Amsterdam, 26 January 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Apexxnar

Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)

Procedure no: EMEA/H/C/005451/P46/005

Note

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

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Status of this report and steps taken for the assessment				
PAM number				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission	21 Oct 2022	21 Oct 2022	☐
☐	Start of procedure	28 Nov 2022	28 Nov 2022	☐
☐	Rapporteur's preliminary Assessment Report	03 Jan 2023	09 Jan 2023	☐
☐	CHMP Members comments	16 Jan 2023	16 Jan 2023	☐
☒	CHMP adoption of conclusions	19 Jan 2023	19 Jan 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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Declarations

This application includes an Active Substance Master File (ASMF):

☐ Yes

☒ No

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List of abbreviations

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
AOM	acute otitis media
CRM_{197}	cross-reactive material 197 (nontoxic variant of diphtheria toxin)
EU	European Union
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
OPA	opsonophagocytic activity
PAM	post-authorisation measure
PCV15	15-valent pneumococcal conjugate vaccine
SAE	serious adverse event
SC	subcutaneous
SmPC	summary of product characteristics

1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of Article 46 for Apexxnar, a 20-valent pneumococcal polysaccharide conjugate vaccine (20vPnC; Compound Number: PF-06482077; EU/1/21/1612/001-006; EMEA/H/C/005451). The MAH (Pfizer Europe MA EEIG) submits results of study B7471016: A Phase 3, Randomized, Double-Blind, Third-Party Unblind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Japanese Infants, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended. A total of 668 participants were enrolled at 38 centers in Japan.

The purpose of the B7471016 study was to provide key safety and comparative immunogenicity data between the 20-valent pneumococcal conjugate vaccine (20vPnC) and the 13-valent pneumococcal conjugate vaccine (13vPnC) in Japanese infants to help support licensure for paediatric use in Japan. Participants aged 2 to 6 months were randomised to receive 4 doses of 20vPnC (by subcutaneous or intramuscular injection), or 13vPnC (by subcutaneous injection as a control). The targeted age of the population for this study, infants ≥2 to ≤6 months of age, has been selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants starts at approximately 2 months of age.

As the B7471016 study is not part of the clinical development program to support the paediatric indication for 20vPnC in Europe, no line-listing is included with the present EU submission under Article 46. The opinion of the MAH is that no update to the EU Product Information for Apexxnar is required based on the results of B7471016, as the study is specific to Japanese infants and the MAH does not plan to apply for inclusion of the subcutaneous route of administration.

Background

Study B7471016 entitled "A Phase 3, Randomized, Double-Blind, Third-Party Unblind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Japanese Infants" is being submitted as a stand-alone PAM (P46 study) for 20vPnC. 20vPnC was approved in the EU on 14 February 2022 for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.

Streptococcus pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and AOM and continue to be a major global public health concern. Children <5 years and adults ≥65 years of age are at particularly increased risk for serious pneumococcal disease. It has been estimated that in 2015, several years following introduction of pneumococcal conjugate vaccines into the national infant immunization programs of more than 100 countries, the global disease burden had declined. However*, Streptococcus pneumoniae* still accounted for 2.6 million cases of severe pneumococcal disease, 332,000 deaths in children <5 years of age, and 11% of deaths in children between the ages of 1 and 5 years.

In Japan, 7-valent pneumococcal conjugate vaccine (7vPnC) and 13-valent pneumococcal conjugate vaccine (13vPnC) have been administered to infants by subcutaneous (SC) injection on a 4-dose vaccination schedule (3 doses for infant series and 1 dose for toddler dose).

The composition of 20vPnC is based on the licensed 13vPnC formulation. 20vPnC uses the same platform and contains the same excipients as 13vPnC but contains an additional 7 polysaccharide conjugates targeting serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC 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 each individually conjugated to the nontoxic variant of diphtheria toxin CRM_{197}, as carrier protein.

The purpose of this study was to provide key safety and comparative immunogenicity data in Japanese infants. The targeted age of the population for this study, infants ≥2 to ≤6 months of age, has been selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants starts at approximately 2 months of age. The participants were administered either 20vPnC (SC or IM injection) or 13vPnC SC by the same injection route for all 4 doses.

Intramuscular (IM) injection was included for clinical development of 20vPnC for infants in Japan as an alternative to SC injection because both injection routes are under development in other pediatric vaccines in Japan and licensure of an IM route could provide flexibility of administration by healthcare practitioners.

2. Methods

Study Design:

Study B7471016, a Phase 3, multicenter, randomized, double-blind, third party unblind study was conducted at 38 investigator sites in Japan. The purpose of this study was to describe safety and conduct the pivotal immunogenicity comparison of 20vPnC administered by SC injection to the licensed

pneumococcal conjugate vaccine, 13vPnC, administered by the currently indicated SC injection in infants to support licensure in Japan for the pediatric population. Data was generated from 20vPnC administered by IM injection, with the 20vPnC administered by SC as a control. A study design overview is provided in Figure 1. Study objectives, estimands, and endpoints are provided in Table 1.

This study planned to enroll 666 infants between 2 through 6 months of age at the time of consent by their parent(s)/legal guardian(s). This study population has been selected as this is the historical population studied for licensure of 13vPnC in infants. Participants were randomized equally to one of the following vaccine groups: (1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group. Participants received the same vaccine (20vPnC or 13vPnC) by the same injection method (SC or IM injection) for all 4 doses at Visits 1, 2, 3, and 5 (Figure 1). This is consistent with the current vaccination schedule recommended by the Japan Pediatric Society for infants in Japan. Doses 1 to 3 were preferred to be administered at 2, 3, and 4 months of age consistent with the vaccination schedule recommended by the Japan Pediatric Society. In addition, Dose 3 was to be completed by 12 months of age and Dose 4 was to be administered ≥60 days after Dose 3. Blood was collected 1 month after Dose 3 (Visit 4), immediately prior to Dose 4 (Visit 5), and 1 month after Dose 4 (Visit 6) to assess immunogenicity. All vaccine groups were blinded to all members of the site involved in the study except unblinded site staff who administered 20vPnC or 13vPnC.

Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medication were prompted for and collected by the participant's parent(s)/legal guardian(s) in an e-diary, via device or application, from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination). Adverse events (AEs) were collected from the time the participant's parent(s)/legal guardian(s) provided informed consent through 1 month after Dose 3 (Visit 4) and from Dose 4 (Visit 5) through 1 month after Dose 4 (Visit 6). SAEs and NDCMCs were collected from informed consent through 1 month after Dose 4 (Visit 6).

Figure 1. Study Design Overview

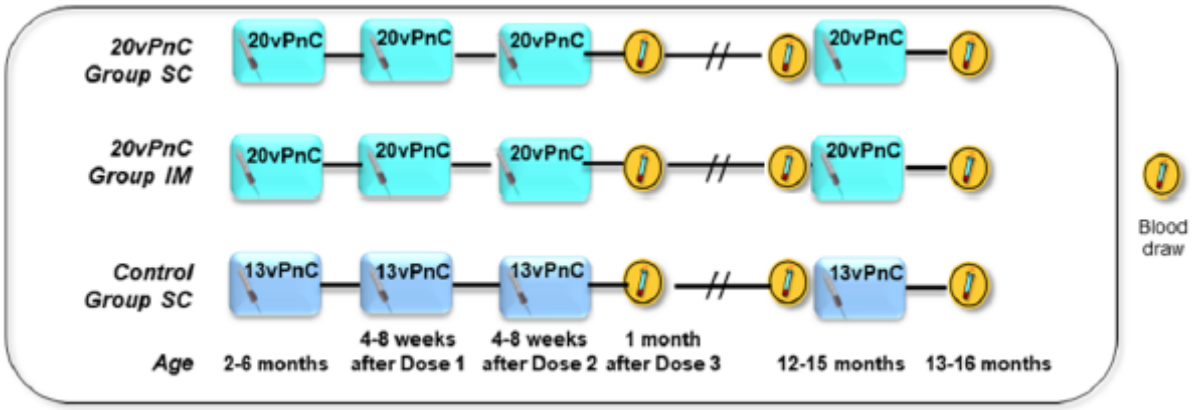


Table 1. Study Objectives, Estimands, and Endpoints

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC by both	In participants receiving at least 1 dose of investigational product and having safety	• Prompted local reactions (redness, swelling, and pain at the injection site)

SC injection and IM injection	data reported after any vaccination: • The percentage of participants reporting prompted local reactions at injection site of investigational product within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentage of participants reporting SAEs up to 1 month after Dose 4 in each group • The percentage of participants reporting NDCMCs up to 1 month after Dose 4 in each group	• Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs
Primary Immunogenicity Objectives	**Estimands**	**Primary Immunogenicity Endpoints**
<u>For 20vPnC SC group:</u>		
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC SC group are noninferior to the	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentage of	• Pneumococcal serotype-specific IgG concentration

percentage of the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group	
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations, between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
<u>For 20vPnC IM group:</u>		
• To describe the immune responses to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentration
Secondary Immunogenicity Objectives	**Estimands**	**Secondary Immunogenicity Endpoints**

• To demonstrate the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC SC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC SC group to the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To demonstrate the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in • 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC SC group to the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: GMR of serotype-specific IgG concentrations from the 20vPnC IM group to the 20vPnC SC group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: Serotype-specific IgG GMCs at 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific IgG concentrations

	In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group	• Pneumococcal serotype-specific OPA titers
	In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentage of participants with the predefined serotype-specific IgG concentration in each group	• Pneumococcal serotype-specific IgG concentrations
	In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
Exploratory Immunogenicity Objectives	**Estimands**	**Exploratory Immunogenicity Endpoints**
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants: • For each of the 20 serotypes in 20vPnC: percentage of participants with ≥4-fold rise in serotype-specific IgG concentrations from before Dose 4 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
	• For each of the 20 serotypes in 20vPnC: percentage of	• Pneumococcal serotype-specific OPA titers

	participants with serotype-specific OPA ≥ LLOQ 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group • For each of the 20 serotypes in 20vPnC: percentage of participants with ≥4-fold rise in serotype-specific OPA titers from before Dose 4 to 1 month after Dose 4 in each group • For each of the 20 serotypes in 20vPnC: GMFRs in serotype-specific OPA titers from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	

Abbreviations: 13vPnC =13-valent pneumococcal conjugate vaccine; 20vPnC = 20-valent pneumococcal conjugate vaccine; AE = adverse event; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMR = geometric mean ratio; IgG = immunoglobulin G; IM = intramuscular; LLOQ = lower limit of quantitation; NDCMC = newly diagnosed chronic medical condition; OPA = opsonophagocytic activity; SAE = serious adverse event; SC = subcutaneous.

Study Population:

Participants included healthy Japanese male or female infants ≥2 months to ≤6 months (defined as the first day the participant is 2 months of age to the last day the participant is 6 months of age) at the time of consent.

Participants were excluded from the study if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product, the specified concomitant vaccines, or any diphtheria toxoid-containing vaccine. Additional exclusion criteria included any contraindication to vaccination with pneumococcal conjugate vaccine or the specified concomitant vaccines, significant neurological disorder or history of seizure, major known congenital malformation or serious chronic disorders, history of microbiologically proven invasive disease caused by *Streptococcus pneumoniae*, known or suspected immunodeficiency or other conditions associated with immunosuppression, congenital, functional, or surgical asplenia, and other acute or chronic medical or psychiatric condition or laboratory abnormality that might increase the risk associated with study participation. Participants were excluded from the study if they had a history of previous vaccination with any licensed or investigational pneumococcal vaccine, prior receipt of *Haemophilus influenzae* type b, Hepatitis B (Hep B), rotavirus, diphtheria, tetanus, acellular

pertussis, and/or poliovirus vaccines, currently receiving treatment with immunosuppressive therapy, or receipt of blood/plasma products or immunoglobulins (including Hep B immunoglobulin and monoclonal antibodies) since birth or planned receipt through the last planned blood sample collection in the study (through Visit 6).

Statistics

The primary safety objectives were evaluated by descriptive summary statistics for local reactions, systemic events and AEs (including SAEs) and NDCMCs. AEs were categorized according to the MedDRA. The primary and secondary immunogenicity objectives for the 20vPnC SC were evaluated by hypothesis test for noninferiority of 20vPnC SC to 13vPnC SC based on serotype-specific IgG results 1 month after Dose 3. The primary immunogenicity objective for 20vPnC IM was descriptive comparison of IgG concentrations 1 month after Dose 3 between 20vPnC IM and 20vPnC SC. Other secondary and exploratory immunogenicity objectives were evaluated by descriptive summary statistics.

