EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2023
EMA/67314/2023
Human Medicines Division

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

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no: EMEA/H/C/001104/P46/067

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 17 October 2022, the MAH submitted the results of paediatric study B7471016 for the assessment of Prevenar 13, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) EU/1/09/590/001-016, EMEA/H/C/1104, as amended and in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study title and number is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study B7471016

13vPnC was a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM197. The vaccine was formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contained 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminium as aluminium phosphate, per 0.5-mL dose.
The 13vPnC supply was considered representative of Prevnar 13, as it was manufactured according to the approved Prevnar 13 commercial drug product process using commercially released vaccine drug substances.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study B7471016.

Study B7471016 is a Phase 3, randomized, double-blind, third-party unblinded trial to evaluate the safety and immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine (20vPnC) in healthy Japanese infants. The purpose of the B7471016 study was to provide key safety and comparative immunogenicity data between 20vPnC and the 13vPnC in Japanese infants to help support licensure for 20vPnC paediatric use in Japan. Participants aged 2 to 6 months were randomised to receive 4 doses of 20vPnC (by subcutaneous (SC) or intramuscular injection), or 13vPnC (by SC injection as a control).

This assessment concerns only participants receiving the 13vPnC vaccine in accordance with Article 46 of Regulation (EC) No1901/2006.

2.3.2. Clinical study B7471016

Description

Methods

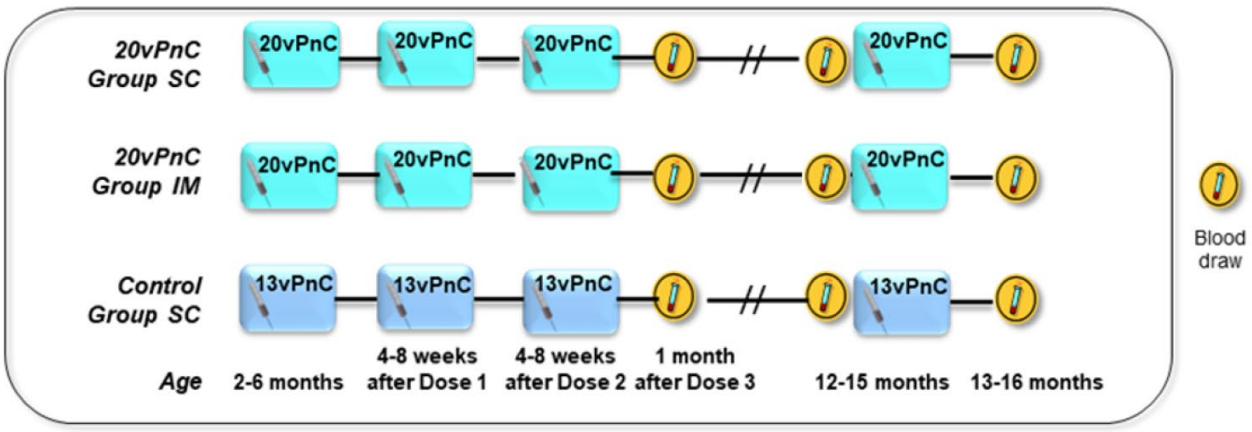
Study participants

This study enrolled approximately 666 infants between 2 through 6 months of age at the time of consent by their parent(s)/legal guardian(s). Participants were randomized equally to one of the following vaccine groups:

20vPnC SC group, 13vPnC SC group (control vaccine), or 20vPnC IM group.

Hereafter, only information and data from the 13vPnC SC group (control vaccine) is described and discussed.

Participants received the same vaccine by the same injection method (SC injection) for all 4 doses at visits 1, 2, 3, and 5. All vaccine groups were blinded to all members of the site involved in the study except unblinded site staff who administered 13vPnC. A brief overview of the study design is presented in Figure 1.



Treatments

Participants received 1 dose of 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5 with Doses 1, 2, 3, and 4). 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.

13vPnC was administered SC by injecting 0.5 mL into the anterolateral thigh (preferably into the left anterolateral thigh) at the vaccination visits.

