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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/P46/060

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

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1. Introduction

On 19 August 2019, the MAH submitted a completed paediatric study for Prevenar 13 (PCV13), 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 A Phase 3, Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Tolerability, and Immunogenicity of a Single Dose of 13-Valent Pneumococcal Conjugate Vaccine in Japanese Subjects Aged 6 to 64 Years Who are Considered to be at Increased Risk of Pneumococcal Disease and Who are Naive to Pneumococcal Vaccines.

Protocol B1851172

EudraCT number: 2018-003054-24 is a stand-alone study.

The current EU-approved indications for the use of PCV13 are:

- *Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to 17 years of age;*
- *Active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults ≥ 18 years of age and the elderly.*

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

13-valent Pneumococcal Conjugate Vaccine (diphtheria CRM197 protein)
Compound Number: PF-05208760,
All subjects received a single dose (0.5 mL) of 13vPnC.
Per 0.5-mL dose, the vaccine is formulated to contain 4.4 µg of saccharide from pneumococcal serotype 6B and 2.2 µg of each of the other 12 saccharides (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- A Phase 3, Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Tolerability, and Immunogenicity of a Single Dose of 13-Valent Pneumococcal Conjugate Vaccine in Japanese Subjects Aged 6 to 64 Years Who are Considered to be at Increased Risk of Pneumococcal Disease and Who are Naive to Pneumococcal Vaccines

Protocol B1851172

2.3.2. Clinical study

Study B1851172: A Phase 3, Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Tolerability, and Immunogenicity of a Single Dose of 13-Valent Pneumococcal Conjugate Vaccine in Japanese Subjects Aged 6 to 64 Years Who are Considered to be at Increased Risk of Pneumococcal Disease and Who are Naive to Pneumococcal Vaccines

Description

The morbidity and mortality of non-invasive and invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae (S pneumoniae*) is a public health concern across the globe, including Japan[1]. While young children and elderly adults are particularly susceptible to pneumococcal disease (PD), individuals 6 to 64 years of age with certain underlying medical conditions are also considered to be at increased risk of PD. In addition, the treatment of pneumococcal infections is becoming more difficult because of a global increase in prevalence of *S. pneumoniae* strains resistant to antibiotics.

Pfizer developed 13-valent pneumococcal conjugate vaccine (13vPnC) for use in infants and young children, and subsequently in adults to prevent PD caused by the 13 pneumococcal serotypes (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) contained in the vaccine. To overcome the limited immunogenicity of pneumococcal polysaccharide (PS) vaccines, which elicit a T-cell–independent immune response, protein conjugation technology was applied to 13vPnC. Each of the pneumococcal PS is covalently conjugated to the diphtheria cross-reactive material 197 (CRM197) protein to elicit a T-cell–dependent immune response, leading to immunological memory and boosting upon repeated vaccination.

In Japan, 13vPnC has been approved for children aged ≥2 months to <6 years and adults aged ≥65 years but it is not approved for use in the 6- to 64-year age group in Japan. In view of its regulatory status and the epidemiology and prevalence of IPD cases in Japan, development of 13vPnC in Japanese individuals aged 6 to <65 years at increased risk of PD has been advocated by Japanese physicians and their professional associations. Therefore, Pfizer conducted Study B1851172 to address the unmet medical needs in the 6- to 64-year age group, the vaccine gap between Japan and other countries, and the request from professional associations. This study assessed the safety, tolerability and immunogenicity of a single dose of 13vPnC in Japanese individuals aged 6 to 64 years who were considered to be at increased risk of PD and who were naïve to pneumococcal vaccine. The large database of safety data from clinical studies in Japan and globally including in healthy individuals, immunocompetent individuals with underlying stable medical conditions, and individuals with immunocompromised status, and the extensive post-marketing experience supported conduct of single-arm, open-label safety and immunogenicity study.

Methods

Safety Objective

The primary objective of this study was to assess the safety and tolerability of a single dose of 13vPnC as measured by the incidence of local reactions, systemic events, adverse events (AEs) and serious adverse events (SAEs).

[1] Morimoto K, Suzuki M, Ishifuji T, et al; Adult Pneumonia Study Group–Japan (APSG J). The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PloS One 2015;10(3):e0122247.

Immunogenicity Objectives

The secondary objective of this study was to describe the immune responses elicited by a single dose of 13vPnC.

- Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination in all age groups.
- Geometric mean fold rise (GMFRs) in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups.
- Serotype-specific IgG geometric mean concentration (GMC)s 1 month after vaccination in all age groups.
- GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

Study design

Study B1851172 was a Phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of a single dose of 13-valent pneumococcal conjugate vaccine (13vPnC) in Japanese subjects aged 6 to 64 years who were considered to be at increased risk of pneumococcal disease (PD) and who were naïve to pneumococcal vaccines.

This study consisted of 2 age groups: 6 to <18 and 18 to <65 years old. Approximately 200 subjects were to be enrolled: approximately 50 subjects in the 6- to <18-year age group and approximately 150 subjects in the 18- to <65-year age group. For the purpose of ensuring a minimum number of subjects in each of the age categories, at least 15 subjects aged 6 to <12 years and 15 subjects aged 12 to <18 years were to be enrolled within the 6- to <18-year age group. Furthermore, at least 50 subjects aged 18 to <50 years and 50 subjects aged 50 to <65 years were to be enrolled within the 18- to <65-year age group. Subjects participated in the study for approximately 1 month (29 to 43 days).

All subjects received a single dose (0.5 mL) of 13vPnC intramuscularly at Visit 1 (Day 1). In total, 2 blood samples were collected at Day 1 prior to receipt of investigational product (IP) and 1 month later (28 to 42 days after Visit 1) for assessment of the immune responses. A quantitative functional opsonophagocytic activity (OPA) assay and Luminex-based antibody binding assay were used to measure antibody-mediated serum OPA and serum concentrations of anticapsular immunoglobulin G (IgG) antibodies for each of the 13 pneumococcal serotypes, respectively.

Starting on the day of vaccination, local reactions (redness, swelling, and pain at the injection site) were recorded in the e-diary for 7 days by the subject's legally acceptable representative/parent/legal guardian for subjects aged 6 to <18 years or 14 days by the subject for subjects aged 18 to <65 years.

Starting on the day of vaccination, systemic events (fatigue, headache, vomiting, diarrhoea, muscle pain, and joint pain), axillary temperature, and the use of antipyretic medication and pain medication for treatment of symptoms were recorded in the e-diary for 7 days by the subject's legally acceptable representative/parent/legal guardian for subjects aged 6 to <18 years or 14 days by the subject for subjects aged 18 to <65 years. Fever was defined as an axillary temperature of >37.5°C and analyzed as a systemic event.

Adverse events (AEs), including serious AEs (SAEs; were recorded on the AE page(s) of the case report form (CRF) from the time the subject/legally acceptable representative/parent/legal guardian provided informed consent through and including Visit 2.

Study population /Sample size

Japanese males and females aged 6 to <65 years with an increased risk of PD were enrolled in this study. All 206 screened subjects (200 planned for enrollment) were enrolled and completed the study.

No enrolled subjects were excluded from the all-available immunogenicity population or the evaluable immunogenicity population and therefore the all-available and evaluable immunogenicity populations were identical.

Treatments

All subjects received a single dose (0.5 mL) of 13vPnC intramuscularly at Visit 1 (Day 1).

Per 0.5-mL dose, the vaccine is formulated to contain 4.4 µg of saccharide from pneumococcal serotype 6B and 2.2 µg of each of the other 12 saccharides (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Outcomes/endpoints

Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary Safety	• To assess the safety and tolerability of a single dose of 13vPnC as measured by the incidence of local reactions, systemic events, AEs, and SAEs.	• Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to the MedDRA in all age groups.
Secondary Immunogenicity	• To describe the immune responses elicited by a single dose of 13vPnC.	• Serotype-specific OPA GMTs 1 month after vaccination in all age groups. • GMFRs in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups. • Serotype-specific IgG GMCs 1 month after vaccination in all age groups. • GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity.

Statistical Methods

Descriptive summaries included the following statistics: number and percent of subjects, mean, standard deviation, median, minimum, maximum, and the 2-sided 95% confidence interval (CI).

Other estimations are presented below.

Geometric Mean: For each serotype, OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs) were calculated.

Geometric Mean Fold Rise: For each serotype, OPA and IgG geometric mean fold rises (GMFRs) were calculated.