3. Immunogenicity Results

3.1. Response to 20vPnC compared to 13vPnC

IgG response 1 month after Dose 3

Table 2. Comparison of the Percentages of Participants With Predefined Levels for Pneumococcal IgG Concentrations for Vaccine Serotypes (20vPnC [SC] – 13vPnC [SC]) – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC (SC)				13vPnC (SC)				20vPnC (SC) – 13vPnC (SC)	
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	221	216	97.7	(94.8, 99.3)	220	218	99.1	(96.8, 99.9)	-1.4	(-4.4, 1.3)
3	≥0.35 µg/mL	221	213	96.4	(93.0, 98.4)	220	218	99.1	(96.8, 99.9)	-2.7	(-6.2, 0.1)
4	≥0.35 µg/mL	221	214	96.8	(93.6, 98.7)	220	218	99.1	(96.8, 99.9)	-2.3	(-5.6, 0.5)
5	≥0.23 µg/mL	221	204	92.3	(88.0, 95.5)	220	214	97.3	(94.2, 99.0)	-5.0	(-9.6, -0.9)
6A	≥0.35 µg/mL	221	199	90.0	(85.3, 93.7)	220	216	98.2	(95.4, 99.5)	-8.1	(-13.0, -4.0)
6B	≥0.10 µg/mL	221	194	87.8	(82.7, 91.8)	220	212	96.4	(93.0, 98.4)	-8.6	(-14.0, -3.7)
7F	≥0.35 µg/mL	221	212	95.9	(92.4, 98.1)	220	218	99.1	(96.8, 99.9)	-3.2	(-6.8, -0.3)
9V	≥0.35 µg/mL	221	212	95.9	(92.4, 98.1)	220	217	98.6	(96.1, 99.7)	-2.7	(-6.4, 0.4)
14	≥0.35 µg/mL	220	213	96.8	(93.6, 98.7)	220	215	97.7	(94.8, 99.3)	-0.9	(-4.4, 2.4)
18C	≥0.35 µg/mL	221	214	96.8	(93.6, 98.7)	220	218	99.1	(96.8, 99.9)	-2.3	(-5.6, 0.5)
19A	≥0.12 µg/mL	221	220	99.5	(97.5, 100.0)	220	219	99.5	(97.5, 100.0)	0.0	(-2.1, 2.1)
19F	≥0.35 µg/mL	221	221	100.0	(98.3, 100.0)	220	220	100.0	(98.3, 100.0)	0.0	(-1.7, 1.7)
23F	≥0.35 µg/mL	221	198	89.6	(84.8, 93.3)	220	206	93.6	(89.6, 96.5)	-4.0	(-9.5, 1.2)
7 Additional											
8	≥0.35 µg/mL	221	220	99.5	(97.5, 100.0)	220	206	93.6	(89.6, 96.5)	5.9	(3.0, 10.0)
10A	≥0.35 µg/mL	221	133	60.2	(53.4, 66.7)	220	206	93.6	(89.6, 96.5)	-33.5	(-40.7, -26.2)
11A	≥0.35 µg/mL	221	221	100.0	(98.3, 100.0)	220	206	93.6	(89.6, 96.5)	6.4	(3.8, 10.4)
12F	≥0.35 µg/mL	221	165	74.7	(68.4, 80.3)	220	206	93.6	(89.6, 96.5)	-19.0	(-25.7, -12.5)
15B	≥0.35 µg/mL	221	219	99.1	(96.8, 99.9)	220	206	93.6	(89.6, 96.5)	5.5	(2.2, 9.6)
22F	≥0.35 µg/mL	221	221	100.0	(98.3, 100.0)	220	206	93.6	(89.6, 96.5)	6.4	(3.8, 10.4)
33F	≥0.35 µg/mL	219	208	95.0	(91.2, 97.5)	220	206	93.6	(89.6, 96.5)	1.3	(-3.2, 6.0)

Abbreviations: IgG = immunoglobulin G; SC = subcutaneous.
a. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the additional 7 serotypes, the compared results are from serotype 23F (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.
e. 2-Sided CIs are calculated using the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:22)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_13_1md3_eval

Table 3. Pneumococcal IgG GMCs and GMRs (20vPnC [SC]/13vPnC [SC]) – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)						
	20vPnC (SC)			13vPnC (SC)			20vPnC (SC) / 13vPnC (SC)
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR[c] (95% CI[d])
13vPnC							
1	221	1.37	(1.25, 1.51)	220	2.21	(1.98, 2.47)	0.62 (0.54, 0.72)
3	221	1.29	(1.18, 1.41)	220	1.81	(1.66, 1.98)	0.71 (0.63, 0.81)
4	221	1.76	(1.57, 1.97)	220	2.96	(2.64, 3.32)	0.60 (0.51, 0.70)
5	221	1.01	(0.89, 1.16)	220	1.72	(1.51, 1.96)	0.59 (0.49, 0.71)
6A	221	1.38	(1.21, 1.57)	220	2.34	(2.09, 2.62)	0.59 (0.50, 0.70)
6B	221	0.42	(0.35, 0.50)	220	0.83	(0.71, 0.97)	0.51 (0.40, 0.64)
7F	221	1.58	(1.43, 1.75)	220	2.19	(1.95, 2.46)	0.72 (0.62, 0.84)
9V	221	1.46	(1.32, 1.61)	220	2.11	(1.88, 2.36)	0.69 (0.60, 0.80)
14	220	2.79	(2.45, 3.18)	220	3.31	(2.90, 3.78)	0.84 (0.70, 1.01)
18C	221	1.67	(1.51, 1.86)	220	2.52	(2.26, 2.82)	0.66 (0.57, 0.77)
19A	221	2.41	(2.19, 2.65)	220	3.19	(2.86, 3.56)	0.76 (0.65, 0.87)
19F	221	2.81	(2.60, 3.04)	220	3.73	(3.41, 4.08)	0.75 (0.67, 0.85)
23F	221	1.32	(1.15, 1.51)	220	2.05	(1.79, 2.34)	0.64 (0.53, 0.78)
7 Additional							
8	221	3.32	(3.05, 3.61)	220	0.83	(0.71, 0.97)	4.01 (3.36, 4.79)
10A	221	0.50	(0.42, 0.60)	220	0.83	(0.71, 0.97)	0.60 (0.48, 0.76)
11A	221	5.63	(5.17, 6.14)	220	0.83	(0.71, 0.97)	6.80 (5.69, 8.13)
12F	221	0.79	(0.67, 0.93)	220	0.83	(0.71, 0.97)	0.95 (0.76, 1.20)
15B	221	6.77	(6.04, 7.60)	220	0.83	(0.71, 0.97)	8.18 (6.75, 9.92)
22F	221	4.94	(4.54, 5.38)	220	0.83	(0.71, 0.97)	5.97 (5.00, 7.12)
33F	219	1.70	(1.51, 1.92)	220	0.83	(0.71, 0.97)	2.06 (1.69, 2.51)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype at the given sampling time point.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. For the 13vPnC serotypes, the GMCs are from the corresponding serotype in the 13vPnC group. For the additional 7 serotypes, the GMCs are from serotype 6B (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.
d. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC [SC] – 13vPnC [SC]) and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:21)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s001_13_aftd3_eval

IgG response 1 month after Dose 4

Table 6. Pneumococcal IgG GMCs (20vPnC [SC] and 13vPnC [SC]) – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC (SC)			13vPnC (SC)		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	217	2.79	(2.50, 3.12)	220	4.62	(4.11, 5.19)
3	217	0.97	(0.87, 1.08)	220	1.44	(1.30, 1.59)
4	217	6.93	(6.14, 7.83)	220	10.01	(8.89, 11.27)
5	217	2.96	(2.63, 3.34)	220	4.64	(4.13, 5.21)
6A	217	11.90	(10.61, 13.34)	220	17.25	(15.66, 18.99)
6B	216	7.18	(6.30, 8.18)	220	10.48	(9.46, 11.61)
7F	217	4.46	(4.04, 4.92)	220	6.62	(5.95, 7.38)
9V	217	4.54	(4.04, 5.09)	220	6.62	(5.93, 7.39)
14	217	8.23	(7.27, 9.31)	220	10.30	(9.25, 11.47)
18C	217	3.95	(3.50, 4.45)	220	5.97	(5.27, 6.75)
19A	217	7.62	(6.82, 8.52)	219	8.97	(8.08, 9.95)
19F	217	8.74	(7.84, 9.73)	220	11.02	(9.96, 12.20)
23F	217	7.01	(6.16, 7.97)	220	11.76	(10.42, 13.28)
7 Additional						
8	217	5.84	(5.23, 6.53)	219	0.02	(0.02, 0.03)
10A	217	6.98	(6.13, 7.93)	220	0.01	(0.01, 0.01)
11A	217	5.73	(5.08, 6.46)	220	0.02	(0.01, 0.02)
12F	217	2.73	(2.41, 3.09)	220	0.01	(0.01, 0.01)
15B	217	18.45	(16.73, 20.36)	220	0.03	(0.03, 0.04)
22F	217	14.07	(12.67, 15.63)	220	0.00	(0.00, 0.01)
33F	217	10.29	(9.28, 11.40)	220	0.02	(0.01, 0.02)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype at the given sampling time point.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:21)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s001_13_1md4_eval

Table 7. Number (%) of Participants With Predefined Levels for Pneumococcal IgG Concentrations for Vaccine Serotypes (20vPnC [SC] and 13vPnC [SC]) – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		20vPnC (SC)				13vPnC (SC)			
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC									
1	≥0.35 µg/mL	217	215	99.1	(96.7, 99.9)	220	220	100.0	(98.3, 100.0)
3	≥0.35 µg/mL	217	199	91.7	(87.2, 95.0)	220	217	98.6	(96.1, 99.7)
4	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	220	100.0	(98.3, 100.0)
5	≥0.23 µg/mL	217	216	99.5	(97.5, 100.0)	220	220	100.0	(98.3, 100.0)
6A	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	220	100.0	(98.3, 100.0)
6B	≥0.10 µg/mL	216	216	100.0	(98.3, 100.0)	220	220	100.0	(98.3, 100.0)
7F	≥0.35 µg/mL	217	216	99.5	(97.5, 100.0)	220	220	100.0	(98.3, 100.0)
9V	≥0.35 µg/mL	217	216	99.5	(97.5, 100.0)	220	220	100.0	(98.3, 100.0)
14	≥0.35 µg/mL	217	215	99.1	(96.7, 99.9)	220	219	99.5	(97.5, 100.0)
18C	≥0.35 µg/mL	217	216	99.5	(97.5, 100.0)	220	220	100.0	(98.3, 100.0)
19A	≥0.12 µg/mL	217	217	100.0	(98.3, 100.0)	219	219	100.0	(98.3, 100.0)
19F	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	220	100.0	(98.3, 100.0)
23F	≥0.35 µg/mL	217	216	99.5	(97.5, 100.0)	220	220	100.0	(98.3, 100.0)
7 Additional									
8	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	219	7	3.2	(1.3, 6.5)
10A	≥0.35 µg/mL	217	215	99.1	(96.7, 99.9)	220	2	0.9	(0.1, 3.2)
11A	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	13	5.9	(3.2, 9.9)
12F	≥0.35 µg/mL	217	213	98.2	(95.3, 99.5)	220	0	0.0	(0.0, 1.7)
15B	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	19	8.6	(5.3, 13.2)
22F	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	4	1.8	(0.5, 4.6)
33F	≥0.35 µg/mL	217	217	100.0	(98.3, 100.0)	220	6	2.7	(1.0, 5.8)

