27 February 2025
EMA/101185/2025
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/P46/073

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	30 Dec 2024	30 Dec 2024
☐	CHMP Rapporteur Assessment Report	03 Febr 2025	04 Febr 2025
☐	CHMP members comments	17 Febr 2025	17 Febr 2025
☐	Updated CHMP Rapporteur Assessment Report	20 Febr 2025	N/A
☒	CHMP adoption of conclusions:	27 Febr 2025	27 Febr 2025

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1. Introduction

On 11 December 2024, the MAH submitted a completed paediatric study for Prevanar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

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 Open-Label Trial to Assess the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Infants and Young Children in China Who are Naive to Pneumococcal Vaccination" B1851178 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Each ready-to-use injectable dose of 0.5 ml of commercially available 13-valent Pneumococcal Polysaccharide Conjugate Vaccine (hereinafter referred to as "13vPnC") was formulated to contain 2.2 μg of polysaccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 μg of serotype 6B. Serotypes were individually conjugated to the CRM197 carrier protein and absorbed on aluminum phosphate (0.125 mg aluminum). Other ingredients included sodium chloride, succinic acid, polysorbate 80 and water for injection. The formulation of 13vPnC for adults is identical to the formulation of the vaccine for infants and children.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- B1851178: "A Phase 3 Open-Label Trial to Assess the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Infants and Young Children in China Who are Naive to Pneumococcal Vaccination".

Description

Methods

Study design

This is a Phase 3, randomized, open-label study to evaluate the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine (13vPnC) in infants and young children who were naïve to pneumococcal vaccination. Approximately 656 Chinese participants were planned to be enrolled in 4 different age cohorts (Cohorts 1, 2, 3, and 4 with N=125, 177, 177, and 177, respectively).

- Cohort 1: Participants 6 weeks (42 days) to 2 months (56 days) of age;
- Cohort 2: Participants 7 months (210 days) to <12 months (<365 days) of age;
- Cohort 3: Participants ≥1 year to <2 years of age;
- Cohort 4: Participants ≥2 years to <6 years of age.

The study was designed to address the Cenre for Drug Evaluation (CDE) request for data in infants and children through 5 years of age and support licensure application for active immunization for the prevention of invasive pneumococcal disease caused by S pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including sepsis, meningitis, bacteremia) in children 7 months to 5 years of age (before the 6th birthday).

Study participants

This study included 4 separate cohorts broken down by age. Cohort 1 included infants 6 weeks to 2 months of age who were then vaccinated with 13vPnC according to the currently licensed infant schedule (2, 4, 6 and 12 to 15 months). The participants in Cohorts 2, 3, and 4 ranged in age from 7 months to 5 years of age (Cohort 2 - 7 months to <12 months of age; Cohort 3 - ≥1 year to <2 years; Cohort 4 - ≥2 years to <6 years of age). Age at vaccination for each cohort is provided in **Table 1**.

Table 1: Age at vaccination.

		Age at First Vaccination	**Days Between First and Second Vaccination**	**Days Between Second and Third Vaccination**	**Age at Fourth Vaccination**
Cohort 1	13vPnC	42 to 56 days of age	42 to 70 days after Visit 1	42 to 70 days after Visit 2	365 to 455 days of age
Cohort 2	13vPnC or Hib vaccine	7 to <12 months of Age	At least 28 days after Visit 1	365 days to <450 days of age and at least 56 days after Visit 2a	N/A
Cohort 3	13vPnC or Hib vaccine	≥1 to <2 years of age	At least 56 days after Visit 1b	N/A	N/A
Cohort 4	13vPnC or Hib vaccine	≥2 to <6 years of age	N/A	N/A	N/A

Abbreviation: N/A = not applicable.

a. Participants in Cohort 2 randomized to Hib vaccine did not receive a vaccination at Visit 3. These participants were allowed to receive a third dose of Hib vaccine according to local practice or national recommendations, at the discretion of the investigator.
b. Participants in Cohort 3 randomized to Hib vaccine did not receive a vaccination at Visit 2.

Treatments

Participants in Cohort 1 received 13vPnC. Participants in Cohort 2, 3, or 4 were randomized in a 2:1 ratio to receive one of the following investigational products:

- 13vPnC
- Hib vaccine (comparator)

Commercially available 13vPnC was provided in accordance with local regulations. A commercially available Hib vaccine was provided for vaccination of participants in Cohorts 2, 3, or 4 randomized to the Hib vaccine group.

Objectives and endpoints

Table 2. Study Objectives and Endpoints

Primary Immunogenicity Objective:	**Primary Immunogenicity Endpoint:**
To assess the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) compared to immune responses in infants 6 weeks to 2 months of age (Cohort 1).	The serotype-specific IgG GMCs for each of the pneumococcal serotypes measured 1 month after the last dose of 13vPnC in Cohorts 2, 3, and 4 compared to IgG GMCs measured 1 month after the infant series in Cohort 1.
Primary Safety Objective:	**Primary Safety Endpoints:**
To evaluate the safety profile of 13vPnC in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) as measured by the incidence rates of local reactions, systemic events (including the use of antipyretic medication), and AEs.	a. The incidence of local reactions and systemic events (including the use of antipyretic medication) in the 7 days after each vaccination (13vPnC or Hib vaccine) in Cohorts 2, 3, and 4. b. The incidence of AEs from the signing of the ICD to 1 month after the last vaccination (13vPnC or Hib vaccine) in Cohorts 2, 3, and 4. c. The incidence of NDCMCs from 1 month after the last study vaccination (13vPnC or Hib vaccine) to 6 months after the last study vaccination in Cohorts 2, 3, and 4. d. The incidence of SAEs from the signing of the ICD to 6 months after the last study vaccination (13vPnC or Hib) in Cohorts 2, 3, and 4.
Secondary Immunogenicity Objectives:	**Secondary Immunogenicity Endpoints:**
To describe the functional antibody responses as measured by OPA to the 13 pneumococcal serotypes induced by 13vPnC in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) compared to responses in infants 6 weeks to 2 months of age (Cohort 1).	The serotype-specific OPA GMTs for each of the pneumococcal serotypes measured in a subset of approximately 50 participants per cohort measured 1 month after the last dose of 13vPnC in Cohorts 2, 3, and 4 compared to OPA GMTs measured 1 month after the infant series in Cohort 1.
To describe the immune responses to 13vPnC compared to Hib vaccine vaccinated controls in Cohorts 2, 3, and 4.	Serotype specific IgG GMC in all participants and OPA GMTs in approximately 50 participants per cohort vaccinated with 13vPnC (Cohorts 2, 3, and 4) and approximately 25 participants per cohorts

	vaccinated with Hib vaccine (Cohorts 2, 3, and 4) using blood drawn at the following visits: • Cohort 2: Visit 1, Visit 4 • Cohort 3: Visit 1, Visit 3 • Cohort 4: Visit 1, Visit 2
	Proportion of participants achieving a serotype-specific IgG concentration ≥0.35 µg/mL for each of the pneumococcal serotypes measured 1 month after the last dose in all participants per cohort vaccinated with 13vPnC (Cohorts 2 ,3, and 4) and all participants per cohort vaccinated with Hib vaccine (Cohorts 2, 3, and 4), and 1 month after the infant series in all participants vaccinated with 13vPnC in Cohort 1.

Sample size

With the 280 additional participants included, a total of 986 participants were screened in this study, of whom 932 participants (125 in Cohort 1, 353 in Cohort 2, 248 in Cohort 3, and 206 in Cohort 4) were assigned or randomized, and received investigational product.

Randomisation and blinding (masking)

Allocation of participants to vaccine groups proceeded using an interactive response technology (IRT) system or equivalent system. This is an open label study. All laboratory testing personnel performing serology assays were blinded to vaccine assigned/received, cohorts, and visits until all the assays were completed and results were finalized.

Statistical Methods

No formal statistical hypothesis test was performed and there were no formal statistical decision rules for this study. A descriptive estimation approach was used to assess all study objectives regarding safety and immunogenicity in the study.