Reverse Cumulative Distribution Curve: For each serotype, the empirical reverse cumulative distribution curves (RCDCs) plotted the percentage of subjects achieving a given titer or concentration.

Methods to Manage Missing Data and Data Below the Lower Limit of Quantitation: For the analysis of the immunogenicity endpoints, missing values were retained as missing and were not imputed. For OPA titers and IgG concentrations, values below the lower limit of quantitation (LLOQ) were set to 0.5 × LLOQ for analysis.

Analysis Populations

The analysis populations are presented below.

- Safety Analysis Set: the safety population included all subjects who received 1 dose of study vaccine. The safety population was the only analysis population for the primary endpoints.
- Evaluable Immunogenicity Population: the evaluable immunogenicity population was the primary immunogenicity analysis population. It included subjects who met the following:
    1. Were eligible for the study based on the inclusion and exclusion criteria.
    2. Received the study vaccine
    3. Received no prohibited vaccines.
    4. Had blood drawn within the specified time frame 1 month after vaccination (28 to 42 days after Visit 1 [i.e., Day 29 to Day 43 when Day 1 was vaccination visit]).
    5. Had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.
    6. Had no major protocol violations as determined by the sponsor's clinician, or any other protocol deviations that would materially affect assessment of immunogenicity endpoints.
- All-Available Immunogenicity Population: The all-available immunogenicity population included all subjects who were enrolled, received the study vaccine, and had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.

Results

Recruitment/ Number analysed

All 206 screened subjects (200 planned for enrolment) were enrolled and completed the study. 53 subjects were at age between 6 to 18.

No enrolled subjects were excluded from the all-available immunogenicity population or the evaluable immunogenicity population and therefore the all-available and evaluable immunogenicity populations were identical.

Baseline data

Overall, 51.9% of subjects were male and 48.1% of subjects were female; all subjects were Japanese. The mean ages at vaccination were 12.7 years (range: 7 to 17 years) in the 6- to <18-year age group and 49.0 years (range: 20 to 64 years) in the 18- to <65-year age group. Considering individuals who smoke are considered to be at increased risk for developing PD, it is worth noting that 22.2% and 22.9% of subjects aged ≥18 years were current or former smokers, respectively, at the time of enrolment.

Demographic characteristics for the all-available immunogenicity and evaluable immunogenicity populations were the same as for the safety population.

Among subjects aged 6 to <18 years, the most common chronic medical conditions that put these subjects at increased risk of PD (and cited in ≥5% of subjects) were grouped under the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) of: cardiac disorders; congenital, familial and genetic disorders; hepatobiliary disorders; neoplasms benign, malignant and unspecified; renal and urinary disorders; respiratory, thoracic and mediastinal disorders.

The most common preferred terms (PTs) that investigators considered increased the risk of PD were: asthma, type 1 DM, nephrotic syndrome, type 2 DM, non-alcoholic fatty liver, and acute lymphocytic leukaemia. In addition, 15.1% of subjects were treated with immunosuppressive therapy during the study, which was also considered a factor that increased risk of PD in these subjects.

Efficacy results

Immunogenicity Results:
For subjects aged 6 to <65 years, opsonophagocytic activity (OPA) GMTs for each of the 13 pneumococcal serotypes were higher 1 month after vaccination compared to before vaccination. The OPA GMFRs observed from baseline to 1 month after vaccination ranged from 5.5 to 61.7 and the lower limits of the 2-sided, 95% CIs for the OPA GMFRs were >1 for each of the 13 serotypes, indicating that subjects had an immune response to the vaccine.

OPA GMT increases and OPA GMFRs were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

The majority of subjects (range: 78.9% to 95.0%) aged 6 to <65 years achieved an OPA titer ≥ lower limit of quantitation (LLOQ) 1 month after vaccination for each of the 13 pneumococcal serotypes. The proportions of subjects who achieved an OPA titer ≥ LLOQ were generally higher in subjects aged 6 to 18 years compared to subjects aged 18 to <65 years.