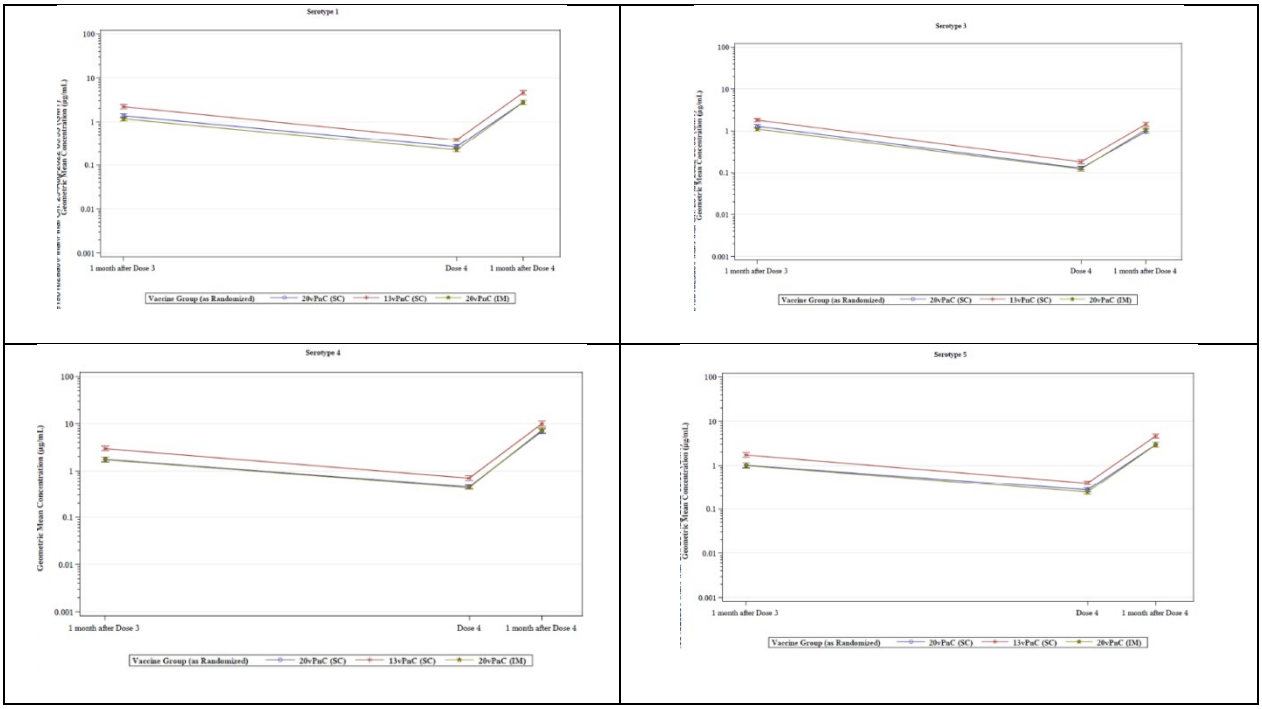
Abbreviations: IgG = immunoglobulin G; SC = subcutaneous.
a. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:22)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_13_1md4_eval

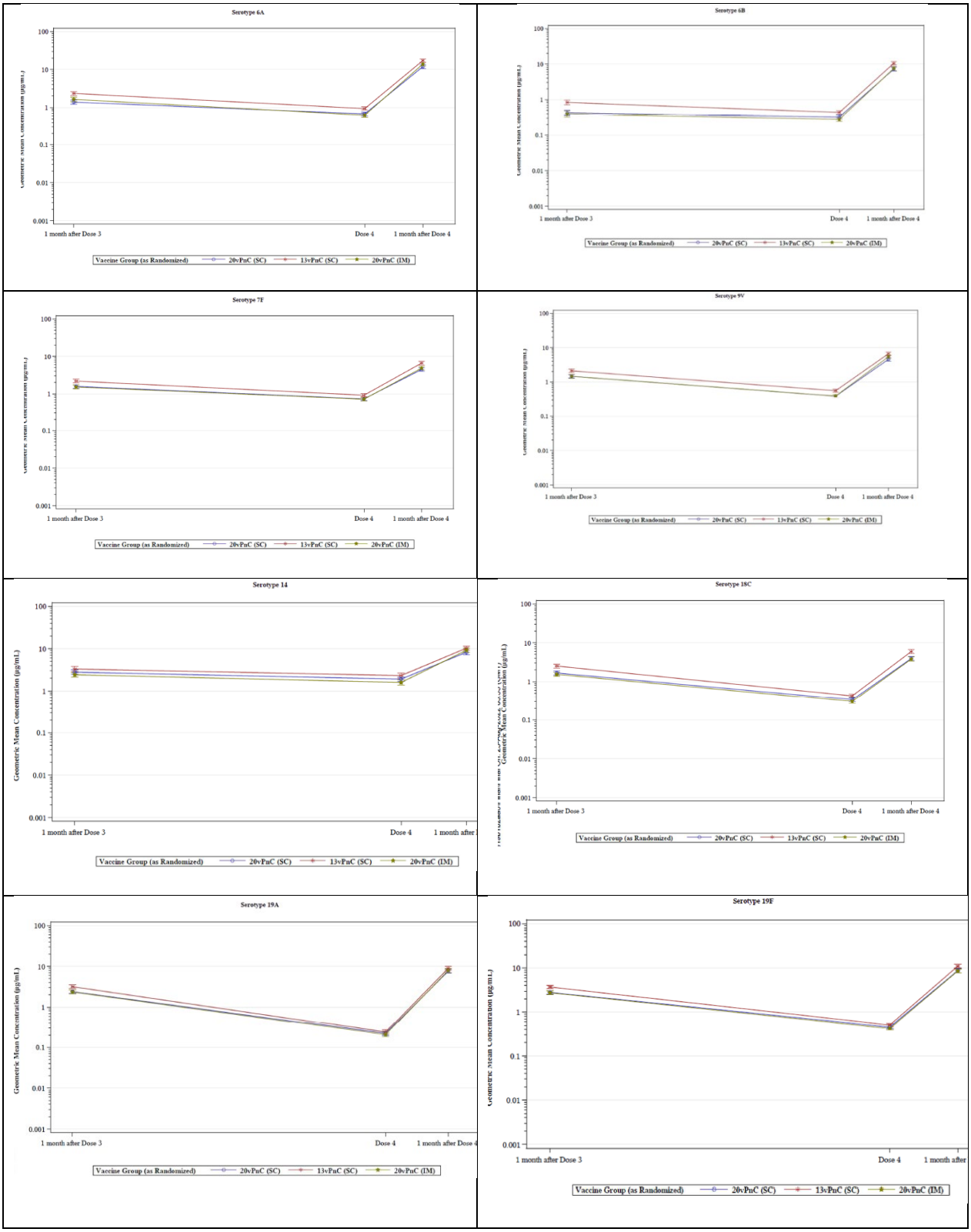
Table 8.
Number (%) of Participants Achieving a ≥4-Fold Rise in Pneumococcal IgG Concentrations From Before Dose 4 to 1 Month After Dose 4 (20vPnC [SC] and 13vPnC [SC]) – Dose 4 Evaluable Immunogenicity Population

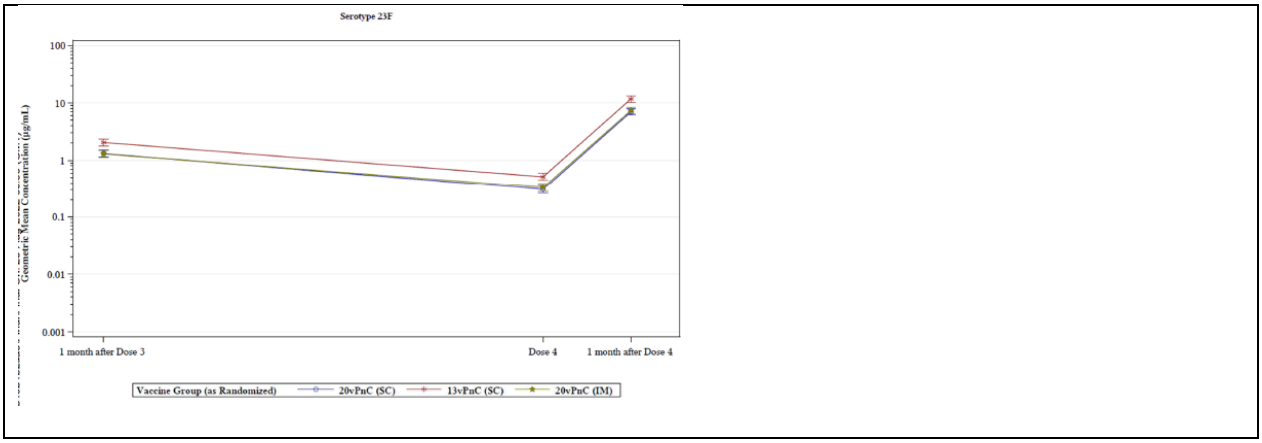
	Vaccine Group (as Randomized)							
	20vPnC (SC)				13vPnC (SC)			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	217	201	92.6	(88.3, 95.7)	220	209	95.0	(91.2, 97.5)
3	217	162	74.7	(68.3, 80.3)	220	182	82.7	(77.1, 87.5)
4	217	203	93.5	(89.4, 96.4)	220	208	94.5	(90.7, 97.2)
5	217	199	91.7	(87.2, 95.0)	220	202	91.8	(87.4, 95.1)
6A	217	210	96.8	(93.5, 98.7)	220	213	96.8	(93.6, 98.7)
6B	215	210	97.7	(94.7, 99.2)	218	217	99.5	(97.5, 100.0)
7F	217	152	70.0	(63.5, 76.1)	220	171	77.7	(71.6, 83.0)
9V	217	199	91.7	(87.2, 95.0)	220	206	93.6	(89.6, 96.5)
14	217	114	52.5	(45.7, 59.3)	220	106	48.2	(41.4, 55.0)
18C	217	203	93.5	(89.4, 96.4)	220	213	96.8	(93.6, 98.7)
19A	217	211	97.2	(94.1, 99.0)	219	214	97.7	(94.8, 99.3)
19F	217	206	94.9	(91.1, 97.4)	220	214	97.3	(94.2, 99.0)
23F	217	208	95.9	(92.3, 98.1)	220	210	95.5	(91.8, 97.8)
7 Additional								
8	217	186	85.7	(80.3, 90.1)	218	15	6.9	(3.9, 11.1)
10A	217	147	67.7	(61.1, 73.9)	220	5	2.3	(0.7, 5.2)
11A	217	158	72.8	(66.4, 78.6)	220	6	2.7	(1.0, 5.8)
12F	217	182	83.9	(78.3, 88.5)	220	1	0.5	(0.0, 2.5)
15B	217	147	67.7	(61.1, 73.9)	220	28	12.7	(8.6, 17.9)
22F	217	176	81.1	(75.3, 86.1)	220	12	5.5	(2.8, 9.3)
33F	217	144	66.4	(59.7, 72.6)	220	11	5.0	(2.5, 8.8)

Abbreviations: IgG = immunoglobulin G; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. N = number of participants with valid assay results at both timepoints for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with a ≥4-fold rise in IgG concentrations from the specified time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:22)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_ig_fold_1md4_eval

Antibody Response Curve up to 1 Month After Dose 4 for IgG GMCs With 2-Sided 95% CIs – Evaluable Immunogenicity Population – shared serotypes




Serotype 6A
Serotype 6B
Serotype 7F
Serotype 9V
Serotype 14
Serotype 18C
Serotype 19A
Serotype 19F
Geometric Mean Concentration (µg/mL)
1 month after Dose 3
Dose 4
1 month after Dose 4
Vaccine Group (as Randomized)
20vPnC (SC)
13vPnC (SC)
20vPnC (IM)


Serotype 23F
Geometric Mean Concentration (µg/mL)
100
10
1
0.1
0.01
0.001
1 month after Dose 3
Dose 4
1 month after Dose 4
Vaccine Group (as Randomized)
20vPnC (SC)
13vPnC (SC)
20vPnC (IM)

