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Committee for Medicinal Products for Human Use (CHMP)

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/P46/006

Note

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

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☐	Rapporteur's preliminary Assessment Report	16 Oct 2023	16 Oct 2023
☐	CHMP Members comments:	30 Oct 2023	30 Oct 2023
☐	Rapporteur's updated Assessment Report	06 Nov 2023	n/a
☒	CHMP adoption of conclusions:	09 Nov 2023	09 Nov 2023

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List of abbreviations

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
CAP	community-acquired pneumonia
COVID-19	coronavirus disease 2019
CRM_{197}	cross-reactive material 197
DTPa	diptheria, tetanus, and pertussis (acellular) vaccine
EMA	European Medicines Agency
MAH	Marketing-authorisation holder
EC	European Commission
EU	European Union
GMC	geometric mean concentration
GMT	geometric mean titer
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
J-NDA	Japan new drug application
LLOQ	lower limit of quantitation
MMR	measles, mumps, and rubella vaccine
NDCMC	newly diagnosed chronic medical condition
NIP	national immunization program
OPA	opsonophagocytic activity
PCV15	15-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCSR	supplemental clinical study report
S pneumoniae	*Streptococcus pneumoniae*
USA	United States of America

1. Introduction

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

Submission of Article 46 for Apexxnar (20vPnC), a 20-valent pneumococcal polysaccharide conjugate vaccine.

The MAH submitted results of study B7471012: *Supplemental Report, Russian Cohort – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants*, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended.

Study B7471012 is part of the Paediatric Investigation Plan P/0239/2022. Study B7471012 was conducted at investigator sites in Europe and Australia, with additional sites in Russia (Russian cohort). It was part of the Phase 3 paediatric clinical development program to support the use of 20vPnC in the paediatric population. The purpose of the study was to generate data on the safety and immunogenicity of 20vPnC in infants when administered as a series of 2 infant doses and 1 toddler dose.

The primary study population was planned to include approximately 1200 infants from sites in Europe and Australia. The study was expanded during study conduct to describe the safety and immunogenicity of 20vPnC in infants from Russia, and for this purpose approximately 60 Russian infants were planned to be enrolled in the study and are referred to as the Russian cohort. The Russian cohort was not intended to be included in the primary study population due to planned earlier completion of study visits in the primary study population and differences in concomitant vaccine schedule and visit windows in the Russian participants.

The results of B7471012 (primary population) were submitted to the EMA in scope of a type II variation (EMEA/H/C/005451/II/0012). This variation is currently under assessment.

The Applicant now submits results for the Russian cohort. No amendments to the Product Information are being submitted as part of this procedure.

2. Summary of data submitted

2.1. Study design

Study B7471012 was a phase 3, multi-centre, randomized, active-controlled, double-blind trial to evaluate the safety, tolerability and immunogenicity of 20vPnC in comparison to the licensed 13vPnC in healthy infants when administered IM as a series of 2 infant doses and 1 toddler dose.

2.2. Objectives, estimands and endpoints

Data of the Russian Cohort were only evaluated descriptively. The study objectives, estimands, and endpoints related to the Russian cohort are provided in Table 1.

Table 1. Study Objectives, Estimands, and Endpoints – Russian Cohort

Safety Objective	Estimands	Safety Endpoints
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

	events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3	
Primary Pneumococcal Immunogenicity Objective	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
To describe the IgG responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 3	• Pneumococcal IgG concentrations
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
To further describe immune responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 3 • OPA GMTs at 1 month after Dose 2 • OPA GMTs at 1 month after Dose 3	• Pneumococcal IgG concentrations • Pneumococcal OPA titers
Exploratory Pneumococcal Immunogenicity Objective	**Estimands**	**Exploratory Pneumococcal Immunogenicity Endpoints**

To describe additional responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC in each vaccine group: • Percentages of participants with ≥4-fold rise in IgG concentrations from before Dose 3 to 1 month after Dose 3 • GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 • GMFRs in OPA titers from before Dose 3 to 1 month after Dose 3 • Percentage of participants with ≥4-fold rise in OPA titers from before Dose 3 to 1 month after Dose 3 • Percentages of participants with OPA titers ≥ LLOQ at available time points	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

2.3. Immunogenicity and Safety Assessments

Blood samples were collected from all participants at Visits 3 (1 month after Dose 2), 4 (prior to Dose 3), and 5 (1 month after Dose 3) for measurement of IgG concentration and OPA titres (opsonophagocytic antibodies). The serotype-specific IgG concentrations will be measured by Pfizer's multiplex Luminex immunoassay also used for the primary population of study B7471012. The functionally important OPA titres were determined on a small subset of participants from each vaccine group using the same immunoassay as for the primary population of study B7471012.

Safety assessments included local reactions (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and antipyretic/pain medication usage for 7 days after each dose of study intervention, recorded by participants' parents/legal guardians using an e-diary.

AEs were collected from the signing of the ICD through and including Visit 3 (1 month after Dose 2) and from Visit 4 (Dose 3 visit) through Visit 5 (1 month after Dose 3). SAEs and NDCMCs were collected from the signing of the ICD to the final visit (Visit 5).

Acute reactions (immediate AEs) occurring within the first 30 minutes after study intervention were assessed and documented as an AE on the CRF and SAE form, as appropriate.

2.4. The Russian Cohort

The Russian cohort included healthy male or female infants born at >36 weeks of gestation and 2 months of age (≥42 to ≤70 days) at the time of consent (the day of birth is considered day of life 1). Exclusion criteria were a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine; significant neurological disorders or history of seizure; a major known congenital malformation or serious chronic disorder; a known or suspected immunodeficiency or other conditions associated with immunosuppression.

The Russian cohort was not intended to be included in the primary study population of study B7471012 due to differences in study design. Enrollment of the Russian cohort commenced after enrollment of

the primary study population is complete. The inclusion criterion for age was ≥42 to ≤70 days of age (≥42 to ≤112 days of age in the primary study population). Participants in the Russian cohort did not receive MMR and varicella vaccinations as part of the study. The timing of visits for participants has been modified for the Russian cohort, to align with the Russian NIP and the age range for Dose 3 vaccination is wider (with an older upper age limit of 15 months). The Russian cohort data was summarised separately and descriptively. No formal hypothesis test was planned.

2.5. Exposure

Approximately 60 Russian infants born at >36 weeks of gestation and ≥42 to ≤70 days of age were planned to be enrolled in the study and are referred to as the Russian cohort. Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at enrolment and received the initial vaccination at that time. A second dose of vaccine was given 60 to 90 days later, and the third vaccination was given between 335 to 455 days of age (11 to 15 months of age) (Doses 1, 2, and 3 respectively). Participants were to receive the same vaccine (either 20vPnC or 13vPnC) for all 3 doses. It was planned that each participant in the Russian cohort participated in the trial for approximately 10 to 14 months (i.e., from Dose 1 until 1 month after the last study vaccination).