Results

Participant flow

A total of 697 participants were screened in this study, of whom 653 participants were assigned or randomized, and received investigational product. Forty-four participants did not receive investigational product, of whom 39 participants were screen failures, 2 participants were not randomized, and 3 participants were withdrawn after randomization, but before receiving investigational product (**Table 3**).

In Cohort 1, 125 participants were assigned to receive 13vPnC, and 92 (73.6%) completed the infant series and post–infant series blood draw visit. Fourteen (11.2%) participants were withdrawn during the infant series, and 19 (15.2%) participants were withdrawn before the post–infant series visit blood draw; with the most common reason for withdrawal being withdrawal by parent/guardian.

In Cohort 2, 177 participants were randomized, with 118 receiving 13vPnC and 58 receiving Hib vaccine. One (1.7%) participant in the Hib vaccine group was withdrawn before vaccination. A total of 128 (72.3%) participants completed the vaccination series and postvaccination series blood draw visit, with the sole reason for withdrawal being withdrawal by parent/guardian.

The relatively high withdrawal rate in Cohorts 1 and 2 of the study was attributed to an incident that occurred in January 2019 when 145 infants and children received expired poliomyelitis vaccine (from another manufacturer) at Jinhu, a county level CDC under Huai An, Jiangsu CDC. Because of this incident, all clinical studies in Jiangsu CDC were put on hold, including Study B1851178. The suspension of clinical trial activities lasted for 1.5 months. Concerns over the expired poliomyelitis vaccine and the suspension of clinical trial activities resulted in a higher than anticipated number of participants being withdrawn in Cohorts 1 and 2.

In Cohort 3, 177 participants were randomized, with 118 receiving 13vPnC and 58 receiving Hib vaccine. One (1.7%) participant in the Hib vaccine group was withdrawn before vaccination. Most of the participants in both groups (81.9%) completed the vaccination series and postvaccination series blood draw visit, with the sole reason for withdrawal being withdrawal by parent/guardian

In Cohort 4, 177 participants were randomized, with 118 receiving 13vPnC and 58 receiving Hib vaccine. One (1.7%) participant in the Hib vaccine group was withdrawn before vaccination. Most of the participants in both groups (94.9%) completed vaccination and the postvaccination blood draw, with the sole reason for withdrawal being withdrawal by parent/guardian.

Table 3. Disposition of All Subjects

	Vaccine Group (as Randomized)				
	13vPnC (N[b]=479)	**Hib Vaccine (N[b]=177)**	**Not Assigned (N[b]=2)**	**Screen Failure[a] (N[b]=39)**	**Total (N[b]=697)**
	n[c] (%)	**n[c] (%)**	**n[c] (%)**	**n[c] (%)**	**n[c] (%)**
Consented[d]	479 (100.0)	177 (100.0)	2 (100.0)	39 (100.0)	697 (100.0)
Cohort 1					
Consented[d]	125 (26.1)	0	0	0	125 (17.9)
Assigned	125 (26.1)	0	0	0	125 (17.9)
Not vaccinated	0	0	0	0	0
Cohort 2					
Consented[d]	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Randomized	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Not vaccinated	0	1 (0.6)	0	0	1 (0.1)
Cohort 3					

Consented[d]	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Randomized	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Not vaccinated	0	1 (0.6)	0	0	1 (0.1)
Cohort 4					
Consented[d]	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Randomized	118 (24.6)	59 (33.3)	0	0	177 (25.4)
Not vaccinated	0	1 (0.6)	0	0	1 (0.1)

a. Number of subjects who signed the informed consent document but were not randomized or vaccinated.
b. N = number of subjects in the specified group or total sample. These values are used as the denominators for percentages.
c. n = Number of subjects in the specified category.
d. Number of subjects who signed the informed consent document.

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Recruitment

First Subject First Visit: 23 June 2018

Data Cutoff Date: 30 September 2019 (all data for Cohorts 2, 3, and 4 and infant series data for Cohort 1).

Baseline data

All participants in this study were Asian. Slightly more males than females participated in the study. The mean age at Dose 1 was within the protocol-specified age range for all 4 cohorts. The demographic characteristics were similar between the 13vPnC and Hib vaccine groups within Cohorts 2, 3, and 4, except for a greater percentage of female participants in the Hib vaccine group compared with the 13vPnC group in Cohort 4.

Numbers analysed

The primary analysis population for this study was the evaluable immunogenicity population. A total of 656 participants (125 participants in Cohort 1, 177 participants in each Cohort 2, 3, and 4) were assigned or randomized in this study.

One participant each in Cohorts 2, 3, and 4 did not receive investigational product and therefore were excluded from their safety populations. Thus, a total of **653** out of 656 participants were included in the safety population.

There was 1 participant each in Cohorts 2, 3, and 4 who did not have a valid and determinate assay result for the proposed analysis, therefore 176 participants were included in the all-available immunogenicity population for these cohorts. All participants in Cohort 1 provided at least 1 valid and determinate assay result and were included in the all-available immunogenicity population. The all-available immunogenicity population for all the cohorts included participants who had a valid and determinate assay result only before vaccination, participants who did not receive all the assigned

vaccinations to which they were randomized, and participants with valid and determinate assay results outside of SAP-specified blood draw collection time frame (27 to 56 days).

In Cohort 1, **72** (57.6%) participants were included in the evaluable immunogenicity population, with the most common reason for exclusion from the evaluable immunogenicity population being they missed the post–infant series blood draw collection time frame or had no valid and determinant post–infant series assay results.

In Cohort 2, **66** (55.9%) participants in the 13vPnC group and 16 (27.1%) participants in the Hib vaccine group were included in the evaluable immunogenicity population, with the most common reason for exclusion from the evaluable immunogenicity population being they missed the postvaccination series blood draw collection time frame or had no valid and determinant postvaccination series assay results.

The Hib vaccine group, compared to the 13vPnC group, had a lower proportion of participants with blood samples collected within the prespecified time frame), which led to a lower proportion of participants included in the evaluable immunogenicity population. This was attributed to the open label design of the trial, where participant's parents/guardians cited that there was no real advantage to receiving the Hib vaccine. During the signing of the ICD, investigators had made it clear that the study was an open label design and their children may be randomized to either 13vPnC group or the Hib vaccine group.

In Cohort 3, **83** (70.3%) participants in the 13vPnC group and 53 (89.8%) participants in the Hib vaccine group were included in the evaluable immunogenicity population, with the most common reason for exclusion from the evaluable immunogenicity population being they missed the postvaccination series blood draw collection time frame or had no valid and determinant postvaccination assay results.

In Cohort 4, most participants (94.9%) in both groups were included in the evaluable immunogenicity population.

Efficacy results

Immunogenicity

Cohort 1 (6 Weeks to 2 Months of Age)

- As expected, robust immune responses were observed for all serotypes 1 month after the 13vPnC infant series based on pneumococcal IgG GMCs, IgG GMFRs, the proportion of participants with IgG concentrations ≥0.35 µg/mL, OPA GMTs, OPA GMFRs (**Table 4**), and the proportion of participants with OPA titers ≥LLOQ (**Table 5**).
- Robust immune responses were observed for all serotypes 1 month after the 13vPnC toddler dose based on pneumococcal IgG GMCs, IgG GMFRs, OPA GMTs, and OPA GMFRs.
- At 1 year after the toddler dose, for all serotypes, the observed IgG GMCs were, with few exceptions, generally higher than or similar to those observed 1 month before the toddler dose, and lower than those observed 1 month after the toddler dose. The observed IgG GMCs generally remained at similar levels from 1 to 4 years after the toddler dose for most serotypes.
- At 1 year after the toddler dose, for all serotypes, the observed OPA GMTs were, with few exceptions, generally higher than or similar to those observed 1 month before the toddler dose, and lower than those observed 1 month after the toddler dose. The observed OPA GMTs

generally remained at similar levels or decreased from 1 to 4 years after the toddler dose. However, with the small number of valid OPA titers for each serotype, interpretations of OPA results should be made with caution.

