPnC targets the same 13 serotypes as Prevenar 13 plus seven additional serotypes which are also targeted by PNEUMOVAX23 (8, 10A, 11A, 12F, 15B, 22F, and 33F). The applicant is also the marketing authorisation holder of Prevenar 13.

During this procedure, Vaxneuvance received a positive CHMP opinion (14 10 2021), with a Commission Decision (authorisation) adopted on 13.12.2021. This pertains a 15-valent pneumococcal vaccine containing the 13 serotypes included in Prevenar 13 and additionally serotypes 22F and 33F. All 15 serotypes are also contained in 20vPnC.

Unmet medical need

While current vaccination campaigns against *S. pneumoniae* have led to a substantial reduction in pneumococcal disease burden, mortality rates particularly for IPD in older adults and adults with certain comorbidities have remained high. According to the Global Burden of Disease Study 2016 (GBD 2016 Lower Respiratory Infections Collaborators, The Lancet), *S. pneumoniae* was "the leading cause of lower respiratory infection morbidity and mortality globally, contributing to more deaths than all other aetiologies combined in 2016 (1 189 937 deaths, 95% UI 690 445–1 770 660)".

Serotype replacement (i.e. more frequent isolation of disease-causing serotypes not covered by current vaccines) is a commonly observed phenomenon. Vaccines with broader serotype coverage, (ideally serotype-independent) and higher effectiveness against certain serotypes targeted by authorised vaccines are highly warranted.

3.1.3. Main clinical studies

The clinical programme to develop 20vPnC consists of six randomised controlled trials (three Phase 3, one Phase 2, two Phase 1 studies) to study immunogenicity and safety. No efficacy studies have been conducted. Since currently no correlate of protection has been established in the target population, the clinical development aims at demonstrating comparative immunogenicity between 20vPnC and vaccines with proven protective efficacy: 13vPnC (for the 13 shared serotypes) and PPSV23 (for the 7 additional serotypes). This immuno-bridging approach is in accordance with the respective EMA guidance (EMEA/CHMP/VWP/164653/2005) and has been agreed on in a Scientific Advice (EMEA/H/SA/3940/1/2018/III CORRIGENDUM).

Immunogenicity data obtained from the Phase 3 studies B7471007 (pivotal) and B7471006 are considered main evidence for this MAA.

B7471007 was the pivotal non-inferiority trial in pneumococcal vaccine naïve adults ≥18 years of age, that was intended to establish the immunological bridge to the comparator vaccines. Participants were enrolled into 3 cohorts based on age. The applicant plans to establish the required immunological bridge to vaccines with known efficacy by establishing non-inferior immune response in cohort 1 first (subjects ≥ 60 yoa) and extend the bridge to other age groups by showing non-inferior immune response of all 20 serotypes in a subset of cohort 1 and the younger cohorts 2 (50-59 yoa) and 3 (18-49 yoa).

Study B7471006 evaluated the safety and immunogenicity of 20vPnC in adults ≥65 yoa with prior pneumococcal vaccination. Participants were enrolled into 3 cohorts based on their pneumococcal vaccination history (PPSV23, 13vPnC or 13vPnC/PPSV23).

In all submitted studies, 20vPnC was administered as a single dose, which is in line with both comparator vaccines. Immunogenicity data was collected immediately before and one month after vaccination in all studies.

3.2. Favourable effects

Opsonophagocytic activity (OPA) titres were used as surrogate marker for immune response in all studies. 20vPnC induced immune response against all 20 serotypes in all studies and subgroups. Immune responses were generally higher in younger subjects and decreased with age but was still present in subjects ≥70 years of age. Subjects without risk factors for pneumococcal disease showed higher immune response compared to subjects with risk factors. Further, pneumococcal vaccine naïve

subjects showed higher titres compared to subjects with pneumococcal vaccination history, especially when previously vaccinated with PPSV23.

Non-inferiority against 13vPnC. The defined non-inferiority criteria – the lower bound of the 2-sided 95% CI for the OPA GMT ratio of 20vPnC/13vPnC > 0.5 - were met for all 13 shared serotypes in adults ≥ 60 yoa (cohort 1, B7471007).