The majority of subjects (range: 56.4% to 80.9%) aged 6 to <65 years achieved a ≥4-fold increase in OPA titer for each of the 13 pneumococcal serotypes. The proportions of subjects who achieved a ≥4-

fold increase in OPA titer were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

For subjects aged 6 to <65 years, reverse cumulative distribution curve (RCDCs) for each of the 13 pneumococcal serotypes showed higher proportions of subjects that achieved a given OPA titer 1 month after vaccination compared to before vaccination. The proportions of subjects achieving the specified pneumococcal OPA titer for each of the 13 serotypes 1 month after vaccination were generally higher across the full range of antibody titers in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

For subjects aged 6 to <65 years, IgG GMCs for each of the 13 pneumococcal serotypes were low before vaccination and higher 1 month after vaccination. The IgG GMFRs observed from baseline to 1 month after vaccination ranged from 4.605 to 47.565 and the lower limits of the 2-sided, 95% CIs for the IgG GMFRs were >1 for each of the 13 serotypes, indicating that subjects had an immune response to the vaccine. IgG GMC increases and IgG GMFRs were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

The majority of subjects (range: 73.3% to 89.3%) aged 6 to <65 years achieved a ≥4-fold increase in IgG concentration for each of the pneumococcal vaccine serotypes except for serotype 3 (49.0% of subjects). The proportions of subjects who achieved a ≥4-fold increase in IgG concentration were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

For subjects aged 6 to <65 years, RCDCs for each of the 13 pneumococcal serotypes showed higher proportions of subjects achieved a given IgG concentration 1 month after vaccination compared to before vaccination. The proportions of subjects achieving the specified pneumococcal IgG concentrations for each of the 13 serotypes 1 month after vaccination were generally higher in subjects aged 6 to <18 years compared to subjects aged 18 to <65 years.

Overall, a single administration of 13vPnC in Japanese subjects aged 6 to <65 years who were considered to be at increased risk of PD (and who were naïve to pneumococcal vaccines) elicited robust immune responses 1 month after vaccination.

Table 2. Immunogenicity of Prevenar 13 among 6 to <18 year old Japanese

14.8. Pneumococcal OPA GMTs and GMFRs – Subjects 6 to <18 Years of Age – Evaluable Immunogenicity Population

	Time Point[a]						Fold Rise		
	Before Vaccination			1 Month After Vaccination			1 Month After Vaccination/Before Vaccination		
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[b]	GMFR[c]	(95% CI[d])
1	53	9	(8.8, 9.6)	53	348	(257.7, 470.6)	53	37.8	(27.92, 51.25)
3	52	25	(17.5, 34.7)	52	196	(157.4, 244.1)	52	7.9	(5.31, 11.90)
4	47	18	(11.2, 27.9)	47	8861	(6797.6, 11550.9)	47	501.9	(301.20, 836.24)
5	49	17	(13.9, 19.8)	49	519	(355.9, 758.2)	49	31.3	(22.04, 44.41)
6A	39	126	(62.4, 253.1)	39	16356	(11175.3, 23937.5)	39	130.1	(63.61, 266.14)
6B	46	83	(48.7, 142.9)	46	7928	(5567.6, 11288.4)	46	95.0	(53.87, 167.46)
7F	46	661	(443.0, 985.7)	46	6003	(4882.8, 7379.1)	46	9.1	(6.18, 13.36)
9V	49	317	(200.4, 501.2)	49	5892	(4557.9, 7615.4)	49	18.6	(11.17, 30.94)
14	46	117	(63.9, 214.4)	46	5859	(4585.2, 7485.7)	46	50.0	(26.44, 94.73)
18C	43	131	(59.9, 285.7)	43	7347	(4977.8, 10845.0)	43	56.1	(26.70, 118.08)
19A	50	76	(42.8, 134.9)	50	3283	(2465.6, 4372.2)	50	43.2	(24.13, 77.44)
19F	52	59	(37.0, 94.9)	52	4909	(3484.5, 6916.0)	52	82.9	(49.88, 137.72)
23F	52	18	(10.7, 31.5)	52	5464	(3925.0, 7607.6)	52	298.2	(170.36, 522.02)

Abbreviations: GMFR = geometric mean fold rise; GMT = geometric mean titer; OPA = opsonophagocytic activity.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified serotype at both the given visits.

c. GMTs and GMFRs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws.

d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.

Program ID: Study B1851172/CP adva_s002.sas. Date of Reporting Dataset Creation: 29MAY2019. Runtime ID: 29MAY2019 20:10. File ID: adva_s002_eval_opa_age1.html.