- At 1 year after the toddler dose, for all serotypes, the observed IgG GMCs and OPA GMTs from Cohort 1 were higher than those observed before the vaccination for Cohorts 2, 3, and 4 of older children.
- At 1, 2, 3, and 4 years after the toddler dose, for all serotypes, the observed IgG GMCs and OPA GMTs were higher than those observed before the infant series.

Table 4. Pneumococcal IgG GMCs (µg/mL) and GMFR – Cohort 1 (Infant Series) – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	n[b]	GMC[c] (95% CI[d])	Vaccine Group (as Assigned) 13vPnC n[e]	GMFR[f] (95% CI[d])
1	Before the infant series	72	0.10 (0.07, 0.15)		
	1 Month after the infant series	72	5.40 (4.43, 6.58)	72	51.75 (34.37, 77.93)
3	Before the infant series	71	0.13 (0.10, 0.18)		
	1 Month after the infant series	72	0.63 (0.54, 0.75)	71	4.68 (3.36, 6.51)
4	Before the infant series	72	0.05 (0.03, 0.08)		
	1 Month after the infant series	72	3.96 (3.24, 4.84)	72	78.37 (49.77, 123.39)
5	Before the infant series	72	0.50 (0.44, 0.57)		
	1 Month after the infant series	72	3.50 (2.91, 4.19)	72	7.00 (5.47, 8.94)
6A	Before the infant series	72	0.60 (0.51, 0.71)		
	1 Month after the infant series	72	5.35 (4.44, 6.44)	72	8.92 (6.68, 11.92)
6B	Before the infant series	72	0.35 (0.28, 0.43)		
	1 Month after the infant series	72	4.62 (3.76, 5.69)	72	13.38 (9.83, 18.23)
7F	Before the infant series	71	0.26 (0.19, 0.35)		
	1 Month after the infant series	72	7.14 (6.00, 8.50)	71	27.36 (18.56, 40.33)
9V	Before the infant series	72	0.36 (0.31, 0.44)		
	1 Month after the infant series	72	3.66 (2.99, 4.50)	72	10.05 (7.32, 13.80)
14	Before the infant series	72	0.83 (0.57, 1.22)		
	1 Month after the infant series	72	15.09 (11.39, 20.00)	72	18.08 (10.45, 31.28)
18C	Before the infant series	72	0.35 (0.29, 0.43)		
	1 Month after the infant series	72	4.94 (4.11, 5.94)	72	13.99 (10.31, 18.97)
19A	Before the infant series	72	0.84 (0.71, 1.01)		
	1 Month after the infant series	72	3.44 (2.85, 4.16)	72	4.07 (3.04, 5.46)
19F	Before the infant series	71	0.50 (0.39, 0.64)		
	1 Month after the infant series	72	4.95 (3.91, 6.26)	71	9.92 (6.71, 14.66)
23F	Before the infant series	72	0.30 (0.25, 0.37)		
	1 Month after the infant series	72	4.36 (3.23, 5.88)	72	14.51 (9.77, 21.53)

Abbreviations: BLQ = below the limit of quantitation; GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.

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

c. GMCs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5 × LOD was assigned for analysis.

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

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

f. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 5. Pneumococcal OPA GMTs and GMFR – Cohort 1 (Infant Series) – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	Vaccine Group (as Assigned) 13vPnC n[b]	GMT[c] (95% CI[d])	13vPnC n[e]	GMFR[f] (95% CI[d])
1	Before the infant series	37	4.1 (3.9, 4.3)		
	1 Month after the infant series	37	201.7 (134.8, 301.8)	37	49.06 (32.87, 73.24)
3	Before the infant series	37	4.1 (3.9, 4.3)		
	1 Month after the infant series	37	112.9 (82.5, 154.4)	37	27.45 (20.19, 37.33)
4	Before the infant series	37	4.9 (4.1, 5.9)		
	1 Month after the infant series	37	1857.8 (1264.8, 2728.8)	37	380.63 (240.77, 601.72)
5	Before the infant series	37	4.0 (4.0, 4.0)		
	1 Month after the infant series	37	645.9 (452.6, 921.8)	37	161.48 (113.14, 230.45)
6A	Before the infant series	37	10.8 (6.3, 18.5)		
	1 Month after the infant series	37	5996.2 (4337.5, 8289.3)	37	556.17 (325.68, 949.78)
6B	Before the infant series	37	15.8 (9.1, 27.2)		
	1 Month after the infant series	37	2331.6 (1481.3, 3670.0)	37	147.85 (74.40, 293.84)
7F	Before the infant series	37	18.7 (9.8, 35.9)		
	1 Month after the infant series	37	10413.4 (7373.1, 14707.3)	37	555.94 (258.72, 1194.62)
9V	Before the infant series	37	6.8 (4.3, 10.7)		
	1 Month after the infant series	37	5386.5 (3634.0, 7984.3)	37	796.70 (397.41, 1597.16)
14	Before the infant series	37	21.8 (12.2, 38.8)		
	1 Month after the infant series	37	2859.4 (1668.9, 4899.3)	37	131.17 (56.81, 302.85)
18C	Before the infant series	37	9.9 (6.0, 16.6)		
	1 Month after the infant series	37	2677.9 (2000.3, 3585.0)	37	269.19 (140.91, 514.23)
19A	Before the infant series	37	7.5 (5.0, 11.2)		
	1 Month after the infant series	37	1677.3 (1159.9, 2425.5)	37	225.07 (126.31, 401.03)
19F	Before the infant series	37	6.4 (4.5, 9.3)		
	1 Month after the infant series	37	744.4 (506.7, 1093.6)	37	115.41 (72.30, 184.23)
23F	Before the infant series	37	5.6 (4.1, 7.7)		

Abbreviations: BLQ = below the limit of quantitation; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. GMTs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.
d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or the fold rise.
e. n = Number of subjects with valid and determinate assay results for the specified serotype at both the given visits.
f. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Cohort 2 (7 Months to <12 Months of Age)

- 13vPnC induced significant increases in pneumococcal IgG GMCs for all serotypes from before to 1 month after the vaccination series. Increases were not seen in participants that received Hib vaccine. IgG GMCs in Cohort 2 were generally comparable to those post–infant series in Cohort 1 and for 8 of 13 serotypes the IgG GMRs would have met noninferiority using standard 2-fold criterion for the comparison of pneumococcal IgG GMCs. The precision of these IgG comparisons may have been impacted by the number of dropouts in both cohorts **Table 6**).
- The reverse cumulative distribution curves (RCDCs) comparing IgG GMCs for Cohorts 2 and 1 showed responses varied by serotypes, but for the majority of the serotypes antibody levels from Cohort 1 and Cohort 2 were generally comparable (**not shown**).
- The ratios of IgG GMCs 1 month after the vaccination series from Cohort 2 to the IgG GMCs 1 month after the infant series from Cohort 1 ranged from 0.42 (serotypes 18C and 23F) to 1.96 (serotype 3). The observed GMRs were greater than 0.5 for 10 of the 13 serotypes (except for serotypes 6B, 18C and 23F), and the lower bounds of the 2-sided 95% CIs for the IgG GMRs were greater than 0.5 for 8 of the 13 serotypes (except for serotypes 6A, 6B, 9V, 18C, and 23F). IgG GMCs for these 8 serotypes in the Cohort 2 13vPnC recipients would have been noninferior to those in Cohort 1 if noninferiority was evaluated using a 2-fold criterion for the comparison of pneumococcal IgG GMCs (**Table 7**).
- Greater than 95% of participants achieved pneumococcal IgG concentrations ≥0.35 µg/mL, an IgG concentration associated with protection against invasive disease in infants (**Table 8**).
- The increases in IgG antibody were associated with significant increases in functional antibody as measured by OPA (**Table 9**) and noted in the GMFRs. OPA GMTs and percent responders (≥ LLOQ) in Cohort 2 were generally comparable to those in Cohort 1 for most serotypes (**Table 10**).
- The MAH concludes that these data support that 13vPnC will be effective in preventing pneumococcal disease in this population.