Due to an unexpected business disruption event related to global security (unrelated to the COVID-19 pandemic), enrolment was halted at 51 participants. There were no other impacts or interruption of study activities due to this event. A total of 51 Russian infants were randomized; 47 (92.2%) participants received all 3 doses and completed all visits per protocol. Disposition of all randomized participants was similar in the 20vPnC and 13vPnC groups.

2.6. Demographic and other Baseline Characteristics

Demographic and baseline characteristics of race, ethnicity, and age for the safety population were generally similar in the 20vPnC and 13vPnC groups (Table 5). There were overall more female infants in the study than male infants (54.9% vs 45.1%). Overall, the majority of participants in the Russian cohort were White (98.0%) and non-Hispanic/non-Latino (92.2%), with a median age of 66 days at Dose 1 and 343 days at Dose 3. Demographic characteristics for the Dose 2 and Dose 3 evaluable immunogenicity populations are similar to those for the safety population.

Table 5. Demographic Characteristics – Safety Population – Russian Cohort

	Vaccine Group (as Administered)		
	20vPnC (N^a=24) n^b (%)	13vPnC (N^a=27) n^b (%)	Total (N^a=51) n^b (%)
Sex			
Male	8 (33.3)	15 (55.6)	23 (45.1)
Female	16 (66.7)	12 (44.4)	28 (54.9)
Race			

White	24 (100.0)	26 (96.3)	50 (98.0)
Asian	0	1 (3.7)	1 (2.0)
Ethnicity			
Non-Hispanic/non-Latino	22 (91.7)	25 (92.6)	47 (92.2)
Not reported	2 (8.3)	2 (7.4)	4 (7.8)
Age at Dose 1 (days)			
Mean (SD)	64.2 (6.98)	63.3 (6.21)	63.7 (6.53)
Median	67.0	64.0	66.0
Min, max	(44, 70)	(49, 71)	(44, 71)
Age at Dose 3 (days)			
Mean (SD)	349.0 (18.87)	346.9 (13.76)	347.9 (16.20)
Median	344.5	342.0	343.0
Min, max	(335, 425)	(336, 382)	(335, 425)

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

2.7. Immunogenicity Results

Serotype-specific IgG Concentrations

IgG GMCs at 1 Month After Dose 2 and 1 Month After Dose 3

Table 8. Pneumococcal IgG GMCs – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population – Russian Cohort

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	24	0.76	(0.49, 1.19)	27	1.04	(0.64, 1.69)
3	24	0.28	(0.19, 0.42)	27	0.47	(0.31, 0.72)
4	24	0.67	(0.45, 1.00)	27	1.00	(0.58, 1.71)
5	24	0.53	(0.31, 0.92)	27	0.75	(0.40, 1.40)
6A	24	0.45	(0.20, 1.03)	27	1.57	(0.80, 3.10)
6B	24	0.07	(0.03, 0.16)	27	0.27	(0.12, 0.63)
7F	24	1.06	(0.68, 1.65)	27	1.89	(1.32, 2.71)
9V	24	0.44	(0.23, 0.84)	27	1.22	(0.73, 2.06)
14	24	1.56	(0.88, 2.75)	27	2.66	(1.46, 4.86)
18C	24	0.94	(0.46, 1.91)	27	0.94	(0.50, 1.78)
19A	24	1.15	(0.47, 2.82)	27	1.21	(0.59, 2.49)
19F	24	1.51	(0.84, 2.72)	27	3.32	(2.03, 5.44)
23F	24	0.25	(0.11, 0.55)	27	0.73	(0.37, 1.42)
7 Additional						
8	24	0.79	(0.37, 1.69)	27	0.07	(0.03, 0.18)
10A	24	0.31	(0.10, 0.94)	27	0.04	(0.01, 0.10)
11A	24	0.83	(0.43, 1.60)	27	0.04	(0.02, 0.09)
12F	24	0.06	(0.03, 0.11)	27	0.02	(0.01, 0.04)
15B	24	1.19	(0.46, 3.05)	27	0.16	(0.05, 0.50)
22F	24	0.48	(0.16, 1.47)	27	0.02	(0.01, 0.06)
33F	24	0.40	(0.18, 0.88)	27	0.07	(0.03, 0.16)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student's t distribution).
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./B7471012_sec/B7471012_CSR_RUSSIAN/adva_s001_igg_20_1md2_rus

Table 9. Pneumococcal IgG GMCs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population – Russian Cohort

	Vaccine Group (as Randomized)					
	20vPnC			13vPnC		
Serotype	n[a]	GMC[b]	(95% CI[b])	n[a]	GMC[b]	(95% CI[b])
13vPnC						
1	22	1.61	(0.93, 2.78)	24	1.65	(0.94, 2.90)
3	22	0.84	(0.44, 1.60)	24	0.57	(0.32, 1.01)
4	22	3.05	(1.50, 6.20)	24	3.04	(1.72, 5.36)
5	22	1.50	(0.80, 2.82)	24	1.72	(0.90, 3.29)
6A	22	6.63	(2.96, 14.86)	24	5.63	(2.96, 10.72)
6B	22	1.94	(0.82, 4.56)	24	1.49	(0.67, 3.32)
7F	22	3.53	(1.97, 6.33)	24	4.14	(2.73, 6.26)
9V	22	2.32	(1.28, 4.19)	24	2.27	(1.19, 4.35)
14	22	4.01	(1.64, 9.77)	24	5.06	(3.04, 8.40)
18C	22	2.60	(1.24, 5.44)	24	2.64	(1.49, 4.69)
19A	22	4.81	(2.07, 11.16)	24	2.69	(1.12, 6.45)
19F	22	4.97	(2.30, 10.76)	24	4.58	(2.36, 8.90)
23F	22	3.52	(1.68, 7.38)	24	2.96	(1.33, 6.56)
7 Additional						
8	22	1.33	(0.50, 3.56)	24	0.09	(0.04, 0.24)
10A	22	1.99	(0.63, 6.29)	24	0.03	(0.01, 0.09)
11A	22	1.50	(0.58, 3.87)	24	0.06	(0.02, 0.16)
12F	22	0.17	(0.05, 0.56)	24	0.02	(0.01, 0.03)
15B	22	4.90	(1.67, 14.37)	24	0.07	(0.03, 0.20)
22F	22	1.52	(0.38, 6.03)	24	0.02	(0.01, 0.08)
33F	22	1.38	(0.53, 3.59)	24	0.04	(0.02, 0.10)

Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. n = Number of participants with valid IgG concentrations for the specified serotype.
b. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student's t distribution).
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Percentage of Participants With Predefined Serotype-specific IgG Concentrations at 1 Month After Dose 2 and at 1 Month After Dose 3

Table 10. Number (%) of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population – Russian Cohort

		Vaccine Group (as Randomized)							
		20vPnC				13vPnC			
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC									
1	≥0.35 µg/mL	24	17	70.8	(48.9, 87.4)	27	21	77.8	(57.7, 91.4)
3	≥0.35 µg/mL	24	9	37.5	(18.8, 59.4)	27	16	59.3	(38.8, 77.6)
4	≥0.35 µg/mL	24	18	75.0	(53.3, 90.2)	27	20	74.1	(53.7, 88.9)
5	≥0.23 µg/mL	24	16	66.7	(44.7, 84.4)	27	22	81.5	(61.9, 93.7)
6A	≥0.35 µg/mL	24	13	54.2	(32.8, 74.4)	27	22	81.5	(61.9, 93.7)
6B	≥0.10 µg/mL	24	5	20.8	(7.1, 42.2)	27	16	59.3	(38.8, 77.6)
7F	≥0.35 µg/mL	24	23	95.8	(78.9, 99.9)	27	25	92.6	(75.7, 99.1)
9V	≥0.35 µg/mL	24	10	41.7	(22.1, 63.4)	27	22	81.5	(61.9, 93.7)
14	≥0.35 µg/mL	24	20	83.3	(62.6, 95.3)	27	23	85.2	(66.3, 95.8)
18C	≥0.35 µg/mL	24	16	66.7	(44.7, 84.4)	27	22	81.5	(61.9, 93.7)
19A	≥0.12 µg/mL	24	21	87.5	(67.6, 97.3)	27	25	92.6	(75.7, 99.1)
19F	≥0.35 µg/mL	24	19	79.2	(57.8, 92.9)	27	26	96.3	(81.0, 99.9)
23F	≥0.35 µg/mL	24	9	37.5	(18.8, 59.4)	27	19	70.4	(49.8, 86.2)
7 Additional									
8	≥0.35 µg/mL	24	18	75.0	(53.3, 90.2)	27	9	33.3	(16.5, 54.0)
10A	≥0.35 µg/mL	24	10	41.7	(22.1, 63.4)	27	5	18.5	(6.3, 38.1)
11A	≥0.35 µg/mL	24	20	83.3	(62.6, 95.3)	27	5	18.5	(6.3, 38.1)
12F	≥0.35 µg/mL	24	3	12.5	(2.7, 32.4)	27	4	14.8	(4.2, 33.7)
15B	≥0.35 µg/mL	24	16	66.7	(44.7, 84.4)	27	9	33.3	(16.5, 54.0)
22F	≥0.35 µg/mL	24	16	66.7	(44.7, 84.4)	27	4	14.8	(4.2, 33.7)
33F	≥0.35 µg/mL	24	11	45.8	(25.6, 67.2)	27	7	25.9	(11.1, 46.3)

Abbreviation: IgG = immunoglobulin G.

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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Table 11. Number (%) of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population – Russian Cohort

		Vaccine Group (as Randomized)							
		20vPnC				13vPnC			
Serotype	Predefined Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
13vPnC									
1	≥0.35 µg/mL	22	20	90.9	(70.8, 98.9)	24	20	83.3	(62.6, 95.3)
3	≥0.35 µg/mL	22	15	68.2	(45.1, 86.1)	24	12	50.0	(29.1, 70.9)
4	≥0.35 µg/mL	22	21	95.5	(77.2, 99.9)	24	24	100.0	(85.8, 100.0)
5	≥0.23 µg/mL	22	20	90.9	(70.8, 98.9)	24	22	91.7	(73.0, 99.0)
6A	≥0.35 µg/mL	22	21	95.5	(77.2, 99.9)	24	24	100.0	(85.8, 100.0)
6B	≥0.10 µg/mL	22	20	90.9	(70.8, 98.9)	24	22	91.7	(73.0, 99.0)
7F	≥0.35 µg/mL	22	21	95.5	(77.2, 99.9)	24	24	100.0	(85.8, 100.0)
9V	≥0.35 µg/mL	22	22	100.0	(84.6, 100.0)	24	20	83.3	(62.6, 95.3)
14	≥0.35 µg/mL	22	20	90.9	(70.8, 98.9)	24	24	100.0	(85.8, 100.0)
18C	≥0.35 µg/mL	22	20	90.9	(70.8, 98.9)	24	23	95.8	(78.9, 99.9)
19A	≥0.12 µg/mL	22	22	100.0	(84.6, 100.0)	24	23	95.8	(78.9, 99.9)
19F	≥0.35 µg/mL	22	22	100.0	(84.6, 100.0)	24	22	91.7	(73.0, 99.0)
23F	≥0.35 µg/mL	22	20	90.9	(70.8, 98.9)	24	19	79.2	(57.8, 92.9)
7 Additional									
8	≥0.35 µg/mL	22	15	68.2	(45.1, 86.1)	24	6	25.0	(9.8, 46.7)
10A	≥0.35 µg/mL	22	15	68.2	(45.1, 86.1)	24	4	16.7	(4.7, 37.4)
11A	≥0.35 µg/mL	22	17	77.3	(54.6, 92.2)	24	5	20.8	(7.1, 42.2)
12F	≥0.35 µg/mL	22	8	36.4	(17.2, 59.3)	24	1	4.2	(0.1, 21.1)
15B	≥0.35 µg/mL	22	20	90.9	(70.8, 98.9)	24	5	20.8	(7.1, 42.2)
22F	≥0.35 µg/mL	22	14	63.6	(40.7, 82.8)	24	3	12.5	(2.7, 32.4)
33F	≥0.35 µg/mL	22	16	72.7	(49.8, 89.3)	24	5	20.8	(7.1, 42.2)

IgG GMFRs from Before to 1 Month After Dose 3 and from 1 Month After Dose 2 to 1 Month After Dose 3

When Dose 3 (toddler dose) was administered after 2 infant doses, 20vPnC boosted serotype- specific IgG concentrations to all 20 vaccine serotypes compared to levels prior to the toddler dose. Additionally, for all serotypes, the responses 1 month after Dose 3 increased relative to the levels 1 month after Dose 2.

13 Matched Serotypes

For the 13 matched serotypes, increases in IgG concentrations *from before to 1 month after Dose 3* were observed in both groups across the 13 matched serotypes. IgG GMFRs ranged from 1.6 (serotype 7F) to 4.7 (serotype 19A) in the 20vPnC group, and from 2.6 (serotype 3) to 6.9 (serotype 6B) in the 13vPnC group.