Non-inferiority against PPSV23. The defined non-inferiority criteria – the lower bound of the 2-sided 95% CI for the OPA GMT ratio of 20vPnC/PPSV23 > 0.5 - were met for six of the seven additional serotypes in adults ≥ 60 yoa (cohort 1, B7471007). Serotype 8 missed the lower margin with a GMT ratio of 0.55 (0.49, 0.62). OPA GMT ratios for the six other serotypes were clearly above 1.

Non-inferiority of younger subjects (cohort 2: 50-59yoa, cohort 3: 18-49 yoa) to older subjects (60-64 yoa). The defined non-inferiority criteria – the lower bound of the 2-sided 95% CI for the respective OPA GMT ratio of younger cohort/(60-64yoa) > 0.5 - were met for all serotypes for both younger cohorts. While the immune responses induced by 20vPnC vaccination in the youngest cohorts (adults 18-49) were higher than in adults ≥ 60 yoa, the immune response in cohort including adults 50-59 yoa was overall similar or higher compared to the oldest cohort.

Additional endpoints further showed similar trends to these results (serotype-specific GMFRs, proportions of participants with a ≥4-fold in OPA titres, serotype-specific OPA titres ≥LLOQ).

Long term data for 20vPnC is available for approx. 200 subjects from phase 2 study (B7471002). Data from 12 months after the first vaccination indicate that OPA GMTs declined over time to approx. 30% (range 11-55%) compared to one month after vaccination but remained above baseline levels.

3.3. Uncertainties and limitations about favourable effects

No efficacy or effectiveness data is available for 20vPnC. The application is based on an immunological bridge comparing humoral immune responses induced by 20vPnC and authorised vaccines (13vPnC and PPSV23) that are known to protect against pneumococcal disease.

No correlate of protection against pneumococcal disease exists in adults. Opsonophagocytic activity (OPA) titres are commonly used as surrogate markers for a protective effect as they reflect the in vivo scenario of antibody-mediated protection, yet no threshold for a protective effect has been established. Comparisons across serotypes are also not possible due to different capsule compositions, potentially resulting in different titres required for protection for each serotype. The comparative approach to vaccines with known efficacy is therefore essential for the interpretation of a potential protective effect of 20vPnC.

The **clinical relevance of the applied non-inferiority margin** of 0.5 has not been justified and it is not known whether meeting the defined criteria will result in a clinically relevant protection. The applicant has been advised accordingly in a scientific advice procedure (EMEA/H/SA/3940/1/2018/III CORRIGENDUM).

Reduced response compared to 13vPnC: Despite meeting non-inferiority for all 13 shared serotypes between 20vPnC and 13vPnC, a consistent trend of numerically lower GMTs with ratios of about 0.8 [20vPnC/13vPnC] became apparent. Further, the upper bound of the 2-sided 95% CI of the GMT ratio did not contain 1.00 for most serotypes. The ~20% reduction has been consistently observed in all studies for which respective data for 13vPnC was available. The lower titres are especially of concern for serotype 3, which is still the second most common serotype causing invasive pneumococcal disease in the EU in younger adults and the most common serotype in subjects >65 yoa (~14% across age groups in 2018; ECDC AER) despite being included in currently approved vaccines.

Serotype 8: The immune response against serotype 8 induced by 20vPnC compared to PPSV23 missed the pre-defined non-inferiority criterion (GMR: 0.55 (0.49; 0.62, 2-sided 95% CI)). Although not meeting the predefined non-inferiority margin of 0.5, might be explained technically by multiplicity aspects, the response differs drastically to all other 6 additional serotypes, which showed much higher titres compared to PPSV23. Concerning the lower titres and the potentially reduced protective effect, the applicant argued that immune response elicited with PPSV23 and 20vPnC are difficult to compare due to the different vaccine types (polysaccharide vs conjugate vaccine), which is in general acknowledged, but this does not mitigate the concerns.

Bridging to younger subjects: A comparison performed by the assessors (based on data in the report annex) shows reduced immune response of 20vPnC compared to 13vPnC also in the younger cohorts. In subjects 50-59 yoa the non-inferiority criteria might have even been missed for some serotypes. Despite being lower compared to 13vPnC in the respective age group, the observed titres are higher than the titres obtained with 13vPnC in cohort 1 (≥60yoa), consequently a protective effect for the induced immune response in both younger cohorts can be assumed for 20vPnC.