Table 6. Pneumococcal IgG GMCs (µg/mL) and GMFR – Cohort 2 – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	13vPnC					Vaccine Group (as Randomized)			Hib Vaccine			
		n[b]	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])
1	Before vaccination	66	0.01	(0.01, 0.02)				16	0.02	(0.01, 0.04)			
	1 Month after the last dose	66	3.72	(3.05, 4.54)	66	334.18	(218.09, 512.07)	16	0.02	(0.01, 0.06)	16	1.35	(0.55, 3.32)
3	Before vaccination	66	0.03	(0.02, 0.04)				16	0.03	(0.01, 0.06)			
	1 Month after the last dose	66	1.25	(1.06, 1.46)	66	49.19	(34.21, 70.74)	16	0.02	(0.01, 0.04)	16	0.65	(0.39, 1.10)
4	Before vaccination	66	0.01	(0.01, 0.01)				16	0.01	(0.00, 0.01)			
	1 Month after the last dose	66	2.61	(2.16, 3.15)	66	320.67	(224.12, 458.80)	16	0.01	(0.00, 0.03)	16	1.48	(0.48, 4.52)
5	Before vaccination	66	0.36	(0.29, 0.46)				16	0.35	(0.27, 0.46)			
	1 Month after the last dose	66	3.32	(2.74, 4.02)	66	9.15	(6.86, 12.21)	16	0.40	(0.30, 0.53)	16	1.14	(0.95, 1.36)
6A	Before vaccination	65	0.13	(0.10, 0.18)				16	0.09	(0.04, 0.21)			
	1 Month after the last dose	66	3.03	(2.40, 3.82)	65	22.25	(15.78, 31.39)	16	0.15	(0.08, 0.30)	16	1.62	(1.01, 2.61)
6B	Before vaccination	66	0.14	(0.10, 0.19)				16	0.14	(0.07, 0.26)			
	1 Month after the last dose	66	2.00	(1.56, 2.55)	66	14.73	(10.30, 21.06)	16	0.15	(0.08, 0.29)	16	1.07	(0.83, 1.38)
7F	Before vaccination	65	0.03	(0.02, 0.04)				16	0.02	(0.01, 0.05)			
	1 Month after the last dose	66	5.54	(4.74, 6.46)	65	216.14	(148.30, 315.00)	16	0.03	(0.01, 0.06)	16	1.27	(0.48, 3.36)
9V	Before vaccination	66	0.08	(0.05, 0.12)				16	0.10	(0.04, 0.28)			
	1 Month after the last dose	66	2.17	(1.80, 2.62)	66	26.94	(17.06, 42.57)	16	0.12	(0.05, 0.32)	16	1.24	(0.76, 2.02)
14	Before vaccination	65	0.03	(0.02, 0.05)				16	0.02	(0.01, 0.04)			
	1 Month after the last dose	66	11.00	(9.23, 13.10)	65	319.61	(213.00, 479.58)	16	0.02	(0.01, 0.03)	16	0.99	(0.87, 1.12)
18C	Before vaccination	66	0.01	(0.01, 0.01)				16	0.01	(0.00, 0.02)			
	1 Month after the last dose	66	2.07	(1.73, 2.47)	66	282.16	(200.12, 397.83)	16	0.01	(0.01, 0.03)	16	1.57	(0.66, 3.74)

19A	Before vaccination	66	0.31	(0.24, 0.39)				16	0.29	(0.15, 0.55)			
	1 Month after the last dose	66	3.61	(3.08, 4.24)	66	11.83	(9.14, 15.30)	16	0.46	(0.29, 0.72)	16	1.60	(0.96, 2.67)
19F	Before vaccination	63	0.04	(0.03, 0.07)				16	0.04	(0.02, 0.11)			
	1 Month after the last dose	66	4.23	(3.36, 5.31)	63	101.18	(61.22, 167.20)	16	0.10	(0.04, 0.23)	16	2.37	(1.11, 5.03)

Abbreviations: BLQ = below the limit of quantitation; GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

g. SAP-specified timing for blood sample collection.

h. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.

i. GMCs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5 × LOD was assigned for analysis.

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

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

l. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 7. Comparison of Pneumococcal IgG GMCs (µg/mL), 1 Month After the Last Dose for Cohort 2 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

Serotype	n[b]	Sampling Time Point[a] and Cohort: 1 Month After Last Dose (Cohort 2)		n[b]	1 Month After Infant Series (Cohort 1)		1 Month After Last Dose (Cohort 2) vs 1 Month After Infant Series (Cohort 1)	
		GMC[c]	(95% CI[d])		GMC[c]	(95% CI[d])	GMR[e]	(95% CI[d])
1	66	3.72	(3.05, 4.54)	72	5.40	(4.43, 6.58)	0.69	(0.52, 0.91)
3	66	1.25	(1.06, 1.46)	72	0.63	(0.54, 0.75)	1.96	(1.56, 2.46)
4	66	2.61	(2.16, 3.15)	72	3.96	(3.24, 4.84)	0.66	(0.50, 0.87)
5	66	3.32	(2.74, 4.02)	72	3.50	(2.91, 4.19)	0.95	(0.73, 1.23)
6A	66	3.03	(2.40, 3.82)	72	5.35	(4.44, 6.44)	0.57	(0.42, 0.76)
6B	66	2.00	(1.56, 2.55)	72	4.62	(3.76, 5.69)	0.43	(0.31, 0.59)
7F	66	5.54	(4.74, 6.46)	72	7.14	(6.00, 8.50)	0.78	(0.61, 0.98)
9V	66	2.17	(1.80, 2.62)	72	3.66	(2.99, 4.50)	0.59	(0.45, 0.78)
14	66	11.00	(9.23, 13.10)	72	15.09	(11.39, 20.00)	0.73	(0.52, 1.01)
18C	66	2.07	(1.73, 2.47)	72	4.94	(4.11, 5.94)	0.42	(0.32, 0.54)
19A	66	3.61	(3.08, 4.24)	72	3.44	(2.85, 4.16)	1.05	(0.82, 1.35)
19F	66	4.23	(3.36, 5.31)	72	4.95	(3.91, 6.26)	0.85	(0.62, 1.18)
23F	66	1.84	(1.44, 2.36)	72	4.36	(3.23, 5.88)	0.42	(0.29, 0.63)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.
c. GMCs were calculated for all subjects in the 13vPnC group with available data from the specified postvaccination blood draw. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5
d. × LOD was assigned for analysis.
e. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations or ratios.
f. GMR is the ratio of GMCs: 1 month after last dose for Cohort 2/1 month after infant series for Cohort 1. GMRs were calculated for all subjects with available data from postvaccination blood draws.

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Table 8. Comparison of Subjects Achieving a Pneumococcal IgG Concentration≥0.35 µg/mL, 1 Month After the Last Dose for Cohort 2 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort									
	1 Month After Last Dose (Cohort 2)				1 Month After Infant Series (Cohort 1)				1 Month After Last Dose (Cohort 2) vs 1 Month After Infant Series (Cohort 1)	
Serotype	N[b]	n[c]	(%)	(95% CI[d])	N[b]	n[c]	(%)	(95% CI[d])	Difference in %[e]	(95% CI[f])
1	66	66	100.0	(94.6, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-5.7, 5.2)
3	66	63	95.5	(87.3, 99.1)	72	60	83.3	(72.7, 91.1)	12.1	(1.6, 23.4)
4	66	66	100.0	(94.6, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-5.7, 5.2)
5	66	66	100.0	(94.6, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-5.7, 5.2)
6A	66	63	95.5	(87.3, 99.1)	72	72	100.0	(95.0, 100.0)	-4.5	(-12.7, 0.8)
6B	66	63	95.5	(87.3, 99.1)	72	72	100.0	(95.0, 100.0)	-4.5	(-12.7, 0.8)
7F	66	66	100.0	(94.6, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-5.7, 5.2)
9V	66	65	98.5	(91.8, 100.0)	72	72	100.0	(95.0, 100.0)	-1.5	(-8.2, 3.7)
14	66	66	100.0	(94.6, 100.0)	72	70	97.2	(90.3, 99.7)	2.8	(-3.0, 9.7)
18C	66	65	98.5	(91.8, 100.0)	72	72	100.0	(95.0, 100.0)	-1.5	(-8.2, 3.7)
19A	66	66	100.0	(94.6, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-5.7, 5.2)
19F	66	65	98.5	(91.8, 100.0)	72	71	98.6	(92.5, 100.0)	-0.1	(-7.0, 6.4)
23F	66	62	93.9	(85.2, 98.3)	72	69	95.8	(88.3, 99.1)	-1.9	(-11.1, 6.5)