Randomisation and blinding (masking)

This was a double-blind, third party unblinded study. The study staff administering the vaccine and confirming the administration route of study intervention were unblinded, but all other site study personnel, including the PI and the parent(s)/guardian(s) of the participant, were blinded. Designated

study team members who were involved in ensuring that protocol requirements for study intervention handling, allocation, and administration were fulfilled at sites were unblinded. All other study team members and all laboratory personnel performing the serology assays remained blinded to vaccine assigned/received throughout the study.

CHMP rapporteur comments:

In the methods described for paediatric study B7471016 it is noted and that all participants in the 13vPnCV group received 0,5 mL of Prevenar 13, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), by a subcutaneous route of administration.

Despite that subcutaneous route of administration is not used in Europe the methods described for study B7471016 for the assessment of Prevenar 13, are relevant and in accordance with Article 46 of the Regulation (EC) No1901/2006.

Results

Number analysed

A total of 668 participants were randomized and 649 (97.2%) participants completed all visits in the study. Disposition of all randomized participants was balanced across vaccine groups. A total of 224 participants were randomized to receive 13vPnC administered SC (Table 2). Of the participants withdrawn from the study, the most common reason was withdrawn by parent/guardian.

Demographic and baseline characteristics of sex, race, ethnicity, and age for the safety population were balanced across the vaccine groups. Across the vaccine groups, all participants were Asian (Japanese), and 49.4% were males. Demographic characteristics for the Dose 3 and Dose 4 evaluable immunogenicity populations were similar to those for the safety population.

Important Protocol Deviations (PDs)

No important PDs that may significantly impact the completeness, accuracy, and/or reliability of the trial occurred in the 13vPnC group. Four (4) PDs were specifically attributed to COVID-19 occurrence. These PDs were due to visits being performed outside the protocol-specified window and were not considered important.

Populations Analyzed

Table 3 provide a summary of participants excluded from the immunogenicity and safety populations, respectively, with reasons for exclusion.

Table 3. Immunogenicity Population for All-Available and Evaluable Participants

	Vaccine Group (as Randomized)			
	20vPnC (SC) n[a] (%)	13vPnC (SC) n[a] (%)	20vPnC (IM) n[a] (%)	Total n[a] (%)
Randomized[b]	226 (100.0)	224 (100.0)	218 (100.0)	668 (100.0)
All-available immunogenicity population	223 (98.7)	221 (98.7)	215 (98.6)	659 (98.7)
Participants excluded from all-available immunogenicity population	3 (1.3)	3 (1.3)	3 (1.4)	9 (1.3)
Reasons for exclusion				
Did not receive any vaccination	0	0	1 (0.5)	1 (0.1)
No valid immunogenicity result	3 (1.3)	3 (1.3)	2 (0.9)	8 (1.2)
Dose 3 evaluable immunogenicity population	221 (97.8)	220 (98.2)	213 (97.7)	654 (97.9)
Participants excluded from Dose 3 evaluable immunogenicity population[c]	5 (2.2)	4 (1.8)	5 (2.3)	14 (2.1)
Reasons for exclusion				
Did not receive assigned vaccine, as randomized, for first 3 doses	4 (1.8)	3 (1.3)	3 (1.4)	10 (1.5)
Did not have blood collected within 27 to 56 days, inclusive, after Dose 3	0	0	2 (0.9)	2 (0.3)
Did not have valid immunogenicity result for at least 1 serotype at 1 month after Dose 3	1 (0.4)	1 (0.4)	0	2 (0.3)
Dose 4 evaluable immunogenicity population	217 (96.0)	220 (98.2)	211 (96.8)	648 (97.0)
Participants excluded from Dose 4 evaluable immunogenicity population[c]	9 (4.0)	4 (1.8)	7 (3.2)	20 (3.0)
Reasons for exclusion				
Did not receive assigned vaccine, as randomized, for all 4 doses	8 (3.5)	4 (1.8)	6 (2.8)	18 (2.7)
Did not have blood collected within 27 to 56 days, inclusive, after Dose 4	1 (0.4)	0	1 (0.5)	2 (0.3)