OPA responses

Table 9. Pneumococcal OPA GMTs at Each Specified Sampling Time Point (20vPnC [SC] and 13vPnC [SC]) – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		20vPnC (SC)			13vPnC (SC)		
Serotype	Sampling Time Point	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC							
1	1 Month after Dose 3	71	55	(43, 71)	70	126	(104, 152)
	Before Dose 4	71	11	(10, 12)	71	13	(11, 16)
	1 Month after Dose 4	70	162	(125, 210)	72	386	(306, 486)
3	1 Month after Dose 3	71	107	(86, 134)	70	170	(147, 196)
	Before Dose 4	70	16	(13, 20)	70	20	(16, 25)
	1 Month after Dose 4	68	131	(114, 150)	70	193	(165, 226)
4	1 Month after Dose 3	71	1864	(1565, 2219)	72	1768	(1393, 2245)
	Before Dose 4	68	25	(18, 37)	67	44	(29, 66)
	1 Month after Dose 4	70	1627	(1232, 2148)	71	2038	(1471, 2825)
5	1 Month after Dose 3	71	95	(79, 114)	70	154	(131, 183)
	Before Dose 4	71	16	(15, 17)	71	18	(16, 19)
	1 Month after Dose 4	70	172	(140, 212)	72	248	(204, 303)
6A	1 Month after Dose 3	71	2709	(2283, 3213)	70	3339	(2777, 4013)
	Before Dose 4	67	83	(56, 122)	70	173	(116, 258)
	1 Month after Dose 4	70	3249	(2686, 3928)	71	5455	(4379, 6795)
6B	1 Month after Dose 3	70	1548	(1247, 1921)	69	2489	(2005, 3088)
	Before Dose 4	68	40	(29, 54)	65	75	(49, 115)
	1 Month after Dose 4	70	2304	(1811, 2933)	70	4319	(3478, 5362)
7F	1 Month after Dose 3	69	4160	(3406, 5081)	74	4428	(3821, 5131)
	Before Dose 4	65	626	(436, 899)	70	761	(579, 1000)
	1 Month after Dose 4	70	4735	(3824, 5863)	71	6361	(5024, 8054)
9V	1 Month after Dose 3	72	1807	(1432, 2279)	74	2388	(1986, 2870)
	Before Dose 4	65	183	(134, 251)	70	204	(151, 274)
	1 Month after Dose 4	70	4199	(3322, 5309)	70	5162	(4349, 6127)
14	1 Month after Dose 3	70	1922	(1429, 2585)	69	2593	(1999, 3362)
	Before Dose 4	68	426	(307, 592)	71	469	(346, 634)
	1 Month after Dose 4	71	1673	(1331, 2102)	70	1706	(1385, 2102)
18C	1 Month after Dose 3	71	5124	(4381, 5992)	74	5355	(4617, 6212)
	Before Dose 4	65	122	(76, 198)	69	173	(112, 267)
	1 Month after Dose 4	70	4477	(3528, 5681)	70	6315	(5081, 7848)
19A	1 Month after Dose 3	72	638	(535, 762)	73	676	(551, 830)
	Before Dose 4	67	13	(10, 18)	71	20	(14, 28)
	1 Month after Dose 4	71	1860	(1530, 2261)	72	2534	(2044, 3143)
19F	1 Month after Dose 3	71	449	(356, 566)	70	624	(494, 788)
	Before Dose 4	70	26	(24, 29)	70	25	(24, 26)
	1 Month after Dose 4	71	1071	(846, 1356)	71	1783	(1364, 2331)
23F	1 Month after Dose 3	72	1580	(1211, 2061)	74	1849	(1499, 2281)
	Before Dose 4	64	42	(24, 73)	70	62	(36, 107)
	1 Month after Dose 4	71	2609	(2015, 3377)	70	3772	(2966, 4796)
7 Additional							
8	1 Month after Dose 3	70	1532	(1215, 1933)	72	16	(15, 18)
	Before Dose 4	65	166	(119, 230)	73	20	(17, 24)
	1 Month after Dose 4	64	2970	(2412, 3658)	71	27	(20, 36)
10A	1 Month after Dose 3	63	6977	(5204, 9354)	75	40	(33, 47)
	Before Dose 4	61	1985	(1422, 2772)	70	78	(51, 118)
	1 Month after Dose 4	61	9030	(6855, 11893)	68	87	(56, 136)
11A	1 Month after Dose 3	73	1894	(1540, 2330)	73	58	(47, 71)
	Before Dose 4	70	416	(258, 670)	70	95	(64, 142)
	1 Month after Dose 4	70	3958	(2973, 5269)	69	90	(62, 132)
12F	1 Month after Dose 3	46	35278	(23575, 52790)	75	24	(24, 25)
	Before Dose 4	58	3984	(3017, 5261)	69	35	(26, 47)
	1 Month after Dose 4	57	15611	(11336, 21499)	74	43	(31, 60)
15B	1 Month after Dose 3	71	6981	(5726, 8511)	74	17	(15, 20)
	Before Dose 4	64	578	(345, 969)	73	26	(18, 39)
	1 Month after Dose 4	65	7280	(5594, 9475)	71	32	(20, 50)
22F	1 Month after Dose 3	62	21864	(16413, 29125)	75	10	(8, 11)
	Before Dose 4	66	2562	(1869, 3512)	72	16	(11, 24)
	1 Month after Dose 4	58	28435	(19414, 41649)	74	18	(12, 27)
33F	1 Month after Dose 3	57	20162	(13581, 29930)	71	177	(160, 195)
	Before Dose 4	56	5678	(4403, 7321)	72	539	(391, 742)
	1 Month after Dose 4	63	18997	(13140, 27463)	71	658	(480, 904)

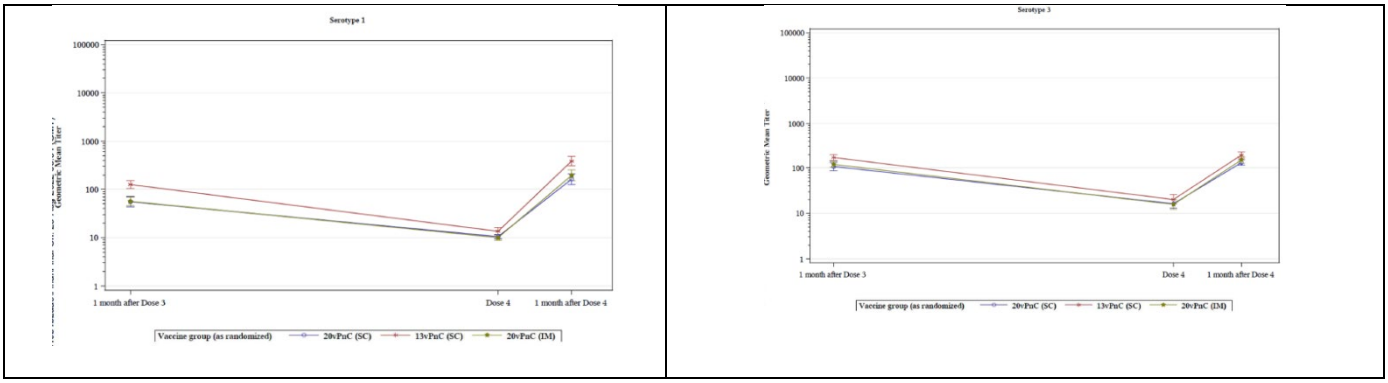
Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity; SC = subcutaneous.
Note: The Dose 3 evaluable immunogenicity population was used for all time points except for 1 month after Dose 4 time point, which used the Dose 4 evaluable immunogenicity population.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from a randomly selected subset of participants assuring equal representation of both vaccine groups.
a. n = Number of participants with valid OPA titers for the specified serotype at the given sampling time point.
b. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:21)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s001_opa_gmt_eval

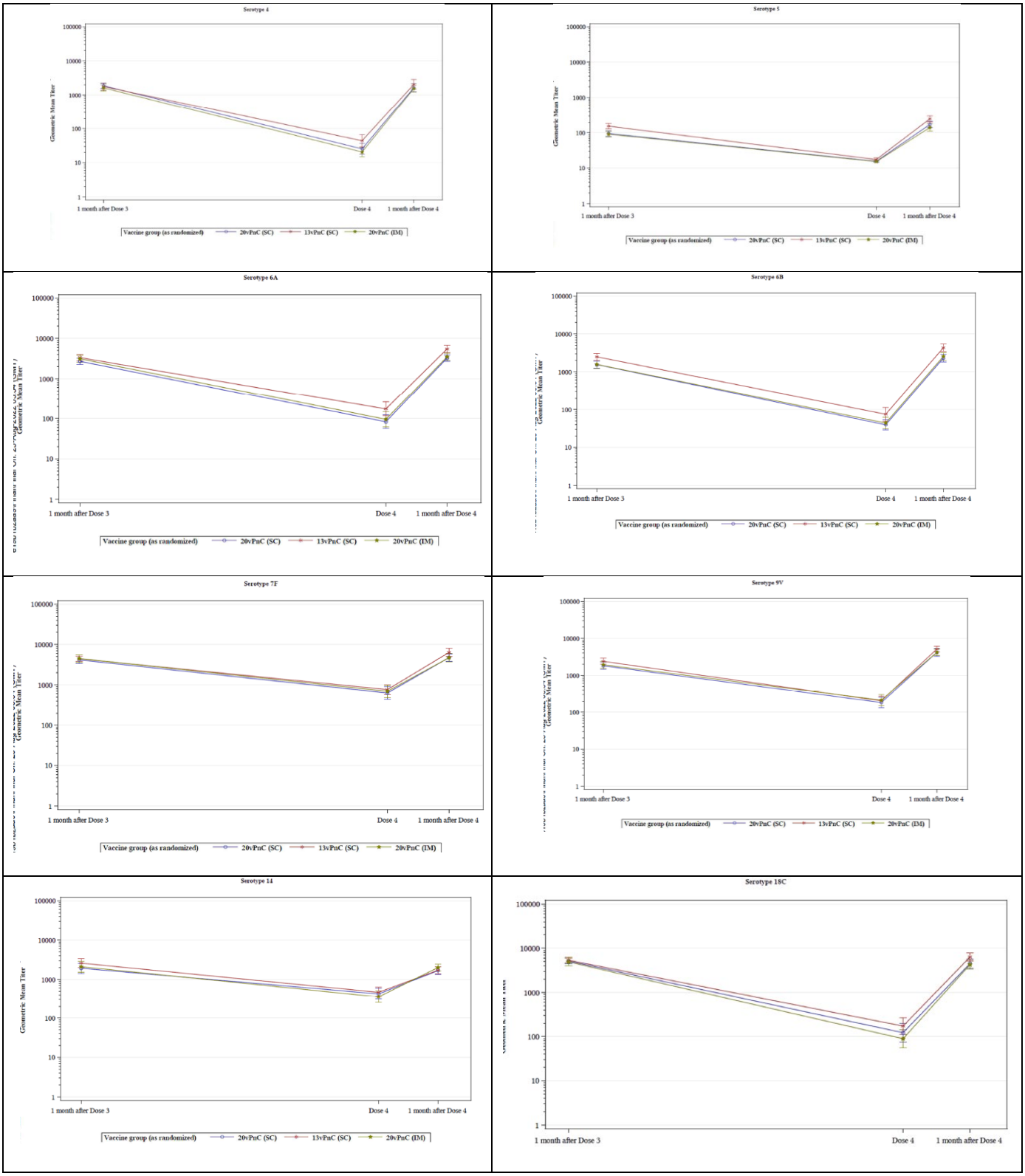
Table 10.
Number (%) of Participants Achieving a ≥4-Fold Rise in Pneumococcal OPA Titers From Before Dose 4 to 1 Month After Dose 4 (20vPnC [SC] and 13vPnC [SC]) – Dose 4 Evaluable Immunogenicity Population