Abbreviations: IgG = immunoglobulin G; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample.

b. N = number of subjects with a valid and determinate postvaccination IgG concentration to the specified serotype. These values are used as the denominators for percentages.

c. n = Number of subjects with IgG concentration ≥0.35 µg/mL for the given serotype.

d. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

e. Risk difference was computed for 1 month after last dose for Cohort 2 - 1 month after infant series for Cohort 1.

f. Exact 2-sided confidence intervals are calculated using Chan and Zhang's method (1999) based upon the observed proportion of subjects.

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Table 9. Pneumococcal OPA GMTs and GMFR – Cohort 2 – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	13vPnC					Vaccine Group (as Randomized)			Hib Vaccine			
		n[b]	GMT[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])
1	Before vaccination	38	4.3	(3.7, 5.0)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	149.9	(91.8, 244.9)	38	34.80	(21.51, 56.30)	11	4.0	(4.0, 4.0)	11	1.00	(1.00, 1.00)
3	Before vaccination	38	4.5	(3.8, 5.3)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	145.5	(105.8, 200.3)	38	32.37	(23.60, 44.39)	11	4.4	(3.6, 5.4)	11	1.10	(0.89, 1.35)
4	Before vaccination	38	5.7	(3.9, 8.4)				11	5.4	(2.8, 10.5)			
	1 Month after the last dose	38	1347.6	(997.6, 1820.4)	38	236.38	(149.48, 373.80)	11	7.6	(2.2, 25.9)	11	1.41	(0.33, 6.09)
5	Before vaccination	38	4.8	(3.5, 6.5)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	360.5	(237.2, 547.9)	38	75.37	(50.82, 111.77)	11	4.5	(3.5, 5.7)	11	1.11	(0.88, 1.41)
6A	Before vaccination	38	4.6	(3.6, 5.9)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	4217.8	(2988.8, 5952.0)	38	912.62	(618.56, 1346.47)	11	6.1	(2.8, 13.3)	11	1.53	(0.70, 3.34)
6B	Before vaccination	38	5.8	(3.8, 8.8)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	791.8	(387.7, 1617.3)	38	136.74	(57.05, 327.71)	11	4.0	(4.0, 4.0)	11	1.00	(1.00, 1.00)
7F	Before vaccination	38	40.0	(17.5, 91.4)				11	37.0	(6.3, 217.9)			
	1 Month after the last dose	38	6795.6	(5336.8, 8653.1)	38	170.07	(68.12, 424.59)	11	160.6	(31.3, 823.4)	11	4.34	(0.59, 31.99)
9V	Before vaccination	38	7.9	(4.6, 13.5)				11	9.5	(3.0, 29.8)			
	1 Month after the last dose	38	5459.0	(3938.7, 7566.2)	38	692.00	(403.60, 1186.48)	11	12.8	(3.3, 50.2)	11	1.35	(0.38, 4.81)
14	Before vaccination	38	6.6	(4.4, 9.8)				11	8.3	(2.9, 23.5)			
	1 Month after the last dose	38	2492.7	(1851.5, 3356.0)	38	377.86	(230.84, 618.53)	11	4.5	(3.5, 5.7)	11	0.54	(0.18, 1.62)
18C	Before vaccination	38	4.7	(3.5, 6.3)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	1243.4	(925.8, 1670.0)	38	263.18	(180.25, 384.26)	11	4.0	(4.0, 4.0)	11	1.00	(1.00, 1.00)

19A	Before vaccination	38	4.4	(3.6, 5.3)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	1640.1	(1153.2, 2332.6)	38	373.12	(257.07, 541.56)	11	4.3	(3.6, 5.2)	11	1.09	(0.90, 1.31)
19F	Before vaccination	38	4.6	(3.6, 5.8)				11	5.4	(2.8, 10.5)			
	1 Month after the last dose	38	706.2	(509.8, 978.2)	38	153.47	(111.63, 210.99)	11	4.0	(4.0, 4.0)	11	0.74	(0.38, 1.44)
23F	Before vaccination	38	5.9	(3.8, 9.1)				11	4.0	(4.0, 4.0)			
	1 Month after the last dose	38	1748.1	(858.2, 3560.7)	38	297.84	(141.11, 628.62)	11	13.3	(2.1, 84.1)	11	3.33	(0.53, 21.03)

Abbreviations: BLQ = below the limit of quantitation; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. GMTs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.
d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or the fold rise.
e. n = Number of subjects with valid and determinate assay results for the specified serotype at both the given visits.
f. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 10. Comparison of Pneumococcal OPA GMTs, 1 Month After the Last Dose for Cohort 2 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort							
	1 Month After Last Dose (Cohort 1)			1 Month After Infant Series (Cohort 2) vs 1 Month After Last Dose 2)			Infant Series (Cohort 1)	
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	GMR[e]	(95% CI[d])
1	38	149.9	(91.8, 244.9)	37	201.7	(134.8, 301.8)	0.74	(0.40, 1.39)
3	38	145.5	(105.8, 200.3)	37	112.9	(82.5, 154.4)	1.29	(0.83, 2.00)
4	38	1347.6	(997.6, 1820.4)	37	1857.8	(1264.8, 2728.8)	0.73	(0.45, 1.17)
5	38	360.5	(237.2, 547.9)	37	645.9	(452.6, 921.8)	0.56	(0.32, 0.96)
6A	38	4217.8	(2988.8, 5952.0)	37	5996.2	(4337.5, 8289.3)	0.70	(0.44, 1.12)
6B	38	791.8	(387.7, 1617.3)	37	2331.6	(1481.3, 3670.0)	0.34	(0.15, 0.78)
7F	38	6795.6	(5336.8, 8653.1)	37	10413.4	(7373.1, 14707.3)	0.65	(0.43, 0.99)
9V	38	5459.0	(3938.7, 7566.2)	37	5386.5	(3634.0, 7984.3)	1.01	(0.61, 1.67)
14	38	2492.7	(1851.5, 3356.0)	37	2859.4	(1668.9, 4899.3)	0.87	(0.47, 1.60)
18C	38	1243.4	(925.8, 1670.0)	37	2677.9	(2000.3, 3585.0)	0.46	(0.31, 0.70)
19A	38	1640.1	(1153.2, 2332.6)	37	1677.3	(1159.9, 2425.5)	0.98	(0.59, 1.61)
19F	38	706.2	(509.8, 978.2)	37	744.4	(506.7, 1093.6)	0.95	(0.58, 1.56)
23F	38	1748.1	(858.2, 3560.7)	37	3833.2	(2216.2, 6630.1)	0.46	(0.19, 1.11)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

e. SAP-specified timing for blood sample collection.

f. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.

g. GMTs were calculated for all subjects in the 13vPnC group with available data from the specified postvaccination blood draw. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.

h. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or ratios.

i. GMR is the ratio of GMTs: 1 month after last dose for Cohort 2/1 month after infant series for Cohort 1. GMRs were calculated for all subjects with available data from postvaccination blood draws.

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Cohort 3 (≥1 Year to <2 Years of Age)

- 13vPnC induced significant increases in pneumococcal IgG GMCs for all serotypes from before to 1 month after the vaccination series *(***Table 11)**. Increases were not seen in participants that received Hib vaccine.

- The RCDCs showed increases in IgG and OPA antibodies after the vaccination series for the 13vPnC recipients for all serotypes (**not shown**).