Abbreviations: IM = intramuscular; SAP = statistical analysis plan; SC = subcutaneous.
a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations by subpopulation.
c. Reasons are listed in hierarchical order. Each excluded participant is counted only once under the first applicable reason.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2022 (14:06) Source Data: adsl Table Generation: 09AUG2022 (10:07)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adsl_all_eval

Exposure

Vaccine administration by dose and non-study vaccines also administered with the 20vPnC or 13vPnC doses are presented in Table 5. Table 5 includes concomitant vaccines which were specified to be administered concomitantly with study intervention at intervals consistent with the vaccination schedule recommended by the Japan Pediatric Society. Approximately 50% of participants received a third dose of rotavirus vaccine according to the rotavirus vaccine schedule (either 2 or 3 infant doses for monovalent or pentavalent, respectively).

Table 5. Vaccine Administration by Vaccine Group – All Randomized Participants

Vaccine (as Administered)	Vaccine Group (as Randomized) 20vPnC (SC) n[a] (%)	13vPnC (SC) n[a] (%)	20vPnC (IM) n[a] (%)	Total n[a] (%)
Randomized[b]	N=226	N=224	N=218	N=668
Not vaccinated[c]	0	0	1 (0.5)	1 (0.1)
Dose 1[d]	N=226	N=224	N=217	N=667
Study intervention	226 (100.0)	224 (100.0)	217 (100.0)	667 (100.0)
Hib	226 (100.0)	224 (100.0)	217 (100.0)	667 (100.0)
HBV	226 (100.0)	224 (100.0)	217 (100.0)	667 (100.0)
Rotavirus	226 (100.0)	224 (100.0)	217 (100.0)	667 (100.0)
Dose 2[d]	N=224	N=222	N=215	N=661
Study intervention	224 (100.0)	222 (100.0)	215 (100.0)	661 (100.0)
Hib	224 (100.0)	222 (100.0)	215 (100.0)	661 (100.0)
DTaP-IPV	224 (100.0)	222 (100.0)	215 (100.0)	661 (100.0)
HBV	224 (100.0)	222 (100.0)	215 (100.0)	661 (100.0)
Rotavirus	224 (100.0)	222 (100.0)	215 (100.0)	661 (100.0)
Dose 3[d]	N=223	N=221	N=215	N=659
Study intervention	223 (100.0)	221 (100.0)	215 (100.0)	659 (100.0)
Hib	223 (100.0)	221 (100.0)	215 (100.0)	659 (100.0)
DTaP-IPV	223 (100.0)	221 (100.0)	215 (100.0)	659 (100.0)
Pentavalent rotavirus vaccine	102 (45.7)	113 (51.1)	106 (49.3)	321 (48.7)
Dose 4[d]	N=219	N=220	N=212	N=651
Study intervention	219 (100.0)	220 (100.0)	212 (100.0)	651 (100.0)
Hib	219 (100.0)	220 (100.0)	212 (100.0)	651 (100.0)
DTaP-IPV	219 (100.0)	220 (100.0)	212 (100.0)	651 (100.0)
MR	219 (100.0)	220 (100.0)	212 (100.0)	651 (100.0)
Varicella	217 (99.1)	220 (100.0)	212 (100.0)	649 (99.7)

Abbreviations: IM = intramuscular; MR = measles and rubella vaccine; SC = subcutaneous.
Note: 1 participant randomized to 20vPnC (SC) received DTaP-IPV with Dose 1 in addition to Doses 2, 3 and 4.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. This value is the denominator for the percentage calculations for the "not vaccinated" row.
c. Not vaccinated with 20vPnC or 13vPnC.
d. N = number of participants receiving the specified dose. This value is the denominator for the percentage calculations for the specified dose.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2022 (14:04) Source Data: adsl Table Generation: 09AUG2022 (10:26)
(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adsl_s003_rand

Efficacy results

Immunogenicity Assessments

IgG concentrations and OPA titers were measured in sera collected at the 3 immunogenicity time points (Visits 4, 5, and 6). OPA titers were measured in a randomly selected subset of participants.