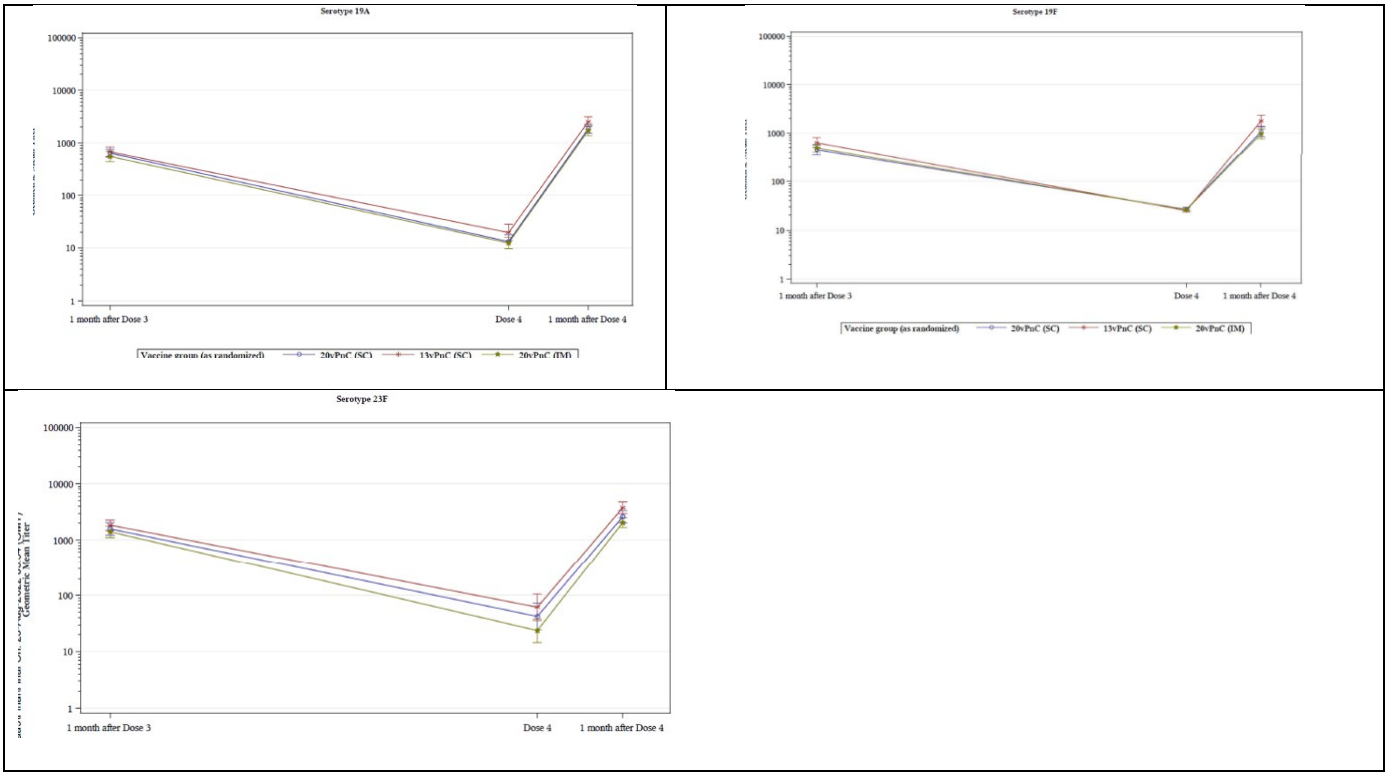
	Vaccine Group (as Randomized)							
	20vPnC (SC)				13vPnC (SC)			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	69	60	87.0	(76.7, 93.9)	72	69	95.8	(88.3, 99.1)
3	66	47	71.2	(58.7, 81.7)	69	56	81.2	(69.9, 89.6)
4	66	63	95.5	(87.3, 99.1)	66	59	89.4	(79.4, 95.6)
5	69	63	91.3	(82.0, 96.7)	72	70	97.2	(90.3, 99.7)
6A	65	60	92.3	(83.0, 97.5)	70	62	88.6	(78.7, 94.9)
6B	66	61	92.4	(83.2, 97.5)	64	60	93.8	(84.8, 98.3)
7F	63	39	61.9	(48.8, 73.9)	68	49	72.1	(59.9, 82.3)
9V	62	60	96.8	(88.8, 99.6)	68	62	91.2	(81.8, 96.7)
14	67	32	47.8	(35.4, 60.3)	70	26	37.1	(25.9, 49.5)
18C	63	57	90.5	(80.4, 96.4)	66	62	93.9	(85.2, 98.3)
19A	65	63	96.9	(89.3, 99.6)	70	67	95.7	(88.0, 99.1)
19F	69	68	98.6	(92.2, 100.0)	70	70	100.0	(94.9, 100.0)
23F	63	56	88.9	(78.4, 95.4)	67	61	91.0	(81.5, 96.6)
7 Additional								
8	59	52	88.1	(77.1, 95.1)	69	9	13.0	(6.1, 23.3)
10A	53	30	56.6	(42.3, 70.2)	65	4	6.2	(1.7, 15.0)
11A	68	41	60.3	(47.7, 72.0)	65	2	3.1	(0.4, 10.7)
12F	49	25	51.0	(36.3, 65.6)	69	4	5.8	(1.6, 14.2)
15B	58	42	72.4	(59.1, 83.3)	70	3	4.3	(0.9, 12.0)
22F	54	41	75.9	(62.4, 86.5)	71	3	4.2	(0.9, 11.9)
33F	49	19	38.8	(25.2, 53.8)	69	9	13.0	(6.1, 23.3)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from a randomly selected subset of participants assuring equal representation of both vaccine groups.
a. N = number of participants with valid assay results at both time points for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with a ≥4-fold rise in OPA titers from the specified time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 01SEP2022 (11:08)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_opa_fold_1md4_eval

Antibody Response Curve up to 1 Month After Dose 4 for OPA GMTs With 2 Sided 95% CIs – Evaluable Immunogenicity Population –shared serotypes




Serotype 4
Serotype 5
Serotype 6A
Serotype 6B
Serotype 7F
Serotype 9V
Serotype 14
Serotype 18C
Geometric Mean Titer
100000
10000
1000
100
10
1
1 month after Dose 3
Dose 4
1 month after Dose 4
Vaccine group (as randomized)
20vPnC (SC)
13vPnC (SC)
20vPnC (IM)


Serotype 19A
100000
10000
1000
100
10
1
1 month after Dose 3
Dose 4
1 month after Dose 4
Vaccine group (as randomized)
20vPnC (SC)
13vPnC (SC)
20vPnC (IM)
Serotype 19F
100000
10000
1000
100
10
1
1 month after Dose 3
Dose 4
1 month after Dose 4
Vaccine group (as randomized)
20vPnC (SC)
13vPnC (SC)
20vPnC (IM)
Serotype 23F
Geometric Mean Titer
100000
10000
1000
100
10
1
1 month after Dose 3
Dose 4
1 month after Dose 4

3.2. Immunogenicity of 20vPnC by route of administration (IM/SC)

Table 11. Comparison of the Percentages of Participants With Predefined Levels for Pneumococcal IgG Concentrations for Vaccine Serotypes (20vPnC [IM] – 20vPnC [SC]) – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC (IM)				20vPnC (SC)				20vPnC (IM) – 20vPnC (SC)	
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference (%)	(95% CI[d])
13vPnC											
1	≥0.35 µg/mL	213	196	92.0	(87.5, 95.3)	221	216	97.7	(94.8, 99.3)	-5.7	(-10.4, -1.7)
3	≥0.35 µg/mL	213	203	95.3	(91.5, 97.7)	221	213	96.4	(93.0, 98.4)	-1.1	(-5.2, 2.9)
4	≥0.35 µg/mL	213	202	94.8	(90.9, 97.4)	221	214	96.8	(93.6, 98.7)	-2.0	(-6.2, 1.9)
5	≥0.23 µg/mL	213	198	93.0	(88.7, 96.0)	221	204	92.3	(88.0, 95.5)	0.7	(-4.5, 5.8)
6A	≥0.35 µg/mL	213	202	94.8	(90.9, 97.4)	221	199	90.0	(85.3, 93.7)	4.8	(-0.2, 10.0)
6B	≥0.10 µg/mL	213	175	82.2	(76.3, 87.1)	221	194	87.8	(82.7, 91.8)	-5.6	(-12.5, 1.1)
7F	≥0.35 µg/mL	213	202	94.8	(90.9, 97.4)	221	212	95.9	(92.4, 98.1)	-1.1	(-5.4, 3.1)
9V	≥0.35 µg/mL	213	198	93.0	(88.7, 96.0)	221	212	95.9	(92.4, 98.1)	-3.0	(-7.7, 1.4)
14	≥0.35 µg/mL	213	205	96.2	(92.7, 98.4)	220	213	96.8	(93.6, 98.7)	-0.6	(-4.4, 3.2)
18C	≥0.35 µg/mL	213	202	94.8	(90.9, 97.4)	221	214	96.8	(93.6, 98.7)	-2.0	(-6.2, 1.9)
19A	≥0.12 µg/mL	213	211	99.1	(96.6, 99.9)	221	220	99.5	(97.5, 100.0)	-0.5	(-3.0, 1.7)
19F	≥0.35 µg/mL	213	213	100.0	(98.3, 100.0)	221	221	100.0	(98.3, 100.0)	0.0	(-1.8, 1.7)
23F	≥0.35 µg/mL	213	189	88.7	(83.7, 92.6)	221	198	89.6	(84.8, 93.3)	-0.9	(-6.9, 5.1)
7 Additional											
8	≥0.35 µg/mL	213	212	99.5	(97.4, 100.0)	221	220	99.5	(97.5, 100.0)	0.0	(-2.2, 2.1)
10A	≥0.35 µg/mL	213	127	59.6	(52.7, 66.3)	221	133	60.2	(53.4, 66.7)	-0.6	(-9.8, 8.6)
11A	≥0.35 µg/mL	213	213	100.0	(98.3, 100.0)	221	221	100.0	(98.3, 100.0)	0.0	(-1.8, 1.7)
12F	≥0.35 µg/mL	213	159	74.6	(68.3, 80.3)	221	165	74.7	(68.4, 80.3)	0.0	(-8.2, 8.2)
15B	≥0.35 µg/mL	213	210	98.6	(95.9, 99.7)	221	219	99.1	(96.8, 99.9)	-0.5	(-3.3, 2.0)
22F	≥0.35 µg/mL	213	213	100.0	(98.3, 100.0)	221	221	100.0	(98.3, 100.0)	0.0	(-1.8, 1.7)
33F	≥0.35 µg/mL	212	196	92.5	(88.0, 95.6)	219	208	95.0	(91.2, 97.5)	-2.5	(-7.5, 2.2)

Abbreviations: IgG = immunoglobulin G; IM = intramuscular; SC = subcutaneous.
a. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. 2-Sided CIs are calculated using the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:22)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_13_1md3_eval_20

Table 12. Pneumococcal IgG GMCs and GMRs (20vPnC [IM]/20vPnC [SC]) – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)						
	20vPnC (IM)			20vPnC (SC)			20vPnC (IM) / 20vPnC (SC)
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])	GMR (95% CI[c])
13vPnC							
1	213	1.17	(1.04, 1.31)	221	1.37	(1.25, 1.51)	0.85 (0.73, 0.99)
3	213	1.10	(0.99, 1.22)	221	1.29	(1.18, 1.41)	0.85 (0.74, 0.98)
4	213	1.73	(1.52, 1.97)	221	1.76	(1.57, 1.97)	0.98 (0.83, 1.16)
5	213	1.00	(0.87, 1.14)	221	1.01	(0.89, 1.16)	0.98 (0.81, 1.19)
6A	213	1.64	(1.42, 1.88)	221	1.38	(1.21, 1.57)	1.19 (0.98, 1.44)
6B	213	0.39	(0.32, 0.48)	221	0.42	(0.35, 0.50)	0.93 (0.72, 1.21)
7F	213	1.52	(1.35, 1.71)	221	1.58	(1.43, 1.75)	0.96 (0.82, 1.12)
9V	213	1.45	(1.29, 1.64)	221	1.46	(1.32, 1.61)	0.99 (0.85, 1.16)
14	213	2.43	(2.13, 2.76)	220	2.79	(2.45, 3.18)	0.87 (0.72, 1.04)
18C	213	1.54	(1.38, 1.72)	221	1.67	(1.51, 1.86)	0.92 (0.79, 1.07)
19A	213	2.36	(2.11, 2.64)	221	2.41	(2.19, 2.65)	0.98 (0.84, 1.13)
19F	213	2.76	(2.53, 3.02)	221	2.81	(2.60, 3.04)	0.98 (0.87, 1.10)
23F	213	1.29	(1.13, 1.48)	221	1.32	(1.15, 1.51)	0.98 (0.81, 1.19)
7 Additional							
8	213	3.29	(2.97, 3.64)	221	3.32	(3.05, 3.61)	0.99 (0.87, 1.13)
10A	213	0.47	(0.39, 0.56)	221	0.50	(0.42, 0.60)	0.94 (0.73, 1.20)
11A	213	5.22	(4.73, 5.77)	221	5.63	(5.17, 6.14)	0.93 (0.81, 1.06)
12F	213	0.72	(0.60, 0.85)	221	0.79	(0.67, 0.93)	0.91 (0.71, 1.15)
15B	213	6.80	(6.03, 7.67)	221	6.77	(6.04, 7.60)	1.00 (0.85, 1.18)
22F	213	4.41	(3.99, 4.88)	221	4.94	(4.54, 5.38)	0.89 (0.78, 1.02)
33F	212	1.62	(1.40, 1.87)	219	1.70	(1.51, 1.92)	0.95 (0.79, 1.15)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; IM = intramuscular; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype at the given sampling time point.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC [IM] – 20vPnC [SC]) and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:21)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s001_13_aftd3_eval_20