Boosting *from 1 month after Dose 2 to 1 month after Dose 3* was also observed for both vaccine groups for all shared serotypes. IgG GMFRs ranged from 2.2 (serotype 1) to 31.3 (serotype 6B) in the 20vPnC group, and from 1.4 (serotype 3) to 6.2 (serotype 6B) in the 13vPnC group.

7 Additional Serotypes

Increases in IgG concentrations *from before to 1 month after Dose 3* of 20vPnC were also observed for the 7 additional serotypes, with the observed GMFRs ranging from 1.8 (serotype 12F) to 4.3 (serotype 11A) in the 20vPnC group. Boosting of IgG concentrations *from 1 month after Dose 2 to 1 month after Dose 3* of 20vPnC was also observed as the IgG GMFRs were all ⩾1.5, with the IgG GMFRs ranging from 1.5 (serotype 8) to 7.2 (serotype 10A). There were no or limited increases in antibody titres in the 13vPnC group for the 7 additional serotypes.

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

13 Matched Serotypes

For the 13 matched serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 31.8 % (serotypes 7F and 18C) to 45.5% (serotypes 6B, 19A, and 23F) in the 20vPnC group and from 33.3 % (serotype 3) to 58.3% (serotypes 6B and 18C) in the 13vPnC group.

7 Additional Serotypes

For the 7 additional serotypes, the percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 31.8 % (serotype 12F) to 50.0% (serotype 11A) in the 20vPnC group. A few participants had ⩾4-fold rises for the 7 additional serotypes in the 13vPnC group (ranged from 8.3 % [serotypes 15B and 22F] to 16.7 % [serotype 11A]).

Serotype-specific OPA Titres

OPA titres were measured only for random subsets of participants in this cohort due to sera volume requirements for each OPA assay, resulting in extremely limited number of available OPA titres, between 3-9 per group and per serotype.

14.13. Pneumococcal OPA GMTs at Each Specified Sampling Time Point – Evaluable Immunogenicity Population – Russian Cohort

		Vaccine Group (as Randomized)					
		20vPnC			13vPnC		
Serotype	Sampling Time Point	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
13vPnC							
1	1 Month after Dose 2	8	17	(7, 40)	9	33	(10, 105)
	Before Dose 3	7	14	(7, 29)	9	17	(6, 48)
	1 Month after Dose 3	8	85	(17, 421)	9	93	(22, 394)
3	1 Month after Dose 2	8	79	(42, 149)	9	31	(13, 73)
	Before Dose 3	7	73	(47, 114)	9	25	(11, 53)
	1 Month after Dose 3	8	126	(41, 383)	9	107	(37, 309)
4	1 Month after Dose 2	8	166	(38, 736)	9	163	(32, 840)
	Before Dose 3	8	223	(41, 1218)	8	147	(21, 1009)
	1 Month after Dose 3	8	310	(86, 1123)	8	429	(38, 4863)
5	1 Month after Dose 2	8	28	(11, 76)	9	31	(14, 71)
	Before Dose 3	8	28	(10, 75)	9	25	(11, 57)
	1 Month after Dose 3	8	116	(28, 476)	9	108	(26, 456)
6A	1 Month after Dose 2	8	222	(32, 1553)	9	247	(60, 1011)
	Before Dose 3	8	172	(22, 1329)	9	98	(23, 422)
	1 Month after Dose 3	7	2922	(311, 27459)	9	1580	(393, 6351)
6B	1 Month after Dose 2	7	314	(27, 3584)	8	216	(39, 1186)
	Before Dose 3	7	310	(28, 3437)	5	79	(6, 965)
	1 Month after Dose 3	7	4417	(998, 19551)	7	1397	(150, 12967)
7F	1 Month after Dose 2	8	809	(481, 1361)	9	717	(246, 2084)
	Before Dose 3	8	957	(473, 1935)	8	1081	(418, 2796)
	1 Month after Dose 3	8	1039	(509, 2122)	8	1411	(373, 5340)
9V	1 Month after Dose 2	8	218	(70, 676)	9	293	(85, 1008)
	Before Dose 3	8	432	(106, 1757)	8	280	(54, 1449)
	1 Month after Dose 3	8	1574	(369, 6711)	7	1067	(150, 7583)
14	1 Month after Dose 2	7	984	(492, 1970)	9	247	(69, 886)
	Before Dose 3	7	266	(54, 1324)	9	158	(48, 524)
	1 Month after Dose 3	7	1151	(321, 4132)	9	628	(137, 2890)
18C	1 Month after Dose 2	8	968	(403, 2326)	9	268	(43, 1655)
	Before Dose 3	8	523	(88, 3126)	8	153	(19, 1259)
	1 Month after Dose 3	8	583	(149, 2284)	8	973	(89, 10606)
19A	1 Month after Dose 2	7	314	(68, 1443)	9	31	(8, 118)
	Before Dose 3	6	284	(15, 5411)	7	34	(4, 300)
	1 Month after Dose 3	8	652	(131, 3234)	7	435	(14, 13833)
19F	1 Month after Dose 2	8	120	(27, 529)	9	230	(48, 1097)
	Before Dose 3	7	64	(13, 325)	9	58	(15, 223)
	1 Month after Dose 3	7	1570	(239, 10337)	9	701	(124, 3958)
23F	1 Month after Dose 2	8	35	(6, 196)	9	56	(9, 346)

14.13. Pneumococcal OPA GMTs at Each Specified Sampling Time Point – Evaluable Immunogenicity Population – Russian Cohort