- IgG GMCs in Cohort 3 were generally comparable to those post–infant series in Cohort 1 and for 9 of 13 serotypes the IgG GMRs would have met noninferiority using standard 2-fold criterion for the comparison of pneumococcal IgG GMCs. The precision of these IgG comparisons may have been impacted by the number of dropouts in both cohorts (**Table 12**).

- The RCDCs comparing IgG GMCs for Cohorts 3 and 1 showed responses varied by serotypes, but for the majority of the serotypes antibody levels from Cohort 3 and Cohort 1 were generally comparable (not shown).

- Greater than 94% of participants achieved pneumococcal IgG concentrations ≥0.35 µg/mL, an IgG concentration associated with protection against invasive disease in infants **(Table 13**).

- The increases in IgG antibody were associated with significant increases in functional antibody as measured by OPA and noted in the GMFRs. OPA GMTs and percent responders (≥ LLOQ) in Cohort 3 were generally comparable to those in Cohort 1 for most serotypes (**Table 14**).

- The MAH concludes that these data support that 13vPnC will be effective in preventing pneumococcal disease in this population.

Table 11. Pneumococcal IgG GMCs (µg/mL) and GMFR – Cohort 3 – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		13vPnC					Hib Vaccine				
Serotype	Sampling Time Point[a]	nb	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])
1	Before vaccination	83	0.07	(0.05, 0.09)				53	0.06	(0.04, 0.10)			
	1 Month after the last dose	83	4.22	(3.41, 5.23)	83	64.09	(43.30, 94.85)	53	0.05	(0.03, 0.09)	53	0.83	(0.45, 1.51)
3	Before vaccination	81	0.05	(0.04, 0.07)				53	0.06	(0.04, 0.09)			
	1 Month after the last dose	83	1.50	(1.27, 1.76)	81	28.87	(20.29, 41.07)	53	0.08	(0.05, 0.12)	53	1.35	(0.88, 2.08)
4	Before vaccination	83	0.02	(0.02, 0.04)				53	0.05	(0.03, 0.08)			
	1 Month after the last dose	83	4.11	(3.35, 5.04)	83	167.42	(105.89, 264.68)	53	0.03	(0.01, 0.05)	53	0.61	(0.34, 1.07)
5	Before vaccination	83	0.74	(0.63, 0.88)				53	0.66	(0.55, 0.79)			
	1 Month after the last dose	83	2.85	(2.46, 3.30)	83	3.82	(3.22, 4.55)	53	0.78	(0.63, 0.98)	53	1.19	(1.03, 1.37)
6A	Before vaccination	83	0.30	(0.24, 0.36)				53	0.36	(0.30, 0.43)			
	1 Month after the last dose	83	2.81	(2.31, 3.42)	83	9.47	(7.14, 12.55)	52	0.42	(0.33, 0.54)	52	1.19	(0.98, 1.44)
6B	Before vaccination	83	0.33	(0.28, 0.39)				53	0.38	(0.31, 0.45)			
	1 Month after the last dose	83	2.26	(1.81, 2.83)	83	6.87	(5.18, 9.12)	53	0.40	(0.32, 0.51)	53	1.08	(0.90, 1.29)
7F	Before vaccination	83	0.08	(0.06, 0.11)				52	0.10	(0.06, 0.15)			
	1 Month after the last dose	83	8.14	(6.81, 9.73)	83	99.80	(69.39, 143.52)	52	0.11	(0.06, 0.20)	51	1.14	(0.66, 1.96)
9V	Before vaccination	82	0.26	(0.20, 0.35)				53	0.27	(0.21, 0.34)			
	1 Month after the last dose	83	3.52	(2.97, 4.17)	82	13.35	(9.91, 17.98)	52	0.34	(0.24, 0.48)	52	1.26	(0.96, 1.65)
14	Before vaccination	83	0.03	(0.02, 0.05)				53	0.06	(0.03, 0.11)			

	1 Month after the last dose	83	9.70	(7.86, 11.96)	83	298.77	(190.99, 467.35)	53	0.07	(0.03, 0.15)	53	1.22	(0.63, 2.38)
18C	Before vaccination	83	0.04	(0.03, 0.06)				53	0.05	(0.03, 0.09)			
	1 Month after the last dose	83	4.18	(3.30, 5.28)	83	106.68	(64.75, 175.74)	53	0.08	(0.04, 0.15)	53	1.44	(0.76, 2.72)
19A	Before vaccination	83	0.68	(0.56, 0.83)				53	0.71	(0.57, 0.88)			
	1 Month after the last dose	83	5.97	(5.02, 7.09)	83	8.77	(6.86, 11.21)	53	0.97	(0.73, 1.29)	53	1.37	(1.07, 1.73)
19F	Before vaccination	83	0.20	(0.15, 0.28)				53	0.19	(0.13, 0.29)			
	1 Month after the last dose	83	4.72	(3.75, 5.93)	83	23.27	(15.51, 34.91)	53	0.22	(0.13, 0.38)	53	1.16	(0.73, 1.86)
23F	Before vaccination	82	0.20	(0.16, 0.24)				52	0.24	(0.20, 0.29)			
	1 Month after the last dose	83	2.41	(1.96, 2.96)	82	12.26	(9.26, 16.22)	53	0.32	(0.23, 0.43)	52	1.34	(1.03, 1.75)

Abbreviations: BLQ = below the limit of quantitation; GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. GMCs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5 × LOD was assigned for analysis.
d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations or the fold rise.
e. n = Number of subjects with valid and determinate assay results for the specified serotype at both the given visits.
f. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 12. Comparison of Pneumococcal IgG GMCs (µg/mL), 1 Month After the Last Dose for Cohort 3 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a] and Cohort							
	n[b]	1 Month After Last Dose Series (Cohort 3) (Cohort 1)		1 Month After Infant			1 Month After Last Dose (Cohort 3) vs 1 Month After Infant Series (Cohort 1)	
		GMC[c] CI[d])	(95% CI[d])	n[b]	GMC[c]	(95%	GMR[e]	(95% CI[d])
1	83	4.22	(3.41, 5.23)	72	5.40	(4.43, 6.58)	0.78	(0.58, 1.05)
3	83	1.50	(1.27, 1.76)	72	0.63	(0.54, 0.75)	2.36	(1.87, 2.97)
4	83	4.11	(3.35, 5.04)	72	3.96	(3.24, 4.84)	1.04	(0.78, 1.38)
5	83	2.85	(2.46, 3.30)	72	3.50	(2.91, 4.19)	0.81	(0.65, 1.02)
6A	83	2.81	(2.31, 3.42)	72	5.35	(4.44, 6.44)	0.53	(0.40, 0.69)
6B	83	2.26	(1.81, 2.83)	72	4.62	(3.76, 5.69)	0.49	(0.36, 0.66)
7F	83	8.14	(6.81, 9.73)	72	7.14	(6.00, 8.50)	1.14	(0.89, 1.46)
9V	83	3.52	(2.97, 4.17)	72	3.66	(2.99, 4.50)	0.96	(0.74, 1.25)
14	83	9.70	(7.86, 11.96)	72	15.09	(11.39, 20.00)	0.64	(0.46, 0.91)
18C	83	4.18	(3.30, 5.28)	72	4.94	(4.11, 5.94)	0.85	(0.63, 1.14)
19A	83	5.97	(5.02, 7.09)	72	3.44	(2.85, 4.16)	1.73	(1.35, 2.24)
19F	83	4.72	(3.75, 5.93)	72	4.95	(3.91, 6.26)	0.95	(0.69, 1.32)
23F	83	2.41	(1.96, 2.96)	72	4.36	(3.23, 5.88)	0.55	(0.38, 0.79)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

j. SAP-specified timing for blood sample collection.

k. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.

l. GMCs were calculated for all subjects in the 13vPnC group with available data from the specified postvaccination blood draw. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5
× LOD was assigned for analysis.

m. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations or ratios.

n. GMR is the ratio of GMCs: 1 month after last dose for Cohort 3/1 month after infant series for Cohort 1. GMRs were calculated for all subjects with available data from postvaccination blood draws.