Table 13. Pneumococcal IgG GMCs (20vPnC [IM] and 20vPnC [SC]) – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	20vPnC (IM)			20vPnC (SC)		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	211	2.78	(2.47, 3.12)	217	2.79	(2.50, 3.12)
3	211	1.08	(0.96, 1.21)	217	0.97	(0.87, 1.08)
4	211	7.31	(6.51, 8.20)	217	6.93	(6.14, 7.83)
5	211	2.94	(2.59, 3.33)	217	2.96	(2.63, 3.34)
6A	211	13.92	(12.43, 15.59)	217	11.90	(10.61, 13.34)
6B	211	7.50	(6.58, 8.55)	216	7.18	(6.30, 8.18)
7F	211	4.85	(4.34, 5.42)	217	4.46	(4.04, 4.92)
9V	211	5.38	(4.81, 6.02)	217	4.54	(4.04, 5.09)
14	211	9.19	(8.10, 10.43)	217	8.23	(7.27, 9.31)
18C	211	3.81	(3.38, 4.30)	217	3.95	(3.50, 4.45)
19A	211	7.92	(7.06, 8.89)	217	7.62	(6.82, 8.52)
19F	211	8.56	(7.66, 9.56)	217	8.74	(7.84, 9.73)
23F	211	7.39	(6.49, 8.42)	217	7.01	(6.16, 7.97)
7 Additional						
8	211	5.88	(5.23, 6.62)	217	5.84	(5.23, 6.53)
10A	211	8.02	(7.02, 9.16)	217	6.98	(6.13, 7.93)
11A	211	5.78	(5.14, 6.50)	217	5.73	(5.08, 6.46)
12F	211	2.69	(2.36, 3.06)	217	2.73	(2.41, 3.09)
15B	211	21.83	(19.53, 24.41)	217	18.45	(16.73, 20.36)
22F	211	14.21	(12.61, 16.00)	217	14.07	(12.67, 15.63)
33F	211	11.13	(9.99, 12.39)	217	10.29	(9.28, 11.40)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; IM = intramuscular; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype at the given sampling time point.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:21)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s001_13_1md4_eval_20

Table 14. Number (%) of Participants With Predefined Levels for Pneumococcal IgG Concentrations for Vaccine Serotypes (20vPnC [IM] and 20vPnC [SC]) – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		20vPnC (IM)				20vPnC (SC)			
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC									
1	≥0.35 µg/mL	211	208	98.6	(95.9, 99.7)	217	215	99.1	(96.7, 99.9)
3	≥0.35 µg/mL	211	193	91.5	(86.9, 94.9)	217	199	91.7	(87.2, 95.0)
4	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
5	≥0.23 µg/mL	211	210	99.5	(97.4, 100.0)	217	216	99.5	(97.5, 100.0)
6A	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
6B	≥0.10 µg/mL	211	211	100.0	(98.3, 100.0)	216	216	100.0	(98.3, 100.0)
7F	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	216	99.5	(97.5, 100.0)
9V	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	216	99.5	(97.5, 100.0)
14	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	215	99.1	(96.7, 99.9)
18C	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	216	99.5	(97.5, 100.0)
19A	≥0.12 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
19F	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
23F	≥0.35 µg/mL	211	210	99.5	(97.4, 100.0)	217	216	99.5	(97.5, 100.0)
7 Additional									
8	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
10A	≥0.35 µg/mL	211	210	99.5	(97.4, 100.0)	217	215	99.1	(96.7, 99.9)
11A	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
12F	≥0.35 µg/mL	211	208	98.6	(95.9, 99.7)	217	213	98.2	(95.3, 99.5)
15B	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
22F	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)
33F	≥0.35 µg/mL	211	211	100.0	(98.3, 100.0)	217	217	100.0	(98.3, 100.0)

Abbreviations: IgG = immunoglobulin G; IM = intramuscular; SC = subcutaneous.

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

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

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

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(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_13_1md4_eval_20

Table 15.
Number (%) of Participants Achieving a ≥4-Fold Rise in Pneumococcal IgG Concentrations From Before Dose 4 to 1 Month After Dose 4 (20vPnC [IM] and 20vPnC [SC]) – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC (IM)				20vPnC (SC)			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	211	195	92.4	(88.0, 95.6)	217	201	92.6	(88.3, 95.7)
3	211	177	83.9	(78.2, 88.6)	217	162	74.7	(68.3, 80.3)
4	211	201	95.3	(91.5, 97.7)	217	203	93.5	(89.4, 96.4)
5	210	192	91.4	(86.8, 94.8)	217	199	91.7	(87.2, 95.0)
6A	211	207	98.1	(95.2, 99.5)	217	210	96.8	(93.5, 98.7)
6B	211	209	99.1	(96.6, 99.9)	215	210	97.7	(94.7, 99.2)
7F	211	161	76.3	(70.0, 81.9)	217	152	70.0	(63.5, 76.1)
9V	211	196	92.9	(88.5, 96.0)	217	199	91.7	(87.2, 95.0)
14	211	133	63.0	(56.1, 69.6)	217	114	52.5	(45.7, 59.3)
18C	211	199	94.3	(90.3, 97.0)	217	203	93.5	(89.4, 96.4)
19A	211	206	97.6	(94.6, 99.2)	217	211	97.2	(94.1, 99.0)
19F	211	200	94.8	(90.9, 97.4)	217	206	94.9	(91.1, 97.4)
23F	211	207	98.1	(95.2, 99.5)	217	208	95.9	(92.3, 98.1)
7 Additional								
8	211	188	89.1	(84.1, 93.0)	217	186	85.7	(80.3, 90.1)
10A	211	159	75.4	(69.0, 81.0)	217	147	67.7	(61.1, 73.9)
11A	211	171	81.0	(75.1, 86.1)	217	158	72.8	(66.4, 78.6)
12F	211	192	91.0	(86.3, 94.5)	217	182	83.9	(78.3, 88.5)
15B	211	166	78.7	(72.5, 84.0)	217	147	67.7	(61.1, 73.9)
22F	211	179	84.8	(79.3, 89.4)	217	176	81.1	(75.3, 86.1)
33F	211	153	72.5	(66.0, 78.4)	217	144	66.4	(59.7, 72.6)

Abbreviations: IgG = immunoglobulin G; IM = intramuscular; LLOQ = lower limit of quantitation; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. N = number of participants with valid assay results at both timepoints for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with a ≥4-fold rise in IgG concentrations from the specified time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 08AUG2022 (14:22)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_ig_fold_1md4_eval_20

Table 16.
Number (%) of Participants Achieving a ≥4-Fold Rise in Pneumococcal OPA Titers From Before Dose 4 to 1 Month After Dose 4 (20vPnC [IM] and 20vPnC [SC]) – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC (IM)				20vPnC (SC)			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC								
1	68	64	94.1	(85.6, 98.4)	69	60	87.0	(76.7, 93.9)
3	65	48	73.8	(61.5, 84.0)	66	47	71.2	(58.7, 81.7)
4	67	66	98.5	(92.0, 100.0)	66	63	95.5	(87.3, 99.1)
5	68	58	85.3	(74.6, 92.7)	69	63	91.3	(82.0, 96.7)
6A	65	63	96.9	(89.3, 99.6)	65	60	92.3	(83.0, 97.5)
6B	66	63	95.5	(87.3, 99.1)	66	61	92.4	(83.2, 97.5)
7F	66	47	71.2	(58.7, 81.7)	63	39	61.9	(48.8, 73.9)
9V	64	53	82.8	(71.3, 91.1)	62	60	96.8	(88.8, 99.6)
14	66	30	45.5	(33.1, 58.2)	67	32	47.8	(35.4, 60.3)
18C	64	60	93.8	(84.8, 98.3)	63	57	90.5	(80.4, 96.4)
19A	63	61	96.8	(89.0, 99.6)	65	63	96.9	(89.3, 99.6)
19F	68	66	97.1	(89.8, 99.6)	69	68	98.6	(92.2, 100.0)
23F	63	56	88.9	(78.4, 95.4)	63	56	88.9	(78.4, 95.4)
7 Additional								
8	61	51	83.6	(71.9, 91.8)	59	52	88.1	(77.1, 95.1)
10A	54	25	46.3	(32.6, 60.4)	53	30	56.6	(42.3, 70.2)
11A	61	50	82.0	(70.0, 90.6)	68	41	60.3	(47.7, 72.0)
12F	47	26	55.3	(40.1, 69.8)	49	25	51.0	(36.3, 65.6)
15B	58	34	58.6	(44.9, 71.4)	58	42	72.4	(59.1, 83.3)
22F	49	37	75.5	(61.1, 86.7)	54	41	75.9	(62.4, 86.5)
33F	50	25	50.0	(35.5, 64.5)	49	19	38.8	(25.2, 53.8)

Abbreviations: IM = intramuscular; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity; SC = subcutaneous.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from a randomly selected subset of participants assuring equal representation of both vaccine groups.
a. N = number of participants with valid assay results at both time points for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of participants with a ≥4-fold rise in OPA titers from the specified time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:59) Source Data: adva Table Generation: 01SEP2022 (11:08)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adva_s006_opa_fold_1md4_eval_20

4. Scientific Discussion – Immunogenicity

Design and conduct of clinical study

The MAH (Pfizer Europe MA EEIG) submitted results of study B7471016: A Phase 3, Randomized, Double-Blind, Third-Party Unblind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Japanese Infants. The scope of this study was to provide safety and comparative immunogenicity data between 20vPnC and 13vPnC in Japanese infants to help support licensure for paediatric use in Japan.

For this study, infants between 2 through 6 months of age at the time of consent by their parent(s)/legal guardian(s) were included. This study population is generally acceptable for the purpose of the study. The selection of 13vPnC as an active comparator is considered appropriate, as 13vPnC is currently an approved treatment option for this age group. The same formulation and dose was administered to infants as currently licensed for adults. Demographic and baseline characteristics of sex, race, ethnicity, and age were balanced across the vaccine groups. Across the vaccine groups, all participants were Asian (Japanese), and 49.4% were males.

According to the MAH, this study was conducted in compliance with GCP guidelines and, where applicable, local country regulations. No substantial changes to the study protocol were made.

No critical issues were identified concerning the overall study design or study conduct.

For 20vPnC, Pfizer's multiplex Luminex-based immunoassay (dLIA) was used for measuring serotype-specific IgG concentrations in serum. Efficacy data and additional analyses

20vPnC SC vs. 13vPnC SC

Primary immunogenicity objectives

The primary immunogenicity objectives were to demonstrate that:

- the **percentage of participants with predefined serotype-specific IgG concentrations** for the 13 serotypes in the 20vPnC SC group are noninferior [i.e. the lower bound of the 2-sided 95% CI for the difference (20vPnC SC group – 13vPnC SC group) in percentages >–10%] to the percentage of the corresponding serotypes in the 13vPnC SC group at **1 month after Dose 3**.

  AND

- the **percentage of participants with predefined serotype-specific IgG concentrations** for the 7 additional serotypes in the 20vPnC SC group are noninferior [i.e. the lower bound of the 2-sided 95% CI for the difference (20vPnC SC group – 13vPnC SC group) in percentages >–10%] to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month **after Dose 3**.

Although only percentage of participants with predefined serotype-specific IgG concentrations was considered a primary objective in this study, for the EU requirements both the percentage of participants with predefined serotype-specific IgG concentrations AND serotype-specific IgG GMC are considered important i.e. the aim should be to show noninferiority for both of these parameters. Serotype-specific IgG GMCs were assessed as secondary endpoints, however with hypothesis testing and predefined noninferiority margins. This is described later in the report under 'Secondary objectives'.

The primary analysis was performed one month after the primary series (post-Dose 3). The chosen timepoint is in accordance with that for which the current pre-defined IgG concentration of 0.35 µg/mL according to the WHO ELISA has been established and reflects the immune response elicited within the first year of life when children are at the highest risk of IPD and is therefore appropriate.

It is noteworthy that, although the non-inferiority margin of -0.1 for the difference in response rate was previously used in clinical studies of approved pneumococcal vaccines, it has not been justified from a clinical perspective, and therefore meeting or not meeting these NI criteria is of unknown clinical relevance.

The NI comparison of immune responses elicited by the 7 additional serotypes to the lowest immune response induced in the 13vPnC SC group is of limited value. Furthermore, as no correlate of protection is established for the 7 additional serotypes, using the cut-off of 0.35 µg/ml is also of limited value.

The NI criteria were met for 11/13 shared serotypes. **Of the 13 shared serotypes, serotypes 6A and 6B missed the NI criterion**. The lower bound of the 2-sided 95% CI for the percentage difference were -13% and -14% for serotypes 6A and 6B, respectively, thereby exceeding the predefined NI margin of -10%. Of note, serotypes 5 and 23F narrowly succeeded in meeting the NI margin, as their lower bound of the 2-sided 95% CI were -9.6 and -9.5, respectively. An overall numerically lower immune response was observed for almost all shared serotypes, despite the majority

of them meeting the pre-defined NI criterion. Exceptions were serotypes 19A and 19F, for which the difference in percentages was zero.