		Vaccine Group (as Randomized)					
		20vPnC			13vPnC		
Serotype	Sampling Time Point	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])
	Before Dose 3	8	138	(13, 1427)	8	40	(4, 371)
	1 Month after Dose 3	8	152	(24, 966)	8	410	(22, 7594)
7 Additional							
8	1 Month after Dose 2	7	203	(19, 2155)	9	38	(9, 161)
	Before Dose 3	6	306	(23, 4017)	8	110	(14, 843)
	1 Month after Dose 3	4	368	(11, 12078)	6	149	(9, 2337)
10A	1 Month after Dose 2	6	559	(50, 6233)	5	232	(8, 6478)
	Before Dose 3	5	1153	(80, 16640)	7	185	(21, 1611)
	1 Month after Dose 3	4	2851	(1309, 6210)	6	117	(15, 916)
11A	1 Month after Dose 2	6	3537	(863, 14497)	7	2717	(470, 15716)
	Before Dose 3	5	1723	(121, 24493)	8	1753	(251, 12261)
	1 Month after Dose 3	4	7137	(1036, 49164)	4	1789	(36, 89068)
12F	1 Month after Dose 2	7	698	(77, 6301)	9	198	(41, 960)
	Before Dose 3	5	933	(59, 14826)	8	160	(17, 1512)
	1 Month after Dose 3	4	757	(15, 37522)	7	241	(16, 3734)
15B	1 Month after Dose 2	7	142	(9, 2269)	8	242	(18, 3267)
	Before Dose 3	6	1302	(86, 19699)	8	426	(38, 4723)
	1 Month after Dose 3	5	822	(42, 16070)	7	147	(10, 2214)
22F	1 Month after Dose 2	7	413	(32, 5406)	8	499	(28, 8837)
	Before Dose 3	5	427	(15, 11907)	7	1426	(128, 15871)
	1 Month after Dose 3	4	1983	(390, 10085)	7	1635	(165, 16157)
33F	1 Month after Dose 2	7	3508	(349, 35250)	9	3961	(706, 22238)
	Before Dose 3	3	1216	(373, 3966)	7	3174	(656, 15368)
	1 Month after Dose 3	3	5903	(53, 657862)	7	3619	(948, 13817)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: The Dose 2 evaluable immunogenicity population was used for all time points, except for 1 month after Dose 3, which used the Dose 3 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 ensuring 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's t distribution).

2.8. Safety Results

Local Reactions

Table 12. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population – Russian Cohort

		Vaccine Group (as Administered)					
		20vPnC			13vPnC		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Dose 1	Redness[d]	24			27		
	Any		2 (8.3)	(1.0, 27.0)		3 (11.1)	(2.4, 29.2)
	Mild		1 (4.2)	(0.1, 21.1)		2 (7.4)	(0.9, 24.3)
	Moderate		1 (4.2)	(0.1, 21.1)		1 (3.7)	(0.1, 19.0)
	Severe		0	(0.0, 14.2)		0	(0.0, 12.8)
	Swelling[d]	24			27		
	Any		1 (4.2)	(0.1, 21.1)		0	(0.0, 12.8)
	Mild		0	(0.0, 14.2)		0	(0.0, 12.8)
	Moderate		1 (4.2)	(0.1, 21.1)		0	(0.0, 12.8)
	Severe		0	(0.0, 14.2)		0	(0.0, 12.8)
	Pain at injection site[e]	24			27		
	Any		2 (8.3)	(1.0, 27.0)		3 (11.1)	(2.4, 29.2)
	Mild		2 (8.3)	(1.0, 27.0)		2 (7.4)	(0.9, 24.3)
	Moderate		0	(0.0, 14.2)		1 (3.7)	(0.1, 19.0)
	Severe		0	(0.0, 14.2)		0	(0.0, 12.8)
	Any local reaction[f]	24	4 (16.7)	(4.7, 37.4)	27	5 (18.5)	(6.3, 38.1)
Dose 2	Redness[d]	23			27		
	Any		1 (4.3)	(0.1, 21.9)		1 (3.7)	(0.1, 19.0)
	Mild		0	(0.0, 14.8)		1 (3.7)	(0.1, 19.0)
	Moderate		1 (4.3)	(0.1, 21.9)		0	(0.0, 12.8)
	Severe		0	(0.0, 14.8)		0	(0.0, 12.8)
	Swelling[d]	23			27		
	Any		2 (8.7)	(1.1, 28.0)		2 (7.4)	(0.9, 24.3)
	Mild		0	(0.0, 14.8)		2 (7.4)	(0.9, 24.3)
	Moderate		2 (8.7)	(1.1, 28.0)		0	(0.0, 12.8)
	Severe		0	(0.0, 14.8)		0	(0.0, 12.8)
	Pain at injection site[e]	23			27		
	Any		3 (13.0)	(2.8, 33.6)		2 (7.4)	(0.9, 24.3)
	Mild		2 (8.7)	(1.1, 28.0)		2 (7.4)	(0.9, 24.3)
	Moderate		1 (4.3)	(0.1, 21.9)		0	(0.0, 12.8)
	Severe		0	(0.0, 14.8)		0	(0.0, 12.8)
	Any local reaction[f]	23	3 (13.0)	(2.8, 33.6)	27	4 (14.8)	(4.2, 33.7)
Dose 3	Redness[d]	22			25		
	Any		1 (4.5)	(0.1, 22.8)		2 (8.0)	(1.0, 26.0)

Table 12. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population – Russian Cohort

		Vaccine Group (as Administered)					
		20vPnC			13vPnC		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Mild		0	(0.0, 15.4)		1 (4.0)	(0.1, 20.4)
	Moderate		1 (4.5)	(0.1, 22.8)		0	(0.0, 13.7)
	Severe		0	(0.0, 15.4)		1 (4.0)	(0.1, 20.4)
	Swelling[d]	22			25		
	Any		2 (9.1)	(1.1, 29.2)		1 (4.0)	(0.1, 20.4)
	Mild		0	(0.0, 15.4)		0	(0.0, 13.7)
	Moderate		2 (9.1)	(1.1, 29.2)		0	(0.0, 13.7)
	Severe		0	(0.0, 15.4)		1 (4.0)	(0.1, 20.4)
	Pain at injection site[e]	22			25		
	Any		3 (13.6)	(2.9, 34.9)		2 (8.0)	(1.0, 26.0)
	Mild		3 (13.6)	(2.9, 34.9)		2 (8.0)	(1.0, 26.0)
	Moderate		0	(0.0, 15.4)		0	(0.0, 13.7)
	Severe		0	(0.0, 15.4)		0	(0.0, 13.7)
	Any local reaction[f]	22	5 (22.7)	(7.8, 45.4)	25	3 (12.0)	(2.5, 31.2)

Note: Local reactions were collected in the e-diary from Day 1 through Day 7 after each dose. If a severe reaction was identified by the investigator as a Grade 4 reaction at a follow-up assessment, it was also reported as an adverse event.
a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.
e. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
f. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.