14.18. Pneumococcal IgG GMCs (µg/mL) and GMFRs – Subjects 6 to <18 Years of Age – Evaluable Immunogenicity Population

	Time Point[a]						Fold Rise		
	Before Vaccination			1 Month After Vaccination			1 Month After Vaccination/Before Vaccination		
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[b]	GMFR[c]	(95% CI[d])
1	53	0.074	(0.054, 0.102)	53	8.393	(6.212, 11.340)	53	113.063	(75.574, 169.149)
3	53	0.234	(0.143, 0.381)	53	1.713	(1.286, 2.281)	53	7.333	(4.774, 11.263)
4	53	0.045	(0.027, 0.076)	53	8.545	(5.819, 12.547)	53	188.446	(127.581, 278.348)
5	53	0.041	(0.025, 0.067)	53	5.701	(3.245, 10.016)	53	140.151	(94.214, 208.487)
6A	53	0.176	(0.101, 0.306)	53	16.891	(9.621, 29.655)	53	95.981	(58.279, 158.073)
6B	53	0.149	(0.082, 0.269)	53	15.377	(8.395, 28.165)	53	103.527	(65.539, 163.532)
7F	53	0.077	(0.047, 0.128)	53	9.065	(6.205, 13.242)	53	117.187	(78.679, 174.544)
9V	53	0.046	(0.031, 0.070)	53	4.614	(3.097, 6.875)	53	99.434	(69.627, 142.002)
14	53	0.121	(0.064, 0.227)	53	14.531	(8.392, 25.161)	53	120.541	(69.962, 207.685)
18C	53	0.079	(0.047, 0.133)	53	6.304	(4.198, 9.466)	53	79.531	(49.156, 128.677)
19A	53	0.628	(0.359, 1.098)	53	23.093	(15.693, 33.981)	53	36.790	(23.106, 58.577)
19F	53	0.239	(0.135, 0.423)	53	16.446	(10.293, 26.277)	53	68.926	(44.522, 106.707)
23F	53	0.116	(0.072, 0.186)	53	23.704	(13.407, 41.908)	53	204.418	(135.131, 309.231)

Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G.

a. Protocol-specified timing for blood sample collection.

b. n = Number of subjects with valid and determinate assay results for the specified serotype at both the given visits.

c. GMCs and GMFRs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws.

d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.

Program ID: Study B1851172/CP adva_s002.sas. Date of Reporting Dataset Creation: 21MAR2019. Runtime ID: 26MAR2019 23:39. File ID: adva_s002_eval_igg_age1.html.

Safety results

The majority of subjects reported any local reactions within 7 days after vaccination in the 6- to <18-year age group (82.7%) and 14 days after vaccination in the 18- to <65-year age group (67.1%). In both age groups, pain at the injection site was the most frequently reported local reaction. The majority of local reactions were mild or moderate in severity, except for 1 case of severe swelling in the 6- to <18-year age group and 2 cases of severe pain at the injection site in the 18- to <65-year age group. The proportions of subjects who reported local reactions were generally higher in the 6- to <18-year age group than in the 18- to <65-year age group.

Table 3. Local reactions after vaccination with Prevenar 13 among 6 to 18 year old Japanese

14.23. Summary of Subjects Reporting Local Reactions by Maximum Severity Within 7 Days After Vaccination – Subjects 6 to <18 Years of Age – Safety Population

	Age Category					
	6 to <12 Years			12 to <18 Years		
Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Redness[d]						
Any	15	5 (33.3)	(11.8, 61.6)	32	5 (15.6)	(5.3, 32.8)
Mild	15	2 (13.3)	(1.7, 40.5)	32	3 (9.4)	(2.0, 25.0)
Moderate	15	3 (20.0)	(4.3, 48.1)	32	2 (6.3)	(0.8, 20.8)
Severe	15	0 (0.0)	(0.0, 21.8)	32	0 (0.0)	(0.0, 10.9)
Swelling[d]						
Any	15	7 (46.7)	(21.3, 73.4)	32	9 (28.1)	(13.7, 46.7)
Mild	15	1 (6.7)	(0.2, 31.9)	32	6 (18.8)	(7.2, 36.4)
Moderate	15	6 (40.0)	(16.3, 67.7)	32	2 (6.3)	(0.8, 20.8)
Severe	15	0 (0.0)	(0.0, 21.8)	32	1 (3.1)	(0.1, 16.2)
Pain at the injection site[e]						
Any	18	16 (88.9)	(65.3, 98.6)	34	25 (73.5)	(55.6, 87.1)
Mild	18	12 (66.7)	(41.0, 86.7)	34	18 (52.9)	(35.1, 70.2)
Moderate	18	4 (22.2)	(6.4, 47.6)	34	7 (20.6)	(8.7, 37.9)
Severe	18	0 (0.0)	(0.0, 18.5)	34	0 (0.0)	(0.0, 10.3)
Any local reaction[f]	18	17 (94.4)	(72.7, 99.9)	34	26 (76.5)	(58.8, 89.3)