The non-inferiority criteria were met for 5/7 additional serotypes. **Of the 7 additional serotypes, serotypes 10A and 12F missed the statistical NI criterion** (lower bounds of the 2-sided 95% CI were -40.7% and -25.7%, respectively).

Secondary immunogenicity objectives

The secondary objectives were to demonstrate that:

- the **serotype-specific IgG GMCs** for the 13 serotypes in the 20vPnC SC group are noninferior [i.e. the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC SC group to the 13vPnC SC group >0.5 (2-fold NI margin)] to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month **after Dose 3**.

AND

- the **serotype-specific IgG GMCs** for the 7 additional serotypes in the 20vPnC SC group are noninferior [i.e. the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC SC group to the 13vPnC SC group >0.5 (2-fold NI margin)] to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month **after Dose 3.**

It is noteworthy that, although the non-inferiority margin of 0.5 for the GMC ratio was previously used in clinical studies of approved pneumococcal vaccines, it has not been justified from a clinical perspective, and therefore meeting or not meeting these NI criteria is of unknown clinical relevance.

Of the 13 shared serotypes, the noninferiority criteria were met for 10/13 shared serotypes. **Serotypes 5, 6A, and 6B missed the statistical NI criterion**, as the lower bounds of the 2-sided 95% CIs of IgG GMR were 0.49, 0.50 and 0.40, respectively. Also for the serotypes that met the NI margin, numerically lower IgG GMC values were observed compared to 13vPnC. For almost all shared serotypes the entire 95% CI was below 1, with the exception of serotype 14, for which the upper bound of the 95% CI barely crossed 1.

Of the 7 additional serotypes, the non-inferiority criteria were met for 6/7 serotypes. **Serotype 10A missed the statistical NI criterion**, as the lower bound of the 2-sided 95% CI was 0.48.

Secondary immunogenicity objectives

- OPA GMTs at 1 month After Dose 3

Regarding the functionally important opsonophagocytic activity (OPA), a clear increase was seen in the 20vPnC SC group. Nonetheless, OPA GMTs for the 13 matched serotypes 1 month after Dose 3 were generally lower in the 20vPnC SC group compared to the 13vPnC SC group, including for the serotypes that missed NI in the primary and secondary comparison between 20vPnC SC and 13vPnC SC (38% worse response for serotypes 5 and 6B, 19% worse response for serotype 6A). Interestingly, OPA GMTs for additional 7 serotypes were of a higher order of magnitude (10^2 or 10^4) compared to the OPA GMTs for 13 shared serotypes (10^1 or 10^3). It is unclear whether this could be ascribed to different OPA assays, however this issue is not further pursued within the assessment of this study.

<u>Pre-dose 4 assessments</u>

- Geometric mean fold-rise (GMFRs) in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4

Pneumococcal IgG GMCs decreased from 1 month after Dose 3 to before Dose 4 for all 13 matched serotypes, similarly in both vaccine groups. The IgG GMFRs for those serotypes ranged from 0.1 (serotypes 3, 19A) to 0.8 (serotype 6B) in the 20vPnC SC group, and from 0.1 (serotypes 3, 19A and 19F) to 0.7 (serotype 14) in the 13vPnC SC group.

For the 7 additional serotypes, the pneumococcal IgG GMCs decreased for some and increased for other serotypes from 1 month after Dose 3 to before Dose 4. The pneumococcal IgG GMFRs 1 month after Dose 3 to before Dose 4 ranged from 0.1 (serotype 11A) to 2.2 (serotype 10A) in the 20vPnC SC group. According to the MAH, the low observed mean GMFR for 11A may be due to the relatively high GMCs observed after Dose 3. As would be expected, there were no or minimal changes in antibody levels in the 13vPnC SC group.

Post toddler dose (post Dose 4) assessments

- *The percentages of participants with predefined serotype-specific pneumococcal IgG concentrations* at 1 month *after Dose 4* of 20vPnC SC were higher compared to the percentage of participants who reached the pre-defined cut-offs at 1 month after Dose 3, for all serotypes except for serotype 3, where a slight decreased was observed (from 96.4% to 91.7%). For all other serotypes, the percentage of participants who reached the pre-defined cut-offs was >98%, including for serotypes that failed primary NI comparisons post-Dose 3 (serotypes 6A, 6B, 10A and 12F).
- *Pneumococcal IgG GMCs* for most of serotypes were higher in both vaccine groups 1 month after Dose 4 compared to 1 month after Dose 3. Only for serotype 3, IgG GMC decreased from post-Dose 3 to post-Dose 4, this finding was observed in both vaccine groups. Despite the overall increase, IgG GMCs were still lower in 20vPnC group compared to 13vPnC group. For the 3 serotypes (5, 6A and 6B) that missed primary NI comparison after Dose 3, IgG increased after Dose 4, notably for serotypes 6A and 6B.
- The *percentages of participants with a ⩾4-fold rise in pneumococcal IgG concentrations before Dose 4 to 1 month after Dose 4* varied between serotypes. In the 20vPnC group, the seroconversion rate ranged from 52.5% (serotype 14) to 97.7% (serotype 6B) among the shared serotypes. Similar results were observed also in the 13vPnC group; the seroconversion rates varied between 48.2% (serotype 14) and 99.5% (serotype 6B). Seroconversion rate was greater than 90% in both groups for the majority of shared serotypes. For the additional 7 serotypes, the seroconversion rates in the 20vPnC group ranged between 67.7% (serotypes 10A and 15B) and 85.7% (serotype 8). This suggests that the seroconversion was generally lower for the additional serotypes compared to the matched serotypes. No substantial increase in the IgG GMCs for the 7 additional serotypes was seen in the PCV13 group, as expected.
- *OPA GMTs after Dose 4* showed a boost 1 month after Dose 4 in both groups but for 13 matched serotypes but the 20vPnC SC group was again generally lower compared to the 13vPnC SC group. Thus, it can be assumed that while 20vPnC elicits functionally important antibody responses to the covered serotypes, responses to the 13 matched serotypes might be generally higher following vaccination with 13vPnC.

20vPnC IM vs 20vPnC

A primary immunogenicity objective regarding the comparison between subcutaneous and intramuscular route of administration was to describe the immune responses to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3.

It should be noted that no comparison has been presented between 20vPnC IM and 13vPnC SC; only comparison 20vPnC IM vs 20vPnC SC is available. In addition, no success criteria were pre-defined. The percentages of participants with predefined serotype-specific pneumococcal IgG concentrations 1 month after Dose 3 of 20vPnC IM for all 20 serotypes were generally slightly lower to those in the 20vPnC SC group. The range of point estimates of the difference was -5.7% (serotype 1) to 4.8% (serotype 6A). This minimal trend was also seen in the additional comparison regarding the Pneumococcal IgG GMCs 1 month after Dose 3. However, Pneumococcal IgG GMCs 1 month after Dose 4 of 20vPnC IM for all 20 serotypes were generally slightly higher to those in the 20vPnC SC group. Likewise, the percentages of participants with predefined serotype-specific pneumococcal IgG concentrations 1 month after Dose 4 of 20vPnC IM for all 20 serotypes were generally similar to those in the 20vPnC SC group. The observed percentages for all serotypes were ⩾99.5% with the exception of serotypes 1, 3, 12F, and 14 (⩾98.6%, ⩾91.5%, ⩾98.2%, and ⩾99.1%, respectively). In addition, no substantial differences regarding immunogenicity were observed regarding the ⩾4-fold rise in pneumococcal IgG concentrations or OPA titers after Dose 4 between the IM and SC routes. Thus, both routes of administration offer a comparable immunogenicity profile according to measured immune parameters.

Conclusion on immunogenicity

Both the percentage of participants with predefined serotype-specific IgG concentrations AND serotype-specific IgG GMC are considered important for the EU requirements, i.e. the aim should be to show noninferiority for both of these parameters. Of the 13 shared serotypes, 10 serotypes showed noninferiority for both parameters, 1 serotype (serotype 5) failed one parameter and 2 serotypes (6A and 6B) failed both parameters. Even for those serotypes for which NI criterion was met, numerically lower immune response was observed, with respect to both the percentage of participants with predefined serotype-specific IgG concentrations and serotype-specific IgG GMC. Of the 7 additional serotypes, 5 serotypes showed noninferiority for both parameters, 1 serotype (serotype 12F) failed one parameter and 1 serotype (serotype 10A) failed both parameters.

According to the study protocol, the primary and specific secondary pneumococcal immunogenicity objectives for noninferiority were to be met if the noninferiority of the immune response (percentage of participants with predefined IgG concentration and IgG GMCs respectively) induced by 20vPnC SC group compared to 13vPnC SC group at 1 month after Dose 3 is *established for all 20 serotypes*. Noninferiority was not met for all of the 20 serotypes and the study failed to meet the primary as well as the secondary objectives of noninferiority. Additional analyses such as OPA GMTs post Dose 3 offer limited reassurance, since OPA GMTs for the 13 matched serotypes 1 month after Dose 3 were generally lower in the 20vPnC SC group compared to the 13vPnC SC group, including for the serotypes that failed primary and/or secondary NI comparisons. Moreover, Antibody Response Curves for OPA GMTs as well as for IgG GMCs show consistently lower immune response with 20vPnC SC compared to 13vPnC SC at all measurement timepoints (1 month after Dose 3, prior to Dose 4 and 1 month after Dose 4) for all shared serotypes.

Analyses after Dose 4 indicated a substantial recall of primed immune responses for the covered serotypes of 13vPnC and 20vPnC, however even after the booster dose, immunogenicity data is still in higher after vaccination with 13vPnC.

With regard to the 7 additional serotypes, the NI comparison of immune responses elicited by to the lowest immune response induced in the 13vPnC SC group is of limited value. Furthermore, as no correlate of protection is established for the 7 additional serotypes, using the cut-off of 0.35 µg/ml is also of limited value. These additional serotypes seem to elicit much higher OPA titres compared to the shared serotypes, however, uncertainties pertaining to the different assays for different serotypes preclude firm conclusions. The percentages of participants with a ⩾4-fold rise in pneumococcal IgG concentrations before Dose 4 to 1 month after Dose 4 suggest that seroconversion was generally lower for the additional serotypes compared to the matched serotypes. No data on seroconversion after Dose 3 could be found.

In conclusion, immune response elicited by the 20vPnC SC is lower compared to that of 13vPnC SC for the shared 13 serotypes. A potential benefit of a broader coverage due to the additional 7 serotypes has not been unequivocally shown.

No apparent differences were detected by route of administration (IM/SC) for 20vPnC after 4 doses although the primary comparison after dose 3 showed numerically higher responses after SC vaccination. The clinical relevance of the results remain unclear since the measured antibody titers are no established correlates of protection.

Overall, no questions are raised regarding immunogenicity results. The data of study B7471016 do not trigger a variation application for the EU PI since only IM administration of 20vPnC is relevant in the EU and the comparison with the reference product was done after SC vaccination. The MAH does not plan to apply for inclusion of subcutaneous route of administration in the EU PI. A dedicated development programme exists for the extension of indication to children in the EU.

5. Safety Results

A total of 667 participants were included in the safety population of which 659 (98.7%) completed the Dose 3 follow-up visit, and 649 (97.2%) completed all visits per protocol. The number of adverse events reported up to 1 month after Dose 4 is shown in Table 17.

Table 17. Adverse Events – Safety Population

Vaccine Group (as administered)	**20vPnC (SC)** N, n, %, (95% CI)	**13vPnC (SC)** N, n, %, (95% CI)	**20vPnC (IM)** N, n, %, (95% CI)
Any event From Dose 1 to 1 Month After Dose 3	225, 107, 47.6, (40.9, 54.3)	224, 124, 55.4, (48.6, 62.0)	217, 127, 58.5, (51.7, 65.2)
Any event from Dose 4 to 1 Month After Dose 4	218, 88, 40.4, (33.8, 47.2)	220, 95, 43.2, (36.5, 50.0)	212, 93, 43.9, (37.1, 50.8)
Abbreviations: IM = intramuscular; SC = subcutaneous. N = number of participants in the specified group. This value is the denominator for the percentage calculations. n = number of participants reporting at least 1 occurrence of any specified event. () Exact 2-sided CI based on the Clopper and Pearson method			

The percentages of participants with any related AEs from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4 were generally low and similar across the 20vPnC SC, 13vPnC SC, and 20vPnC IM groups (Table 18 and Table 19, respectively).