Persistence. Throughout the clinical development programme, humoral immune responses were compared one month after vaccination. The phase 2 study (B7471002) is the only study included in the application that provides (exploratory) long-term data one year after vaccination. Unfortunately, this study does not allow for a direct comparison between 20vPnC and 13vPnC at this later time point, as sequential regimes 20vPnC/saline and 13vPnC/PPSV23 were compared. Therefore, it is unknown whether OPA GMTs induced by 20vPnC vs 13vPnC differ over time.

Whether a protective effect can be claimed or how long such an effect could be claimed for **subjects with already reduced immune response** is currently unclear, including subjects with risk factors and subjects with prior pneumococcal vaccination with PPSV23.

No dedicated studies in adults at high risk for pneumococcal disease (e.g. asplenia, HIV, haematopoietic stem cell transplants or other immunocompromising conditions) were conducted. The applicant argues that prior (albeit limited) experience with 7vPnC and 13vPnC in these populations is also applicable to 20vPnC. This strategy had been considered acceptable in a previous scientific advice provided that comparable immunogenicity and safety in immunocompetent subjects can be shown between 20vPnC and 13vPnC. Given the observed reduced immune response, it is currently not clear whether data from 13vPnC can be extrapolated in this population.

Concomitant vaccination. No data on concomitant vaccination with other vaccines relevant to the target population were provided.

3.4. Unfavourable effects

The safety profile of 20vPnC was overall comparable to the safety profile of the control vaccines (13vPnC/ PPSV23).

Across all age groups and independent of the previous pneumococcal vaccination status, observations about solicited AEs were consistent, with the majority of participants experiencing 1 or more solicited AEs, and injection-site pain being the most frequently reported solicited AE, followed by myalgia and fatigue. In addition, most AEs were mild to moderate in intensity and resolved within 1-3 days.

In subjects naïve to pneumococcal vaccines, local and systemic solicited AEs were reported with a similar frequency after 20vPnC and Prevenar 13:

- Pain at the injection site: 55% to 79% after 20vPnC, 54% to 78% after 13vPnC;
- Redness: 7.3% to 8.2% after 20vPnC; 5.4% to 7.3% after 13vPnC;

- Swelling: 7.5% to 9.1% after 20vPnC; 8.0% to 10.8% after 13vPnC;
- Myalgia: 39% to 63% after 20vPnC; 37% to 65% after 13vPnC;
- Fatigue: 30% to 47% after 20vPnC; 30% to 44% after 13vPnC;
- Headache: 21.5% to 36.7% after 20vPnC; 23.3% to 36.6% after 13vPnC;
- Arthralgia: 12.6% to 16.2% after 20vPnC; 13.7% to 20.7% after 13vPnC.

In subjects ≥65 years of age with prior pneumococcal vaccination local and systemic reactions were overall reported with a similar frequency. Frequencies of AE were slightly higher in the 20vPnC arm compared to 13vPnC and similar or slightly lower in 20vPnC when compared to PPSV23:

- Pain at the injection site: 44% to 61% after 20vPnC; 43% to 56% after control vaccines;
- Redness: 4.8% to 8.6% after 20vPnC; 2.5% to 13% after control vaccines;
- Swelling: 4.0% to 9.9% after 20vPnC; 6.6% to 14% after control vaccines
- Myalgia: 32% to 38% after 20vPnC; 31% to 46% after control vaccines;
- Fatigue: 28.9% to 32.8% after 20vPnC; 22.3% to 33.3% after control vaccines;
- Headache: 13.5% to 19.2% after 20vPnC; 18.2% to 21.4% after control vaccines;
- Arthralgia: 6.7% to 16.8% after 20vPnC; 10.7% to 15.9% after control vaccines.

In both groups (pneumococcal vaccine naïve and with prior pneumococcal vaccination) the proportions of subjects reporting any AE were comparable across age groups and were similar for subjects who received 20vPnC or control vaccine. The most frequently reported AEs were in the SOC Infections and Infestations. In subjects ≥65 years of age unsolicited local reaction were slightly less frequent in previously vaccinated compared to naïve subjects over 65 years.

AEs considered related to study vaccine were reported with a similar frequency after 20vPnC and after control vaccines for both subjects naïve to pneumococcal vaccine and subjects ≥65 years of age with prior pneumococcal vaccination status.