Table 13. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Safety Population – Russian Cohort

		Vaccine Group (as Administered)					
		20vPnC			13vPnC		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Dose 1	Fever	24			27		
	≥38.0°C		1 (4.2)	(0.1, 21.1)		0	(0.0, 12.8)
	≥38.0°C to 38.4°C		1 (4.2)	(0.1, 21.1)		0	(0.0, 12.8)
	>38.4°C to 38.9°C		0	(0.0, 14.2)		0	(0.0, 12.8)
	>38.9°C to 40.0°C		0	(0.0, 14.2)		0	(0.0, 12.8)
	>40.0°C		0	(0.0, 14.2)		0	(0.0, 12.8)
	Decreased appetite[d]	24			27		
	Any		4 (16.7)	(4.7, 37.4)		5 (18.5)	(6.3, 38.1)
	Mild		4 (16.7)	(4.7, 37.4)		4 (14.8)	(4.2, 33.7)
	Moderate		0	(0.0, 14.2)		1 (3.7)	(0.1, 19.0)
	Severe		0	(0.0, 14.2)		0	(0.0, 12.8)
	Drowsiness[e]	24			27		
	Any		7 (29.2)	(12.6, 51.1)		8 (29.6)	(13.8, 50.2)
	Mild		5 (20.8)	(7.1, 42.2)		5 (18.5)	(6.3, 38.1)
	Moderate		2 (8.3)	(1.0, 27.0)		3 (11.1)	(2.4, 29.2)
	Severe		0	(0.0, 14.2)		0	(0.0, 12.8)
	Irritability[f]	24			27		
	Any		6 (25.0)	(9.8, 46.7)		6 (22.2)	(8.6, 42.3)
	Mild		3 (12.5)	(2.7, 32.4)		2 (7.4)	(0.9, 24.3)
	Moderate		2 (8.3)	(1.0, 27.0)		4 (14.8)	(4.2, 33.7)
	Severe		1 (4.2)	(0.1, 21.1)		0	(0.0, 12.8)
	Any systemic event[g]	24	8 (33.3)	(15.6, 55.3)	27	10 (37.0)	(19.4, 57.6)
	Use of antipyretic or pain medication[h]	24	1 (4.2)	(0.1, 21.1)	27	0	(0.0, 12.8)
Dose 2	Fever	23			27		
	≥38.0°C		1 (4.3)	(0.1, 21.9)		3 (11.1)	(2.4, 29.2)
	≥38.0°C to 38.4°C		0	(0.0, 14.8)		3 (11.1)	(2.4, 29.2)
	>38.4°C to 38.9°C		1 (4.3)	(0.1, 21.9)		0	(0.0, 12.8)
	>38.9°C to 40.0°C		0	(0.0, 14.8)		0	(0.0, 12.8)
	>40.0°C		0	(0.0, 14.8)		0	(0.0, 12.8)
	Decreased appetite[d]	23			27		
	Any		2 (8.7)	(1.1, 28.0)		3 (11.1)	(2.4, 29.2)
	Mild		1 (4.3)	(0.1, 21.9)		2 (7.4)	(0.9, 24.3)
	Moderate		1 (4.3)	(0.1, 21.9)		1 (3.7)	(0.1, 19.0)

Table 13. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Safety Population – Russian Cohort

		Vaccine Group (as Administered)					
		20vPnC			13vPnC		
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
	Severe		0	(0.0, 14.8)		0	(0.0, 12.8)
	Drowsiness[e]	23			27		
	Any		1 (4.3)	(0.1, 21.9)		2 (7.4)	(0.9, 24.3)
	Mild		1 (4.3)	(0.1, 21.9)		1 (3.7)	(0.1, 19.0)
	Moderate		0	(0.0, 14.8)		1 (3.7)	(0.1, 19.0)
	Severe		0	(0.0, 14.8)		0	(0.0, 12.8)
	Irritability[f]	23			27		
	Any		4 (17.4)	(5.0, 38.8)		12 (44.4)	(25.5, 64.7)
	Mild		3 (13.0)	(2.8, 33.6)		6 (22.2)	(8.6, 42.3)
	Moderate		1 (4.3)	(0.1, 21.9)		5 (18.5)	(6.3, 38.1)
	Severe		0	(0.0, 14.8)		1 (3.7)	(0.1, 19.0)
	Any systemic event[g]	23	5 (21.7)	(7.5, 43.7)	27	13 (48.1)	(28.7, 68.1)
	Use of antipyretic or pain medication[h]	23	1 (4.3)	(0.1, 21.9)	27	2 (7.4)	(0.9, 24.3)
Dose 3	Fever	22			25		
	≥38.0°C		1 (4.5)	(0.1, 22.8)		1 (4.0)	(0.1, 20.4)
	≥38.0°C to 38.4°C		0	(0.0, 15.4)		0	(0.0, 13.7)
	>38.4°C to 38.9°C		0	(0.0, 15.4)		1 (4.0)	(0.1, 20.4)
	>38.9°C to 40.0°C		1 (4.5)	(0.1, 22.8)		0	(0.0, 13.7)
	>40.0°C		0	(0.0, 15.4)		0	(0.0, 13.7)
	Decreased appetite[d]	22			25		
	Any		4 (18.2)	(5.2, 40.3)		2 (8.0)	(1.0, 26.0)
	Mild		2 (9.1)	(1.1, 29.2)		2 (8.0)	(1.0, 26.0)
	Moderate		2 (9.1)	(1.1, 29.2)		0	(0.0, 13.7)
	Severe		0	(0.0, 15.4)		0	(0.0, 13.7)
	Drowsiness[e]	22			25		
	Any		3 (13.6)	(2.9, 34.9)		6 (24.0)	(9.4, 45.1)
	Mild		3 (13.6)	(2.9, 34.9)		5 (20.0)	(6.8, 40.7)
	Moderate		0	(0.0, 15.4)		1 (4.0)	(0.1, 20.4)
	Severe		0	(0.0, 15.4)		0	(0.0, 13.7)
	Irritability[f]	22			25		
	Any		8 (36.4)	(17.2, 59.3)		6 (24.0)	(9.4, 45.1)
	Mild		6 (27.3)	(10.7, 50.2)		4 (16.0)	(4.5, 36.1)
	Moderate		2 (9.1)	(1.1, 29.2)		2 (8.0)	(1.0, 26.0)
	Severe		0	(0.0, 15.4)		0	(0.0, 13.7)
	Any systemic event[g]	22	9 (40.9)	(20.7, 63.6)	25	9 (36.0)	(18.0, 57.5)
	Use of antipyretic or pain medication[h]	22	3 (13.6)	(2.9, 34.9)	25	2 (8.0)	(1.0, 26.0)

Note: Systemic events and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after each dose. If a severe event was identified by the investigator as a Grade 4 event at a follow-up assessment, it was also reported as an adverse event.
a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
e. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling, not interested in usual daily activity.
f. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
g. Any systemic event: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
h. The numbers in the table reflect yes responses (ie, number of events reported).