MAH conclusion on response to 20vPnC compared to 13vPnC (in short)

The percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 of 20vPnC SC was noninferior to 13vPnC SC for 11 of the 13 matched serotypes (all but serotypes 6A and 6B), and to the lowest serotype in the 13vPnC SC group for 5 of 7 additional serotypes (all but serotypes 10A and 12F). Out of the 13 matched serotypes, 6A and 6B missed this endpoint by a small margin. The totality of data supports that the immune responses elicited by 20vPnC are expected to be effective against disease caused by the 20 vaccine serotypes, including those that missed NI.

• Post hoc analysis with alternative defined level of ≥0.15 µg/mL for IgG concentrations at this time

point showed that serotype 6A would have met NI of 20vPnC SC to 13vPnC SC at this level with the same NI criterion.
• The majority of participants (90.0% for serotype 6A and 87.8% for serotype 6B) in the 20vPnC SC group had predefined IgG concentrations for those serotypes 1 month after Dose 3, with increases at 1 month after Dose 4 of 20vPnC SC (100% for serotypes 6A and 6B) comparable to 13vPnC SC.
• The IgG GMCs 1 month after Dose 3 of 20vPnC SC were noninferior to 13vPnC SC for 10 of the 13 matched serotypes and to 6 of the 7 additional serotypes compared to the lowest in the 13vPnC SC group. Serotypes 5, 6A, 6B, and 10A missed NI; serotypes 5, 6A, and 10A missed the statistical criterion by a small margin.
• 20vPnC SC elicited robust OPA antibody responses to the 20 vaccine serotypes in terms of OPA GMTs. The percentage of participants with OPA titers ≥LLOQ for these serotypes were generally similar to those in the 13vPnC SC group 1 month after Dose 3 or Dose 4.
• Following 3 infant doses of 20vPnC SC, infants were primed for memory responses to the 13 matched vaccine serotypes, similar to the 13vPnC SC. This was shown by IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4 >1.0 for all serotypes except serotype 3. The IgG GMFRs in the 20vPnC SC group for the serotypes that missed NI for the primary objective (serotypes 6A, 6B, 10A, and 12F) were 3.4 or higher 1 month after Dose 4. Boosting from before Dose 4 to 1 month after Dose 4 was also observed for all serotypes. Increases in OPA GMTs and ≥4-fold rises in OPA titers were observed for most serotypes after Dose 4.
• Observed IgG and OPA responses for all 7 additional serotypes were much higher in the 20vPnC SC group (consistent with superior, statistically significantly higher antibody levels) when compared with the corresponding serotype responses in the 13vPnC SC group. Therefore, 20vPnC elicits potentially protective antibody responses in infants that are not available in existing vaccines.

CHMP rapporteur comments:

The rapporteur agrees on MAH summary on immunogenicity results.

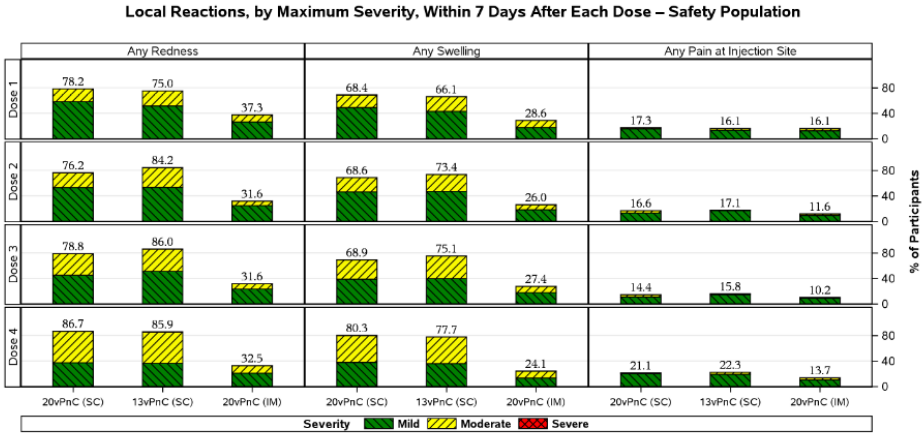
Safety results

Safety assessment 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 following vaccination, recorded by participants' parents/legal guardians using an e-diary.
AEs and SAEs were collected from the signing of the ICD through and including Visit 4, and from Visit 5 to Visit 6. Between Visit 4 and Visit 5, only SAEs and NDCMCs were reported.
Immediate (acute) AEs occurring within the first 30 minutes after each investigational product administration were assessed and documented as an AE or SAE, as appropriate, in the CRF.