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Table 13. Comparison of Subjects Achieving a Pneumococcal IgG Concentration ≥0.35 µg/mL, 1 Month After the Last Dose for Cohort 3 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort									
	1 Month After Last Dose (Cohort 3)				1 Month After Infant Series (Cohort 1)				1 Month After Last Dose (Cohort 3) vs 1 Month After Infant Series (Cohort 1)	
Serotype	N[b]	n[c]	(%)	(95% CI[d])	N[b]	n[c]	(%)	(95% CI[d])	Difference in %[e]	(95% CI[f])
1	83	80	96.4	(89.8, 99.2)	72	72	100.0	(95.0, 100.0)	-3.6	(-10.3, 1.8)
3	83	79	95.2	(88.1, 98.7)	72	60	83.3	(72.7, 91.1)	11.8	(1.7, 23.1)
4	83	80	96.4	(89.8, 99.2)	72	72	100.0	(95.0, 100.0)	-3.6	(-10.3, 1.8)
5	83	83	100.0	(95.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-4.5, 5.3)
6A	83	81	97.6	(91.6, 99.7)	72	72	100.0	(95.0, 100.0)	-2.4	(-8.4, 3.1)
6B	83	81	97.6	(91.6, 99.7)	72	72	100.0	(95.0, 100.0)	-2.4	(-8.4, 3.1)
7F	83	81	97.6	(91.6, 99.7)	72	72	100.0	(95.0, 100.0)	-2.4	(-8.4, 3.1)
9V	83	82	98.8	(93.5, 100.0)	72	72	100.0	(95.0, 100.0)	-1.2	(-6.9, 4.3)
14	83	81	97.6	(91.6, 99.7)	72	70	97.2	(90.3, 99.7)	0.4	(-6.1, 7.6)
18C	83	81	97.6	(91.6, 99.7)	72	72	100.0	(95.0, 100.0)	-2.4	(-8.4, 3.1)
19A	83	83	100.0	(95.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-4.5, 5.3)
19F	83	80	96.4	(89.8, 99.2)	72	71	98.6	(92.5, 100.0)	-2.2	(-9.1, 4.3)
23F	83	81	97.6	(91.6, 99.7)	72	69	95.8	(88.3, 99.1)	1.8	(-4.9, 9.6)

Abbreviations: IgG = immunoglobulin G; SAP = statistical analysis plan.

o. SAP-specified timing for blood sample.

p. N = number of subjects with a valid and determinate postvaccination IgG concentration to the specified serotype. These values are used as the denominators for percentages.

q. n = Number of subjects with IgG concentration ≥0.35 µg/mL for the given serotype.

r. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

s. Risk difference was computed for 1 month after last dose for Cohort 3 - 1 month after infant series for Cohort 1.

t. Exact 2-sided confidence intervals are calculated using Chan and Zhang's method (1999) based upon the observed proportion of subjects.

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Table 14. Comparison of Pneumococcal OPA GMTs, 1 Month After the Last Dose for Cohort 3 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort							
	1 Month After Last Dose (Cohort 3)			1 Month After Infant Series (Cohort 1)			1 Month After Last Dose (Cohort 3) vs 1 Month After Infant Series (Cohort 1)	
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	GMR[e]	(95% CI[d])
1	52	80.0	(55.4, 115.3)	37	201.7	(134.8, 301.8)	0.40	(0.23, 0.68)
3	52	262.2	(208.7, 329.5)	37	112.9	(82.5, 154.4)	2.32	(1.60, 3.37)
4	52	2663.8	(2109.8, 3363.2)	37	1857.8	(1264.8, 2728.8)	1.43	(0.92, 2.24)
5	52	172.4	(131.8, 225.5)	37	645.9	(452.6, 921.8)	0.27	(0.17, 0.41)
6A	52	7153.2	(5297.2, 9659.5)	37	5996.2	(4337.5, 8289.3)	1.19	(0.77, 1.86)
6B	52	5346.1	(4005.4, 7135.5)	37	2331.6	(1481.3, 3670.0)	2.29	(1.38, 3.80)
7F	52	15597.2	(12124.4, 20064.7)	37	10413.4	(7373.1, 14707.3)	1.50	(0.99, 2.26)
9V	52	12079.6	(9620.0, 15167.9)	37	5386.5	(3634.0, 7984.3)	2.24	(1.43, 3.52)
14	52	6026.9	(4646.0, 7818.2)	37	2859.4	(1668.9, 4899.3)	2.11	(1.17, 3.81)
18C	52	2410.6	(1884.9, 3082.8)	37	2677.9	(2000.3, 3585.0)	0.90	(0.62, 1.31)
19A	52	4596.7	(3550.3, 5951.5)	37	1677.3	(1159.9, 2425.5)	2.74	(1.78, 4.21)
19F	52	1898.3	(1474.3, 2444.3)	37	744.4	(506.7, 1093.6)	2.55	(1.65, 3.94)
23F	52	6980.3	(4197.6, 11607.8)	37	3833.2	(2216.2, 6630.1)	1.82	(0.86, 3.85)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

u. SAP-specified timing for blood sample collection.

v. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.

w. GMTs were calculated for all subjects in the 13vPnC group with available data from the specified postvaccination blood draw. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.

x. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or ratios.

y. GMR is the ratio of GMTs: 1 month after last dose for Cohort 3/1 month after infant series for Cohort 1. GMRs were calculated for all subjects with available data from postvaccination blood draws.

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Cohort 4 (≥2 Years to <6 Years of Age)

- 13vPnC induced significant increases in pneumococcal IgG GMCs for all serotypes from before to 1 month after vaccination). Increases were not seen in participants that received Hib vaccine (**Table 15**).
- The RCDCs showed increases in IgG and OPA antibodies after vaccination for the 13vPnC recipients for all serotypes (**not shown**).
- IgG GMCs in Cohort 4 were generally comparable to those post–infant series in Cohort 1 and for 9 of 13 serotypes the IgG GMRs would have met noninferiority using standard 2-fold criterion for the comparison of pneumococcal IgG GMCs. The precision of these IgG comparisons may have been impacted by the number of dropouts in Cohort 1 (**Table *16***).
- The RCDCs comparing IgG GMCs for Cohorts 4 and 1 showed responses varied by serotypes, but for the majority of the serotypes antibody levels from Cohort 4 and Cohort 1 were generally comparable (**not shown**).

- Greater than 96% of participants achieved pneumococcal IgG concentrations
- ≥0.35 µg/mL, an IgG concentration associated with protection against invasive disease in infants (***Table 17***).

- The increases in IgG antibody were associated with significant increases in functional antibody as measured by OPA and noted in the GMFRs (**Table 17**). OPA GMTs and percent responders (≥ LLOQ) in Cohort 4 were generally comparable to those in Cohort 1 for most serotypes (**Table 18**).

- The MAH conclude that these data support that 13vPnC will be effective in preventing pneumococcal disease in this population.