a. N = number of subjects reporting "yes" for at least 1 day or "no" for all days. These values are the denominators for the percentage calculations.
b. n = Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
d. For subjects 6 to <12 years of age, mild is 0.5 to 2.0 cm, moderate is >2.0 to 7.0 cm, severe is >7.0 cm; for subjects 12 to <18 years of age, mild is 2.5 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. "Any local reaction" = any redness, any swelling, or any pain at the injection site.
Program ID: Study B1851172/CP adce_s010.sas. Date of Reporting Dataset Creation: 20DEC2018. Runtime ID: 20DEC2018 04:37. File ID: adce_s010_age1.html.

The majority of subjects reported any systemic events within 7 days after vaccination in the 6- to <18-year age group (60.8%) and 14 days after vaccination in the 18- to <65-year age group (58.6%). In both age groups, the 3 most frequently reported systemic events were fatigue, muscle pain, and headache. The majority of systemic events were mild or moderate in severity, except for 1 case each of severe fatigue and severe headache in the 6- to <18-year age group, and 1 case each of severe diarrhoea, severe muscle pain, and severe joint pain in the 18- to <65-year age group. The proportions of subjects who reported systemic events were broadly similar in the 6- to <18-year and 18- to <65-year age groups.

Table 4. Systemic reaction to Prevenar 13 among 6 to 18 year old Japanese

Systemic Events

14.39. Summary of Subjects Reporting Systemic Events by Maximum Severity Within 7 Days After Vaccination – Subjects 6 to <18 Years of Age – Safety Population

	Age Category					
	6 to <12 Years			12 to <18 Years		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Fever (≥37.5°C)						
≥37.5°C	16	3 (18.8)	(4.0, 45.6)	32	4 (12.5)	(3.5, 29.0)
37.5°C to 38.4°C	16	2 (12.5)	(1.6, 38.3)	32	4 (12.5)	(3.5, 29.0)
38.5°C to 38.9°C	16	1 (6.3)	(0.2, 30.2)	32	0 (0.0)	(0.0, 10.9)
39.0°C to 40.0°C	16	0 (0.0)	(0.0, 20.6)	32	0 (0.0)	(0.0, 10.9)
>40.0°C	16	0 (0.0)	(0.0, 20.6)	32	0 (0.0)	(0.0, 10.9)
Fatigue[d]						
Any	15	6 (40.0)	(16.3, 67.7)	33	12 (36.4)	(20.4, 54.9)
Mild	15	4 (26.7)	(7.8, 55.1)	33	8 (24.2)	(11.1, 42.3)
Moderate	15	1 (6.7)	(0.2, 31.9)	33	4 (12.1)	(3.4, 28.2)
Severe	15	1 (6.7)	(0.2, 31.9)	33	0 (0.0)	(0.0, 10.6)
Headache[d]						
Any	15	3 (20.0)	(4.3, 48.1)	34	9 (26.5)	(12.9, 44.4)
Mild	15	0 (0.0)	(0.0, 21.8)	34	8 (23.5)	(10.7, 41.2)
Moderate	15	2 (13.3)	(1.7, 40.5)	34	1 (2.9)	(0.1, 15.3)
Severe	15	1 (6.7)	(0.2, 31.9)	34	0 (0.0)	(0.0, 10.3)
Vomiting[e]						
Any	15	0 (0.0)	(0.0, 21.8)	32	0 (0.0)	(0.0, 10.9)
Mild	15	0 (0.0)	(0.0, 21.8)	32	0 (0.0)	(0.0, 10.9)
Moderate	15	0 (0.0)	(0.0, 21.8)	32	0 (0.0)	(0.0, 10.9)
Severe	15	0 (0.0)	(0.0, 21.8)	32	0 (0.0)	(0.0, 10.9)
Diarrhea[f]						
Any	15	0 (0.0)	(0.0, 21.8)	33	4 (12.1)	(3.4, 28.2)
Mild	15	0 (0.0)	(0.0, 21.8)	33	4 (12.1)	(3.4, 28.2)
Moderate	15	0 (0.0)	(0.0, 21.8)	33	0 (0.0)	(0.0, 10.6)
Severe	15	0 (0.0)	(0.0, 21.8)	33	0 (0.0)	(0.0, 10.6)
Muscle pain[d]						
Any	15	3 (20.0)	(4.3, 48.1)	34	12 (35.3)	(19.7, 53.5)
Mild	15	3 (20.0)	(4.3, 48.1)	34	10 (29.4)	(15.1, 47.5)
Moderate	15	0 (0.0)	(0.0, 21.8)	34	2 (5.9)	(0.7, 19.7)
Severe	15	0 (0.0)	(0.0, 21.8)	34	0 (0.0)	(0.0, 10.3)
Joint pain[d]						
Any	16	1 (6.3)	(0.2, 30.2)	32	2 (6.3)	(0.8, 20.8)
Mild	16	1 (6.3)	(0.2, 30.2)	32	1 (3.1)	(0.1, 16.2)
Moderate	16	0 (0.0)	(0.0, 20.6)	32	1 (3.1)	(0.1, 16.2)
Severe	16	0 (0.0)	(0.0, 20.6)	32	0 (0.0)	(0.0, 10.9)
Use of antipyretic or pain medication[g]	15	1 (6.7)	(0.2, 31.9)	32	2 (6.3)	(0.8, 20.8)
Any systemic event[h]	17	9 (52.9)	(27.8, 77.0)	34	22 (64.7)	(46.5, 80.3)