Overall, the proportion of patients with SAEs occurring 6 months after vaccination was low and comparable between study and control vaccine in both vaccine naïve (≤2.4%) and previously vaccinated subjects (20vPnC (≤2.4%) and control vaccine (≤1.6%). In pneumococcal naïve treatment group SAEs were reported at a slightly higher frequency among subjects ≥60 years of age (2.4% after 20vPnC, 1.9% after 13vPnC) than in younger age groups (≤0.9% after either vaccine). In subjects ≥65 years of age serious AE were slightly less frequent in previously vaccinated (0.8% to 2.4% in 20vPnC vs 1.6% in control) compared to naïve subjects (3.7% in 20vPnC vs 2.8.6% in control) over 65 years.

As expected, increasing age led to a decrease in reactogenicity, most noticeably for injection-site pain. Beside the lower frequency, the overall profile of AE remained similar.

Prior pneumococcal vaccination does not seem to have a major impact on the safety profile of 20vPnC, as the overall safety profile in participants with prior exposure to 13vPnC/PPSV23 was similar to the safety profile in the pneumococcal vaccine naïve population and no new safety signals are observed.

Deaths: In total, two participants died during the studies due to traumatic injuries, The deaths were considered not related to study vaccine.

In total 20 participants had AEs leading to study discontinuation. Out of AEs which led to discontinuation, 5/12 (20vPnC arm) and 4/8 (13vPnC arm) were vaccine related. Related AEs were mostly injection site reactions and the intensity (severity) of AEs ranged from mild to severe in both arms, with severe AEs being swelling and erythema (following 20vPnC) and bronchial hyperreactivity (following Prevenar 13).

3.5. Uncertainties and limitations about unfavourable effects

Comparison to PPSV23: In all three Phase 3 trials, the safety of 20vPnC was mainly evaluated in comparison to 13vPnC. PPSV23 was used as an additional comparator vaccine in most studies. A direct comparison between 20vPnC and PPSV23 included only a limited number of subjects, hampering conclusions (Study B7471006, Cohort B: 246 participants treated with 20vPnC and 127 participants treated with PPSV23).

Serious AEs: No assessment of SAEs and their relatedness to the study vaccine could be made based on the initially provided data. In order to confirm the applicant's claims of unrelatedness, subject narratives for all serious adverse events reported in the Phase 3 studies were requested. Following additional information provided by the applicant, investigator's conclusions on the relationship to the medicine (or lack thereof) seemed justified and were accepted.

Limited information is available on 20nPvC use in:

- Patients with relevant comorbidities. Only in the B7471007 safety population, approximately 34% of participants had risk factors for serious pneumococcal disease at enrolment including smoking (13%), chronic cardiovascular disease (5.5%), chronic pulmonary disease including asthma (8.7%), chronic liver disease (0.4%), and diabetes mellitus (14%);
- Individuals with impaired responsiveness, whether due to use of immunosuppressive therapy or other causes (HIV infection, HSCT, genetic defect);
- Pregnant and lactating women. Information regarding use in pregnant women will be collected through routine pharmacovigilance

No data on sequential vaccination with other pneumococcal vaccines or a booster dose are available for Apexxnar.

3.6. Effects Table

Table 50: Effects Table for Apexxnar (20vPnC) indicated for the active immunisation for the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by *Streptococcus pneumoniae* in adults ≥ 18 years of age.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immune response	NI of 13 shared serotypes to 13vPnC	OPA GMT ratio	Non-inferiority met for all 13 serotypes (13vPnC)		For most serotypes GMT ratio around 0.8 and 95%-CI below 1 Only in subjects ≥60yoa	CSR B7471007
Immune response	NI of the 7 additional serotypes to PPSV23	OPA GMT ratio	Non-inferiority met for 6/7 serotypes (PPSV23)		Reduced titre for serotype 8	CSR B7471007
Immune response	NI of younger cohorts (Cohort 2: 50-59yoa; Cohort 3: 18-49 yoa)	OPA GMT ratio	Non-inferiority met for all serotypes (20vPnC)		No comparison to comparator vaccines; NI expected as immune response declines with age	CSR B7471007
Immune response	In subjects with risk factors	OPA GMT	Lower immune response in subjects with risk factors		Pooled analysis despite large titre differences between age groups	CSR B7471007