Local Reactions
The percentages of participants with local reactions after Doses 1 through 4 were 81.7%, 90.1%, 87.8%, and 88.2% in the 13vPnC SC group. Injection site redness was the most reported local reaction. Most local reactions reported were mild or moderate. One (1) participant had injection site subcutaneous bleeding reported on Day 1 after Dose 3 which was reported as resolved on Day 92. This event was reported as an AE, was mild in severity, and resolved.
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.

Local reactions reported by participants, by maximum severity, within 7 days after vaccination with 20vPnC SC, 13vPnC SC, or 20vPnC IM are presented in figure 14.17. The percentages of participants with local reactions 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 reported local reaction. Most local reactions reported were mild or moderate. There were no apparent differences in the incidence or severity of local reactions between the 20vPnC SC and 13vPnC SC groups. There was a lower proportion of reported swelling and redness in the 20vPnC IM group than in either of the SC vaccine groups.

14.17. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population



Abbreviations: IM = intramuscular; SC = subcutaneous.
PFIZER CONFIDENTIAL SDTM Creation: 02AUG2022 (19:58) Source Data: adfacevd Table Generation: 08AUG2022 (14:22)(Cutoff date : not applicable; Snapshot date : 22JUL2022) Output File: ./jnda1/B7471016_CSR/adce_f001_lr1_saf

Systemic Events

The percentages of participants with any systemic event after Doses 1 through 4 were 64.3%, 65.3%, 56.1%, and 59.5% in the 13vPnC SC group. Irritability and drowsiness were the most reported events. There were no clinically important differences in the rates of systemic events. Most systemic events were mild or moderate.

The percentage of participants with any fever reported was (<43%). An increase in the frequency of fever of ≥ 38.9°C was observed following Dose 4 for which the MAH considered concomitant vaccine administration as having a contributory role. Fever > 40°C was not reported in the 13vPnC SC group. The percentage of participants with reported use of antipyretic or pain medication was low in the 13vPnC SC group (0%, 0%, 0.9%, and 7.3%).

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 days.

Summary of Adverse Events

At least 1 AE was reported from Dose 1 to 1 month after Dose 3 in 55.4% of participants in the 13vPnC SC group. The SOC of infections and infestations was reported most frequently and included nasopharyngitis (16.5%) and upper respiratory tract infection (2.2%).

At least 1 AE was reported from Dose 4 to 1 month after Dose 4 in 43.2% of participants. As with the AEs from Dose 1 to 1 month after Dose 3, the SOC of infections and infestations were reported most frequently and included nasopharyngitis (15.5%) and upper respiratory tract infection (1.4%).

Related Adverse Event. The most frequently reported related AEs were in the SOC of general disorders and administration site conditions. No AE was reported in the 13vPnC SC group that was considered by the investigator to be related.

Immediate Adverse Events
Immediate AEs were reported infrequently in the 13vPnC SC group. These were generally cutaneous events at the injection site. There were no events that were consistent with anaphylaxis or serious allergic reaction. One (1) participant was withdrawn from the study due to the related immediate AE of generalized erythema. This event was according to the MAH moderate in severity, resolved on the day of onset, and was not considered an SAE.

Severe Adverse Events
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).

Newly Diagnosed Chronic Medical Conditions (NDCMCs)
The percentages of participants with NDCMCs after Dose 1 were low (≤10.7%) 1 month after Dose 4. NDCMCs were reported for ≤2.7% of participants from Dose 1 to 1 month after Dose 3 and reported for ≤0.9% of participants from Dose 4 to 1 month after Dose 4. The majority of NDCMCs were new diagnoses of allergic conditions.

Deaths
No deaths were reported in the 13vPnC SC group.