Summary of Adverse Events

14.22. Adverse Events Reported From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Safety Population – Russian Cohort

	Vaccine Group (as Administered)					
	20vPnC (N[a]=24)			13vPnC (N[a]=27)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	2	8.3	(1.0, 27.0)	1	3.7	(0.1, 19.0)
Gastrointestinal disorders	1	4.2	(0.1, 21.1)	0	0	(0.0, 12.8)
Infantile colic	1	4.2	(0.1, 21.1)	0	0	(0.0, 12.8)
Infections and infestations	0	0	(0.0, 14.2)	1	3.7	(0.1, 19.0)
Oral candidiasis	0	0	(0.0, 14.2)	1	3.7	(0.1, 19.0)
Skin and subcutaneous tissue disorders	1	4.2	(0.1, 21.1)	0	0	(0.0, 12.8)
Urticaria	1	4.2	(0.1, 21.1)	0	0	(0.0, 12.8)

Note: MedDRA (v26.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

14.23. Adverse Events Reported From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Safety Population – Russian Cohort

	Vaccine Group (as Administered)					
	20vPnC (N[a]=22)			13vPnC (N[a]=25)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	1	4.5	(0.1, 22.8)	0	0	(0.0, 13.7)
Infections and infestations	1	4.5	(0.1, 22.8)	0	0	(0.0, 13.7)
Upper respiratory tract infection	1	4.5	(0.1, 22.8)	0	0	(0.0, 13.7)

Note: MedDRA (v26.0) coding dictionary applied.
a. N = number of participants who received Dose 3 in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event," n = number of participants reporting at least 1 occurrence of any event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

Related Adverse Events and Immediate Adverse Events

There were no related AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 in the 20vPnC and 13vPnC groups. There were no immediate AEs in the 20vPnC and 13vPnC groups.

Severe Adverse Events and Newly Diagnosed Chronic Medical Conditions

There were no severe AEs reported in the 20vPnC and 13vPnC groups. There were no NDCMCs in the 20vPnC and 13vPnC groups.

Deaths and Serious Adverse Events

There were no deaths during the study. There were no SAEs reported in the 20vPnC and 13vPnC groups.

There were no discontinuations from study intervention or the study due to AEs.

3. Scientific discussion

3.1. Design and Conduct of Clinical Study

Study B7471012 was conducted at investigator sites in Europe and Australia, with additional sites in Russia (Russian cohort). The Russian cohort was not intended to be included in the primary study population (Europe and Australia) due to several differences in study design e.g. slightly different inclusion criterion for age, different timing of visits and the broader age range for Dose 3 vaccination, MMR and varicella vaccination were not given as concomitant study vaccines. The data for the Russian Cohort data was summarized only descriptively. Only 51 subjects were randomised in the Russian cohort (compared to ~1200 in the primary study population).

Considering the differences between the Russian Cohort and the primary study population, separate evaluation of cohorts can be followed.

Demographic and baseline characteristics of race, ethnicity, and age for the safety population were generally similar in the 20vPnC and 13vPnC groups. More female infants were enrolled in the 20vPnC group than the 13vPnC group, which is not considered an issue.

Blood samples were collected from all participants at Visits 3 (1 month after Dose 2), 4 (prior to Dose 3), and 5 (1 month after Dose 3) for measurement of IgG concentration and OPA titres (immunogenicity time points). No immunogenicity data prior to dose 2 is available. Hence, no information is provided about the serostatus before Dose 1 or the initial immune responses to the vaccines.

OPA titres were determined only on subsets (3-9 individuals per group) of participants. This low sample size limits possible conclusions on the functionality of the antibody response induced by the investigated pneumococcal vaccines.

Safety events were recorded using an e-diary. AEs were collected from the signing of the ICD through and including Visit 3 and from Visit 4 through Visit 5. SAEs and NDCMCs were collected from the signing of the ICD to the final visit (Visit 5). The safety assessments are considered acceptable.

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

3.2. Immunogenicity Discussion

A variation application for the extension of indication to children has already been submitted to EMA and is currently under assessment (EMEA/H/C/005451/II/0012). No questions are raised in this P46 procedure regarding the immunogenicity results of the Russian cohort.

Interpretations and conclusions from the immunogenicity evaluation of the Russian cohort are limited due to the small sample size.

The immunogenicity data of the Russian Cohort were only summarized descriptively:

The primary Pneumococcal Immunogenicity Objective was to describe the IgG responses induced by 20vPnC in the Russian Cohort examining Pneumococcal IgG concentrations for each of the 20 serotypes in comparison to the 13vPnC group. The primary analysis was performed one month after the primary series (post-Dose 2; IgG GMCs and percentages of participants with predefined IgG concentrations) and 1 month after Dose 3 (toddler dose; IgG GMCs).

Immune response after last infant dose (Dose 2)

<u>13 shared serotypes</u>

Observed pneumococcal IgG GMCs at 1 month after Dose 2 were lower after 20vPnC compared to 13vPnC for 12/13 shared serotypes.

Likewise, the observed percentages of participants with predefined serotype-specific IgG concentrations (response rate) at 1 month after Dose 2 were lower in the 20vPnC group for the majority of shared serotypes. The response rate ranged from 20.8% (serotype 6B) to 95.8% (serotype 7F) in the 20vPnC group; and from 59.3% (serotypes 3 and 6B) to 96.3% (serotype 19F) in the 13vPnC group for the 13 matched serotypes.

<u>7 additional serotypes</u>

20vPnC elicited substantially higher immune responses to the majority of additional 7 serotypes compared to 13vPnC, as assessed by IgG GMCs at 1 month after Dose 2. Observed IgG GMCs for the serotype 12F in the 20vPnC group were low (0.06 µg/mL).

The observed response rate ranged from 12.5% (serotype 12F) to 83.3% (serotype 11A) for the 7 additional serotypes in the 20vPnC group. Immune responses to the 7 additional serotypes were also detected in the 13vPnC group. The response rate in the 13vPnC group ranged from 14.8% (serotype 12F) to 33.3% (serotypes 8 and 15B). 13vPnC does not contain the conjugates for the 7 serotypes and according to the Applicant, observed responses represent background levels including maternally transferred IgG antibody. This finding was not observed in the primary study population and the reference to maternally transferred antibodies has not been further substantiated. However, the IgG GMCs to 7 additional serotypes in the 13vPnC group were generally very low.

Immune response after toddler dose (Dose 3)

13 matched serotypes

IgG GMCs at 1 month after Dose 3 were overall comparable between vaccine groups across the 13 shared serotypes. The observed response rates were also comparable between 20vPnC and 13vPnC groups reaching >80% for almost all serotypes. The response rates were ≥90.9% in the 20vPnC group for 12 of the 13 matched serotypes. In the 13vPnC group, the observed percentages of participants with predefined serotyped-specific IgG concentrations were ≥79.2% for 12 of the 13 matched serotypes. Therefore, immunogenicity of 20vPnC is substantially improved after Dose 3 compared to after Dose 2.