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Immune response	In primed subjects	OPA GMT	Lower immune response observed for subjects with prior PPSV23 vaccination (alone or 13vPnC/PPSV23) compared to subjects primed with 13vPnC		No comparison to comparator vaccines or pneumococcal vaccine naïve subjects	CSR B7471006
Unfavourable Effects						
Injection-site AE	Injection-site pain	%	55-79 (44-61)	54-78 (43-56)	These were the most commonly reported AEs in subjects ≥ 18 years of age or older naïve to pneumococcal vaccine (Studies B7471007 and B7471008). Numbers in parentheses represent incidence of AEs in subjects ≥65 years of age previously vaccinated with 13vPnC, PPSV23, or both (Studies B7471006 and B7471007). Ranges refer to incidences of AEs observed in different age cohorts.	CSR B7471006, CSR B7471007, CSR B7471008
Systemic AE	myalgia	%	39-63 (32-38)	37-65 (31-46)		
	Fatigue	%	30-47 (29-33)	30-44 (22-33)		

Abbreviations: 13vPnC = Prevenar 13, PPSV23 = Pneumovax23, CSR = clinical study report, AE = adverse event

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 vaccines with known protective efficacy against pneumococcal disease (13vPnC and PPSV23). No efficacy or effectiveness data has been submitted. This approach is in general acceptable and in line with respective EMA guidance and previous scientific advice.

In the pivotal study, in subjects ≥ 60 yoa, the defined non-inferior criteria were met for all 13 serotypes shared with 13vPnC and for 6 of the 7 additional serotypes also targeted by PPSV23 (except serotype 8, which showed a pronounced difference compared to the other new serotypes). Nevertheless, consistently numerically lower titres have been observed for most shared serotypes (GMT ratios of about 0.8 [20vPnC/13vPnC] and the upper limit of the 95% CI below 1). This approx. 20% reduction was consistently observed in all other studies in which 13vPnC comparator data were generated. The clinical relevance of this reduction is currently unclear, especially since 20vPnC is essentially the same vaccine as 13vPnC. These findings have been reflected in the SmPC to provide relevant information to the prescriber. The applicant also outlined how the clinical relevance of the numerically reduced immune response of most shared serotypes and serotype 8 will be further investigated and how inferring effectiveness of 20vPnC will be further confirmed by appropriate post-marketing studies. Taken together, the presented post-marketing studies are expected to provide

valuable information on 20vPnC effectiveness, and the remaining uncertainties related to the clinical impact of numerically reduced immune responses elicited by 20vPnC compared to the majority of serotypes shared with 13vPnC and serotype 8.

The planned post-marketing studies are included as post-authorisation measures in SmPC Annex II.

Notably, in Europe serotype 8 is the most common serotype causing IPD in subjects 18-65 yoa (approx. 22-32% of reported IPD cases) and after serotype 3 (14.7%) the second most common IPD causing serotype in adults ≥65 yoa (14.0%). Both serotypes are increasing in prevalence in the last years (2018; ECDC AER). At the same time, however, it is acknowledged, that 20vPnC offers the potential benefits of a conjugate vaccine to target serotype 8, which is so far only included in the polysaccharide vaccine PPSV23.

Regarding the bridge to younger subjects, all non-inferiority criteria were met when comparing 20vPnC vaccination in adults 60-64 yoa to adults 50-59 yoa or 18-49 yoa. This was expected as immune responses generally decline with age. No formal comparison between 13vPnC and 20vPnC in younger subjects was performed by the applicant. However, a comparison by the assessors shows similar reduced immune response of 20vPnC compared to 13vPnC also in the younger cohorts. The titres induced by 20vPnC are, however, higher than the titres induced by 13vPnC in 60-64-year-old subjects, which is assumed to provide a protective effect. Therefore, although this aspect of the bridging approach is not considered ideal, it can be concluded that 20vPnC has a similar effect regardless of age and that initially protective titres are reached in subjects younger than 60 years.

Even if the titres induced by primary vaccination with 20vPnC can be assumed to provide a protective effect, the consistently lower immune response affects the ability to extrapolate other aspects like persistence and expected magnitude of a potential booster response from 13vPnC. Numerically lower initial titres might lead to an earlier loss of protection compared to 13vPnC. However, OPA GMTs induced by 20vPnC and 13vPnC followed one month later by PPSV23 decline to a similar extent one year after vaccination, which is preliminarily reassuring. Still, it has to be assumed that, given the numerically lower induced titres and a similar decline, the protective effect of 20vPnC will wane off earlier than the protective effect induced by 13vPnC. The need of another vaccination schedule (e.g. additional dose), especially for risk groups has not been discussed.