Serious Adverse Events
The percentages of participants with SAEs after Dose 1 was low (≤7.4%). The most frequently reported SAEs were under the SOC of infections and infestations and were largely associated with respiratory syncytial virus infection (Table 23).
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. No SAEs were considered related to study intervention.

Table 23. Serious Adverse Events Reported From Dose 1, 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	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.
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_ser_d1_1md4_saf

Discontinuations from Study Intervention or Study Due to Adverse Events

One (1) participant in the 13vPnC SC group was withdrawn from the trial because of an immediate AE of generalized erythema.

Narratives of participants withdrawn from the study because of AEs are provided below.

- A 4-month-old participant from Japan with no relevant medical history, received 2 doses of 13vPnC subcutaneously (SC) Day 1; Dose 1 and Day 36; Dose 2. Haemophilus influenzae type b vaccine, hepatitis B virus vaccine, and Rotarix (rotavirus vaccine live oral 1V) were administered at the same time as Doses 1 and 2. Additionally, the participant received Tetrabik (diphtheria, tetanus, acellular pertussis, and poliovirus vaccine) with Dose 2. The participant experienced generalized erythema 2 minutes after receiving Dose 2 Day 36; Relative Day 1. No mucosal lesions, or gastrointestinal or respiratory symptoms were observed. The participant received oral steroid (Rinderon syrup) for erythema, which resolved on the same day of onset.

  The participant was withdrawn from further vaccination because of the generalized erythema. In the opinion of the investigator, there was a reasonable possibility that the generalized erythema was related to the 13vPnC SC. Because redness and swelling developed at the time of first pneumococcal vaccination, pneumococcal vaccine was suspected most. However, the possibility of other vaccines causing this reaction could not be ruled out.

Other Significant Adverse Events

No events of special interest, narratives of any seizures or seizure-like events were reported as serious or nonserious AEs during the applicable collection period.

CHMP rapporteur comments:

It is noted that local reactions reported by participants, by maximum severity, within 7 days after vaccination with 20vPnC SC or 13vPnC SC was high. The percentages of participants with local reactions 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. Most local reactions reported were mild or moderate. However, there was a lower proportion of reported swelling and redness in the 20vPnC IM group than in either of the SC vaccine groups, and thereby it is assessed that the high frequency of local reactions is caused by the subcutaneous route of 13vPnC.

There was 1 participant who experienced generalized erythema 2 minutes after receiving Dose 2 (Day 36; Relative Day 1). No mucosal lesions, or gastrointestinal or respiratory symptoms were observed. The participant was withdrawn from further vaccination on because of the generalized erythema. In the opinion of the investigator, there was a reasonable possibility that the generalized erythema was related to the 13vPnC SC. Because redness and swelling developed at the time of first pneumococcal vaccination, pneumococcal vaccine was suspected most. However, the possibility of other vaccines causing this reaction could not be ruled out. The overall assessment of this case is agreed upon.

Overall, no new safety concerns detected in participants receiving 4-dose series of SC 13vPnC.

2.3.3. Conclusions

MAH Conclusion

The opinion of the MAH is that no update to the EU Product Information for Prevenar 13 is required based on the results of B7471016, as the study is specific to Japanese infants, the SC route of administration is not used in Europe, and the benefit/risk profile of 13vPnC remains unchanged.

CHMP rapporteur comments: MAH conclusion is agreed. No changes are being proposed to the Prevenar 13 label.

The submitted study does not change the benefit-risk balance for Prevenar 13.

2.3.4. Discussion on clinical aspects

The present study confirmed the safety of Prevenar 13 among Japanese infants administered by the SC route. The safety population was small (N= 224) and therefore the chance to detect rare AEs and SAEs is low.

The subcutaneous route of administration is not used in Europe. Despite differences in the route of administration in Europe (IM) compared to Japan (SC) no new safety concern is raised from this study and the benefit/risk profile of 13vPnC remains unchanged.

3. Overall conclusion and recommendation

The results of this study indicate no new safety concern. The P46 procedure is considered fulfilled.

☒ **Fulfilled:**

No regulatory action required.