a. N = number of subjects reporting "yes" for at least 1 day or "no" for all days. These values are the denominators for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
d. Mild = does not interfere with activity; moderate = some interference with activity; severe = prevents daily activity.
e. Mild = 1 to 2 times in 24 hours; moderate = >2 times in 24 hours; severe = requires intravenous hydration.
f. Mild = 2 to 3 loose stools in 24 hours; moderate = 4 to 5 loose stools in 24 hours; severe = 6 or more loose stools in 24 hours.
g. Severity was not collected for this event. The numbers in the table reflect "yes" responses (ie, number of events reported).
h. "Any systemic event" = any fever ≥37.5°C, any fatigue, any headache, any vomiting, any diarrhea, any muscle pain, or any joint pain. □

Overall, few AEs were reported (16.0% of subjects overall). There were no SAEs, life-threatening AEs, or immediate AEs reported during the study. There were no deaths, and no subjects were withdrawn for safety-related reasons during the study.

AEs that were assessed by the investigator to be related to IP were reported by 6 (2.9%) subjects. These were mild events associated with IP injection site reaction, except for 1 event each of decreased appetite and middle insomnia.

Two (2) subjects reported severe AEs, including 1 AE of severe back pain and 1 AE of severe asthma, neither of which was assessed as vaccine related.

Overall, 13vPnC was well tolerated with an acceptable safety profile in Japanese subjects aged 6 to <65 years who were considered at increased risk of PD and naïve to pneumococcal vaccines.

Conclusions
In Japanese individuals aged 6 to <65 years who were considered to be at increased risk of PD and who were naïve to pneumococcal vaccines, 13vPnC was immunogenic for each of the 13 serotypes and was well-tolerated with an acceptable safety profile. The results support the extension of the indication of 13vPnC for the prevention of PD in Japan.

2.3.3. Discussion on clinical aspects

Present study confirmed immunogenicity and safety of Prevenar 13 among Japanese individuals aged 6 to <65 years. The results are in agreement with previously reported studies. No concern regarding lacking efficacy is raised from this study.

The study population was relatively small (N= 206) and including only small fraction of children at age 6 to <18 (N=53) and therefore the chance to detect rare AEs and SAEs is low. The safety results are also in agreement with previously reported studies. No new safety concern is raised from this study.

3. CHMP overall conclusion and recommendation

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

☒ Fulfilled:

No regulatory action required.