In addition, it is unclear how these findings manifest regarding initial and long-term protection in subjects with numerically lower immune response compared to healthy subjects, including subjects with risk factors regardless of age or subjects with prior PPSV23 vaccination, for whom no comparative data to 13vPnC is available. Furthermore, it is not clear whether data from 13vPnC can be extrapolated for subjects at high risk of pneumococcal infection (e.g. with immunocompromising conditions), who have not been included in the development programme. Respective wording for the SmPC has been implemented.

Although post-marketing plans have been outlined, some aspects of 20vPnC vaccine effectiveness are not specifically addressed including (younger) subjects at risk for pneumococcal disease, primed subjects or immunocompromised patients. Nevertheless, if vaccine effectiveness is shown in the planned studies, this will provide reassurance concerning those populations.

The documented safety exposure is considered sufficient for the assessment of the safety profile of 20vPnC.

The safety profile of 20vPnC was overall comparable to the safety profile of 13vPnC/PPSV23. In the six studies submitted in the dossier, no new safety signals were observed for 20vPnC compared to 13vPnC/PPSV23. In subjects ≥65 years of age with prior pneumococcal vaccination 20vPnC was slightly more reactogenic compared to 13vPnC, leading to a higher percentage of participants experiencing 1 or more AEs; and similar or less reactogenic compared to PPSV23. For all three

interventions, most participants experienced 1 or more AEs in all studies and the most commonly reported AEs were solicited AEs. 20vPnC is well-tolerated since most of the AEs are mild in intensity, of short duration (≤ 3 days) and the discontinuations due to adverse events are low.

3.7.2. Balance of benefits and risks

20vPnC was immunogenic across all subgroups tested. Several uncertainties have been identified that preclude final conclusions on the potential clinical benefit. Although additional coverage of seven serotypes with 20vPnC compared to 13vPnC is considered beneficial, the observed reduced immune response of 11 of the 13 serotypes shared with 13vPnC and of serotype 8 are of concern. While the advantage of targeting 6 additional serotypes is acknowledged - together they currently account for about 21% of confirmed cases of invasive pneumococcal disease (2018; ECDC AER) - the clinical relevance of the observed lower GMTs for serotype 8 and serotypes shared with 13vPnC is unknown. Since invasive pneumococcal disease/pneumonia can be life-threatening or severely debilitating, especially for at-risk populations, the observed reduction in GMTs, especially for both most common serotypes causing invasive disease, is still of concern. The applicant confirmed that 20vPnC real –world effectiveness as regards impact on IPD as well as VT- CAP will be addressed further in the post-marketing. Information on breakthrough disease will be collected through European national and ECDC surveillance systems to be submitted annually. This is considered important to address the remaining uncertainties regarding the lower titres induced by 20vPnC vaccination compared to 13vPnC and to serotype 8.

The currently outlined post-marketing strategy does not foresee to specifically study 20vPnC effectiveness in at-risk subjects. However, it is expected that 20vPnC effectiveness data generated post-approval in the general population will also provide further information to this more vulnerable group. In addition, these findings have been reflected in the SmPC to provide relevant information to the prescriber.

The safety profile of 20vPnC is characterised by injection-site pain, muscle pain, fatigue, headache, joint pain, swelling and redness.

Overall, the benefit risk balance is deemed positive.

3.8. Conclusions

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

4. Recommendations

Outcome

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

> Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.
>
> See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.
>
> Apexxnar should be used in accordance with official recommendations

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy studies (PAES): 1. In order to further investigate the long-term effectiveness of Apexxnar for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*, the MAH should conduct and submit the results of US study B7471015, a Phase 4 study using a test-negative design to evaluate the effectiveness of Apexxnar 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 Apexxnar for active immunisation for the prevention of pneumonia caused by *Streptococcus pneumoniae*,	CSR due

Description	Due date
the MAH should conduct and submit the results of a Phase 4 observational, real-world study to evaluate the effectiveness of Apexxnar against vaccine-type community-acquired pneumonia in Europe according to an agreed protocol.	31/12/2030
3. In order to further investigate the long-term effectiveness of Apexxnar 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 Apexxnar against vaccine-type invasive pneumococcal disease in Europe according to an agreed protocol.	CSR due 31/12/2030

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) contains five new serotypes, 8, 10A, 11A, 12F and 15B conjugated to CRM197 carrier protein which can be qualified as new active substances.