7 additional serotypes

Overall, 20vPnC elicited substantially higher immune responses to the additional 7 serotypes compared to 13vPnC, as assessed by IgG GMCs at 1 month after Dose 3.

The observed percentages of participants with predefined serotype-specific IgG concentrations were substantially higher after 20vPnC compared to 13vPnC and ranged from 36.4% (serotype 12F) to 90.9% (serotype 15B) in the 20vPnC group, and from 4.2% (serotype 12F) to 25.0% (serotype 8) in the 13vPnC group. In a small number of participants in 13vPnC group, the IgG titres for some or all additional serotypes were unexpectedly high, however for most subjects, titres were generally low.

Rise in IgG concentrations

13 Matched Serotypes

For the 13 matched serotypes, increases in IgG concentrations from before to 1 month after Dose 3 of 20vPnC or 13vPnC were observed in both vaccine groups across the 13 matched serotypes. IgG GMFRs ranged from 1.6 (serotype 7F) to 4.7 (serotype 19A) in the 20vPnC group, and from 2.6 (serotype 3) to 6.9 (serotype 6B) in the 13vPnC group. Boosting from 1 month after Dose 2 to 1 month after Dose 3 was also observed for both vaccine groups for all shared serotypes.

This supportive evidence indicates the priming of a memory response against the 13 shared serotypes in both vaccine groups following the infant doses.

7 Additional Serotypes

Increases in IgG concentrations from before to 1 month after Dose 3 of 20vPnC were also observed for the 7 additional serotypes, with the observed GMFRs ranging from 1.8 (serotype 12F) to 4.3 (serotype 11A) in the 20vPnC group. Boosting of IgG concentrations from 1 month after Dose 2 to 1 month after Dose 3 of 20vPnC was also observed as the IgG GMFRs were all ⩾1.5, with the IgG GMFRs ranging from 1.5 (serotype 8) to 7.2 (serotype 10A).

The percentages of participants with a ≥4-fold rise in IgG concentrations from before to 1 month after Dose 3 ranged from 31.8 % (serotype 12F) to 50.0% (serotype 11A) in the 20vPnC group.

Serotype-specific OPA Titres

Regarding the functionally important opsonophagocytic activity (OPA), titres were measured only in a very small subset of participants in this cohort due to sera volume requirements for each OPA assay, (between 3-9 per group and per serotype). Hence, only very limited conclusions can be drawn from this small dataset. In addition, no correlate of protection exists with this readout.

Both vaccine groups elicited OPA responses (GMTs) for the 13 shared serotypes after Dose 2 and 3 and an increased OPA response after Dose 3. OPA titres against the 13 shared serotypes after Dose 2 were generally comparable between 13vPnC and 20vPnC groups. Responses to the 7 additional serotypes were also observed in both vaccine groups. For the 7 additional serotypes, albeit responses were overall stronger in the 20vPnC group compared to the 13vPnC group.

3.3. Conclusion on Immunogenicity

The clinical conclusions that can be derived from the small and descriptive dataset of the Russian Cohort are limited.

20vPnC elicited immune responses to all 20 serotypes. However, consistently lower IgG responses were observed with 20vPnC compared to 13vPnC for the majority of the 13 shared serotypes after Dose 2. After 3 doses, immunogenicity was comparable between 20vPnC and 13vPnC groups.

Responses to the 7 additional serotypes were generally higher after 20vPnC compared to 13vPnC. The response rates to the 7 additional serotypes with 13vPnC were unexpectedly high, given that 13vPnC does not contain these additional serotypes.

According to the Applicant, these represent background levels including maternally transferred IgG antibody. This finding was not observed in the primary study population and the reference to maternally transferred antibodies has not been further substantiated. In contrast, the IgG GMCs to 7 additional serotypes in the 13vPnC group were very low for most sera, as expected.

Apart from the higher-than-expected response rate to the additional serotypes with 13vPnC, the findings derived from the Russian Cohort (N≈50) are in line with data obtained with the primary study cohort (N≈1200).

3.4. Safety Discussion

Only limited conclusions can be drawn based on the small sample size of the Russian Cohort.

Across all administered doses, the observed percentages of participants with prompted local reactions were generally similar (<20%) in the 20vPnC and 13vPnC groups after Dose 1 and Dose 2. After Dose 3 however, local reactions occurred more frequently in the 20vPnC group (22.7%) compared to the 13vPnC group (12.0%). The most frequently reported local reactions after Dose 1 were redness and pain at injection site and the most frequently reported local reaction after Doses 2 and 3 was pain at injection site.

Local reactions such as redness and swelling were mostly mild or moderate in severity. The number and percentage of participants with systemic events (most frequently drowsiness or irritability) after all Doses were overall low and similar in the 20vPnC and 13vPnC groups. Fever was reported in both vaccine groups in 1-3 participants (up 11.1% of individuals in the 13vPnC group) across all doses. One participant in the 20vPnC had a fever of ≥38.0 for 5 days after Dose 3. There were no cases of fever above 40°C in either vaccine group.

The AE rates were low in both groups (3 participants had AEs in the 20vPnC group; 1 participant had an AE in the 13vPnC group). AEs in the 20vPnC group included infantile colic, urticaria and upper respiratory tract infection; the AE in the 13vPnC group was oral candidiasis.

Overall, 20vPnC and 13vPnC groups exhibited comparable safety profiles.

Importantly, there were no deaths, related AEs, SAEs, or NDCMCs reported in either the 20vPnC or the 13vPnC groups. There were no discontinuations from study intervention or the study due to AEs.

Taken together, no significant safety issues were identified in the small dataset of the Russian cohort and the mostly mild AEs were similarly distributed across vaccine groups.

4. Overall conclusion

The MAH submitted results of study B7471012: *Supplemental Report, Russian Cohort – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants*, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended.

Study B7471012 is part of the Paediatric Investigation Plan P/0239/2022.

Currently there is no data regarding infants in the EU SmPC of Apexxnar. The purpose of study B7471012 was to generate data on the safety and immunogenicity of 20vPnC in infants when administered as a series of 2 infant doses and 1 toddler dose. It was part of the Phase 3 paediatric clinical development program to support the use of 20vPnC in the paediatric population. The results of B7471012 (primary population) were submitted to the EMA in scope of a type II variation to add a paediatric indication, EMEA/H/C/005451/II/0012, which is currently under assessment.

The submitted Russian cohort was not intended to be included in the primary study population and was evaluated separately in a descriptive manner due to differences in study design, which is acceptable.

Overall, results from the Russian Cohort are similar to the results from the primary population.

No questions are raised regarding the results of the Russian Cohort and no further actions are required.

☒ PAM fulfilled

No regulatory action required.