Table 18. Related Adverse Events Reported From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)								
	20vPnC (SC) (N[a]=225)			13vPnC (SC) (N[a]=224)			20vPnC (IM) (N[a]=217)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	15	6.7	(3.8, 10.8)	14	6.3	(3.5, 10.3)	1	0.5	(0.0, 2.5)
General disorders and administration site conditions	14	6.2	(3.4, 10.2)	11	4.9	(2.5, 8.6)	0	0	(0.0, 1.7)
Injection site erythema	5	2.2	(0.7, 5.1)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Injection site haemorrhage	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Injection site induration	2	0.9	(0.1, 3.2)	7	3.1	(1.3, 6.3)	0	0	(0.0, 1.7)
Injection site mass	7	3.1	(1.3, 6.3)	3	1.3	(0.3, 3.9)	0	0	(0.0, 1.7)
Injection site swelling	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Skin and subcutaneous tissue disorders	1	0.4	(0.0, 2.5)	4	1.8	(0.5, 4.5)	1	0.5	(0.0, 2.5)
Eczema	0	0	(0.0, 1.6)	2	0.9	(0.1, 3.2)	1	0.5	(0.0, 2.5)
Erythema	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Purpura	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Skin induration	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)

Abbreviations: IM = intramuscular; SC = subcutaneous.
Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2022 (14:13) Source Data: adae Table Generation: 08AUG2022 (16:06)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adae_rel_1_saf

Table 19. Related Adverse Events Reported From Dose 4 to 1 Month After Dose 4, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) 20vPnC (SC) (N[a]=218) n[b]	%	(95% CI[c])	13vPnC (SC) (N[a]=220) n[b]	%	(95% CI[c])	20vPnC (IM) (N[a]=212) n[b]	%	(95% CI[c])
Any event	8	3.7	(1.6, 7.1)	17	7.7	(4.6, 12.1)	2	0.9	(0.1, 3.4)
Gastrointestinal disorders	0	0	(0.0, 1.7)	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.7)
Vomiting	0	0	(0.0, 1.7)	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.7)
General disorders and administration site conditions	8	3.7	(1.6, 7.1)	15	6.8	(3.9, 11.0)	1	0.5	(0.0, 2.6)
Injection site erythema	4	1.8	(0.5, 4.6)	6	2.7	(1.0, 5.8)	1	0.5	(0.0, 2.6)
Injection site induration	4	1.8	(0.5, 4.6)	8	3.6	(1.6, 7.0)	0	0	(0.0, 1.7)
Injection site mass	1	0.5	(0.0, 2.5)	1	0.5	(0.0, 2.5)	0	0	(0.0, 1.7)
Injection site swelling	1	0.5	(0.0, 2.5)	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)
Pyrexia	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.5)	0	0	(0.0, 1.7)
Nervous system disorders	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)
Febrile convulsion	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)

Abbreviations: IM = intramuscular; SC = subcutaneous.
Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group receiving Dose 4. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2022 (14:13) Source Data: adae Table Generation: 08AUG2022 (14:20)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adae_rel_2_saf

The percentages of participants with local reactions within 7 days after vaccination after Doses 1 through 4 were generally similar across the 20vPnC SC group (82.7%, 80.3%, 82.4%, and 90.4%) and 13vPnC SC group (81.7%, 90.1%, 87.8%, and 88.2%), respectively. Injection site redness was the most commonly reported local reaction. Most local reactions reported were mild or moderate. The median day of onset for local reactions was between Day 1 and Day 2. The median duration of local reactions was between 1 and 5 days.

The percentages of participants with any systemic event within 7 days after vaccination after Doses 1 through 4 were generally similar across the 20vPnC SC group (56.9%, 57.8%, 47.7%, and 59.2%), the 13vPnC SC group (64.3%, 65.3%, 56.1%, and 59.5%), and the 20vPnC IM group (58.1%, 60.0%, 54.0%, and 60.8%), respectively. Irritability and drowsiness were the most commonly reported events. The majority of systemic events were mild or moderate. The median day of onset for systemic events was between Day 1 and Day 3. The median duration of systemic events was between 1 and 2 day.

Severe AEs were reported infrequently from Dose 1 to 1 month after Dose 3 (for ⩽2.3% of participants) and from Dose 4 to 1 month after Dose 4 (for <1% of participants) for all vaccine groups, with similar percentages (Table 20 and Table 21, respectively).

Table 20.
Severe Adverse Events Reported From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)								
	20vPnC (SC) (N[a]=225)			13vPnC (SC) (N[a]=224)			20vPnC (IM) (N[a]=217)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	2	0.9	(0.1, 3.2)	2	0.9	(0.1, 3.2)	5	2.3	(0.8, 5.3)
Congenital, familial and genetic disorders	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Laryngomalacia	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Infections and infestations	2	0.9	(0.1, 3.2)	1	0.4	(0.0, 2.5)	4	1.8	(0.5, 4.7)
Croup infectious	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Pharyngitis	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Pyelonephritis acute	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Respiratory syncytial virus infection	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Urinary tract infection	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Respiratory, thoracic and mediastinal disorders	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Asthma	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)

Abbreviations: IM = intramuscular; SC = subcutaneous.
Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2022 (14:13) Source Data: adae Table Generation: 08AUG2022 (14:20)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adae_s150_sev_d1_1md3_saf

Table 21.
Severe Adverse Events Reported From Dose 4 to 1 Month After Dose 4, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)								
	20vPnC (SC) (N[a]=218)			13vPnC (SC) (N[a]=220)			20vPnC (IM) (N[a]=212)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)
Cardiac disorders	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)
Cardio-respiratory arrest	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)
Injury, poisoning and procedural complications	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)
Near drowning	0	0	(0.0, 1.7)	0	0	(0.0, 1.7)	1	0.5	(0.0, 2.6)

Abbreviations: IM = intramuscular; SC = subcutaneous.
Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group receiving Dose 4. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
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The percentages of participants with NDCMCs after Dose 1 were low (⩽10.7%) and were similar across the 20vPnC SC, 13vPnC SC, and 20vPnC IM groups. NDCMCs were reported for ⩽2.7% of participants from Dose 1 to 1 month after Dose 3 of 20vPnC SC, 13vPnC SC, or 20vPnC IM and reported for ⩽0.9% of participants from Dose 4 to 1 month after Dose 4 of 20vPnC SC, 13vPnC SC, or 20vPnC IM. The majority of NDCMCs were new diagnoses of allergic conditions.

The percentages of participants with SAEs after Dose 1 were low and similar across the 20vPnC SC (6.2%), 13vPnC SC (⩽4.0%), and 20vPnC IM (⩽7.4%) groups (Table 22). SAEs were reported for ⩽ 2.3% of participants from Dose 1 to 1 month after Dose 3 and ⩽0.9% of participants from Dose 4 to 1 month after Dose 4 of 20vPnC SC, 13vPnC SC, or 20vPnC IM.

Table 22. Serious Adverse Events Reported From Dose 1, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) 20vPnC (SC) (N[a]=225) n[b]	%	(95% CI[c])	13vPnC (SC) (N[a]=224) n[b]	%	(95% CI[c])	20vPnC (IM) (N[a]=217) n[b]	%	(95% CI[c])
Any event	14	6.2	(3.4, 10.2)	9	4.0	(1.9, 7.5)	16	7.4	(4.3, 11.7)
Cardiac disorders	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Cardio-respiratory arrest	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Congenital, familial and genetic disorders	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Congenital mitral valve incompetence	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Laryngomalacia	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Patent ductus arteriosus	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
General disorders and administration site conditions	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	2	0.9	(0.1, 3.3)
Pyrexia	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	2	0.9	(0.1, 3.3)
Immune system disorders	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Food allergy	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Milk allergy	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Infections and infestations	9	4.0	(1.8, 7.5)	8	3.6	(1.6, 6.9)	11	5.1	(2.6, 8.9)
Asymptomatic COVID-19	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Bronchiolitis	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Bronchitis	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Cellulitis orbital	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Croup infectious	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Exanthema subitum	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Infectious mononucleosis	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Pharyngitis	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Pneumonia	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Pneumonia bacterial	0	0	(0.0, 1.6)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Pneumonia respiratory syncytial viral	1	0.4	(0.0, 2.5)	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.7)
Pyelonephritis acute	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Respiratory syncytial virus bronchiolitis	4	1.8	(0.5, 4.5)	2	0.9	(0.1, 3.2)	1	0.5	(0.0, 2.5)
Respiratory syncytial virus infection	4	1.8	(0.5, 4.5)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Urinary tract infection	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	2	0.9	(0.1, 3.3)
Injury, poisoning and procedural complications	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Burns second degree	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Clavicle fracture	1	0.4	(0.0, 2.5)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Near drowning	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Nervous system disorders	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Febrile convulsion	2	0.9	(0.1, 3.2)	0	0	(0.0, 1.6)	0	0	(0.0, 1.7)
Respiratory, thoracic and mediastinal disorders	1	0.4	(0.0, 2.5)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Asthma	1	0.4	(0.0, 2.5)	1	0.4	(0.0, 2.5)	1	0.5	(0.0, 2.5)
Skin and subcutaneous tissue disorders	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Tuberculid	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Vascular disorders	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)
Kawasaki's disease	0	0	(0.0, 1.6)	0	0	(0.0, 1.6)	1	0.5	(0.0, 2.5)

Abbreviations: IM = intramuscular; SC = subcutaneous.
Note: MedDRA (v24.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
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Two febrile convulsions occurred within 2 days after Dose 4 of study vaccine (1 participant each in the 20vPnC SC and 20vPnC IM groups). The event in the 20vPnC IM group was considered by the investigator to be related to the vaccines received at Visit 5 (visit for Dose 4), not specifically due to

20vPnC alone, but also to the effects of the concomitant vaccines. The event in the 20vPnC SC group was not considered by the investigator to be related to vaccine, but rather due to concurrent illness.

6. Scientific discussion - Safety

All subjects who received a study treatment were included in the safety population. At least 1 AE was reported from Dose 1 to 1 month after Dose 3 in 47.6% of participants in the 20vPnC SC group, 55.4% of participants in the 13vPnC SC group, and 58.5% of participants in the 20vPnC IM group. The percentages of participants with any related AEs from Dose 4 to 1 month after Dose 4 were also similar across the 20vPnC SC, 13vPnC SC, and 20vPnC IM groups. Hence, 20vPnC showed comparable safety in the study population with the licensed 13vPnC.

The majority of AEs across all groups was mild. The most frequent AEs were redness and swelling at the injection site which were lower in the 20vPnC IM compared to the 20vPnC SC group. Irritability and drowsiness were the most frequently reported systemic events. There were no pronounced differences in the rates of systemic events between the groups. However, the percentages of participants with any systemic event within 7 days after vaccination after Doses 1 through 4 were slightly lower in the 20vPnC SC compared to the 20vPnC IM group.

Severe AEs after Dose 1 to 1 month after Dose 3 were reported for $\leqslant$0.9% of participants in the 20vPnC SC and 13vPnC SC groups and $\leqslant$2.3% of participants in the 20vPnC IM group. No SAEs were considered related to study intervention. SAEs were mostly considered related to infections. However, one participant in the 20vPnC IM group was diagnosed with Kawasaki's disease 234 days after Dose 3, a vascular disorder with unknown cause and pathomechanism.

Furthermore, two febrile convulsions occurred within 2 days after Dose 4 of study vaccine. The event in the 20vPnC IM group was considered by the investigator to be related to the received vaccines. The febrile convulsion in the 20vPnC SC group was not considered to be related to the vaccination due to a current illness, although causality is difficult to determine in such a setting.

Taken together, no significant safety issues were identified and the mostly mild AEs were similarly distributed across groups.

7. Overall conclusion

The purpose of the B7471016 study was to provide key safety and comparative immunogenicity data between 20vPnC and 13vPnC in Japanese infants to help support licensure for paediatric use in Japan.

The CHMP (Co-)Rapporteurs agreed that study B7471016 could be submitted only via Article 46 (P46) in October 2022, given that the study is specific to Japan and the MAH does not plan to apply for inclusion of subcutaneous route of administration in the EU SmPC.

Currently there is no data regarding infants in the EU SmPC of Apexxnar but a variation to the current marketing authorisation with the aim of extending the indication to children from 6 weeks to less than 18 years of has already been submitted and is currently under assessment (EMEA/H/C/005451/II/0012).

The data of study B7471016 does not warrant an inclusion in the EU SmPC since only IM administration of 20vPnC is relevant in the EU and the comparison with the reference product was conducted after SC vaccination. The benefit/risk for the currently approved indication in the EU i.e. intramuscular administration in adult subjects remains unaltered.

☒ PAM fulfilled

No regulatory action required.