Table 15. Pneumococcal IgG GMCs (µg/mL) and GMFR – Cohort 4 – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	Vaccine Group (as Randomized)											
		13vPnC						Hib Vaccine					
		n[b]	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])
1	Before vaccination	111	0.17	(0.13, 0.22)				57	0.20	(0.14, 0.28)			
	1 Month after study vaccination	111	4.35	(3.64, 5.20)	111	25.35	(18.96, 33.90)	57	0.15	(0.10, 0.23)	57	0.77	(0.60, 0.98)
3	Before vaccination	111	0.14	(0.10, 0.19)				57	0.14	(0.08, 0.26)			
	1 Month after study vaccination	111	1.15	(0.98, 1.35)	111	8.35	(6.42, 10.86)	57	0.13	(0.07, 0.23)	57	0.89	(0.76, 1.05)
4	Before vaccination	111	0.07	(0.05, 0.10)				57	0.07	(0.04, 0.10)			
	1 Month after study vaccination	111	4.57	(3.99, 5.25)	111	67.21	(47.36, 95.38)	57	0.05	(0.03, 0.08)	57	0.78	(0.55, 1.11)
5	Before vaccination	111	1.07	(0.94, 1.22)				57	1.01	(0.86, 1.20)			
	1 Month after study vaccination	111	3.07	(2.67, 3.54)	111	2.88	(2.47, 3.35)	57	0.91	(0.74, 1.13)	57	0.90	(0.78, 1.04)
6A	Before vaccination	109	0.80	(0.67, 0.95)				57	0.81	(0.64, 1.02)			
	1 Month after study vaccination	109	3.36	(2.74, 4.13)	108	4.23	(3.46, 5.17)	57	0.82	(0.65, 1.04)	57	1.02	(0.96, 1.08)
6B	Before vaccination	111	0.82	(0.69, 0.97)				57	0.68	(0.55, 0.84)			
	1 Month after study vaccination	111	2.92	(2.39, 3.56)	111	3.57	(2.96, 4.30)	57	0.59	(0.45, 0.77)	57	0.87	(0.73, 1.03)
7F	Before vaccination	110	0.25	(0.20, 0.31)				54	0.24	(0.17, 0.34)			
	1 Month after study vaccination	111	7.07	(6.09, 8.22)	110	28.49	(21.96, 36.96)	57	0.21	(0.14, 0.30)	54	0.91	(0.69, 1.21)
9V	Before vaccination	111	0.54	(0.45, 0.65)				57	0.41	(0.29, 0.58)			
	1 Month after study vaccination	111	3.69	(3.17, 4.29)	111	6.77	(5.62, 8.16)	57	0.45	(0.37, 0.56)	57	1.11	(0.89, 1.39)
14	Before vaccination	110	0.17	(0.11, 0.28)				57	0.18	(0.09, 0.35)			
	1 Month after study vaccination	111	6.69	(5.26, 8.51)	110	38.50	(25.90, 57.25)	57	0.18	(0.09, 0.35)	57	1.01	(0.77, 1.33)
18C	Before vaccination	110	0.19	(0.14, 0.27)				57	0.18	(0.11, 0.30)			
	1 Month after study vaccination	111	5.51	(4.58, 6.62)	110	28.75	(20.50, 40.31)	56	0.18	(0.11, 0.29)	56	0.97	(0.75, 1.26)
19A	Before vaccination	111	1.72	(1.43, 2.06)				57	1.45	(1.10, 1.90)			
	1 Month after study vaccination	111	11.59	(9.53, 14.10)	111	6.75	(5.59, 8.15)	57	1.32	(1.00, 1.75)	57	0.91	(0.83, 1.00)
19F	Before vaccination	111	0.61	(0.46, 0.80)				57	0.56	(0.38, 0.82)			
	1 Month after study vaccination	111	5.51	(4.43, 6.86)	111	9.06	(6.83, 12.01)	57	0.50	(0.34, 0.74)	57	0.90	(0.69, 1.18)
23F	Before vaccination	111	0.52	(0.44, 0.62)				57	0.44	(0.34, 0.57)			

1 Month after study vaccination	111	2.84	(2.31, 3.49)	111	5.43	(4.56, 6.46)	57	0.43	(0.33, 0.56)	57	0.98	(0.88, 1.08)

Abbreviations: BLQ = below the limit of quantitation; GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LOD = limit of detection; SAP = statistical analysis plan.

m. SAP-specified timing for blood sample collection.

a. n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.

b. GMCs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The LOD was established as 50% of the LLOQ. For IgG concentrations below the LLOQ, or denoted BLQ, 0.5 × LOD was assigned for analysis.

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

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

e. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 16. Comparison of Subjects Achieving a Pneumococcal IgG Concentration ≥0.35 µg/mL, 1 Month After Study Vaccination for Cohort 4 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort									
	1 Month After Study Vaccination (Cohort 1)				1 Month After Infant Series (Cohort 4)			1 Month After Study Vaccination (Cohort 4) vs 1 Month After Infant Series (Cohort 1)		
Serotype	N[b]	n[c]	(%)	(95% CI[d])	N[b]	n[c]	(%)	(95% CI[d])	Difference in %[e]	(95% CI[f])
1	111	110	99.1	(95.1, 100.0)	72	72	100.0	(95.0, 100.0)	-0.9	(-5.0, 4.4)
3	111	109	98.2	(93.6, 99.8)	72	60	83.3	(72.7, 91.1)	14.9	(5.9, 25.5)
4	111	110	99.1	(95.1, 100.0)	72	72	100.0	(95.0, 100.0)	-0.9	(-5.0, 4.4)
5	111	110	99.1	(95.1, 100.0)	72	72	100.0	(95.0, 100.0)	-0.9	(-5.0, 4.4)
6A	109	109	100.0	(96.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-3.5, 5.2)
6B	111	111	100.0	(96.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-3.6, 5.2)
7F	111	110	99.1	(95.1, 100.0)	72	72	100.0	(95.0, 100.0)	-0.9	(-5.0, 4.4)
9V	111	111	100.0	(96.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-3.6, 5.2)
14	111	111	100.0	(96.7, 100.0)	72	70	97.2	(90.3, 99.7)	2.8	(-1.0, 9.7)
18C	111	111	100.0	(96.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-3.6, 5.2)
19A	111	111	100.0	(96.7, 100.0)	72	72	100.0	(95.0, 100.0)	0.0	(-3.6, 5.2)
19F	111	111	100.0	(96.7, 100.0)	72	71	98.6	(92.5, 100.0)	1.4	(-2.2, 7.6)
23F	111	107	96.4	(91.0, 99.0)	72	69	95.8	(88.3, 99.1)	0.6	(-5.6, 8.5)

Abbreviations: IgG = immunoglobulin G; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample.

b. N = number of subjects with a valid and determinate postvaccination IgG concentration to the specified serotype. These values are used as the denominators for percentages.

c. n = Number of subjects with IgG concentration ≥0.35 µg/mL for the given serotype.

d. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

e. Risk difference was computed for 1 month after study vaccination for Cohort 4 - 1 month after infant series for Cohort 1.

f. Exact 2-sided confidence intervals are calculated using Chan and Zhang's method (1999) based upon the observed proportion of subjects.

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Table 17. Pneumococcal OPA GMTs and GMFR – Cohort 4 – Evaluable Immunogenicity Population

Serotype	Sampling Time Point[a]	Vaccine Group (as Randomized)											
		13vPnC						Hib Vaccine					(95% CI[d])
		n[b]	GMT[c]	(95% CI[d])	n[e]	GMFR[f]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[e]	GMFR[f]	
	1 Month after study vaccination	60	6927.4	(5080.3, 9445.9)	60	81.20	(37.30, 176.77)	30	204.1	(78.7, 529.6)	30	1.49	(0.88, 2.54)
18C	Before vaccination	60	12.4	(7.9, 19.7)				30	17.1	(8.1, 36.1)			
	1 Month after study vaccination	60	2138.1	(1619.4, 2822.9)	60	171.94	(105.34, 280.65)	30	21.7	(10.0, 46.9)	30	1.27	(0.72, 2.25)
19A	Before vaccination	60	51.6	(30.4, 87.6)				30	42.0	(17.9, 98.7)			
	1 Month after study vaccination	60	2956.0	(1986.8, 4397.9)	60	57.31	(29.29, 112.11)	30	48.3	(23.1, 101.1)	30	1.15	(0.57, 2.33)
19F	Before vaccination	60	22.5	(13.5, 37.7)				30	34.4	(15.4, 77.0)			
	1 Month after study vaccination	60	1763.3	(1414.2, 2198.6)	60	78.30	(45.59, 134.47)	30	38.2	(16.7, 87.0)	30	1.11	(0.70, 1.76)
23F	Before vaccination	60	112.8	(60.5, 210.1)				30	53.3	(21.5, 131.9)			
	1 Month after study vaccination	60	3938.8	(2555.5, 6070.9)	60	34.93	(18.08, 67.49)	30	78.4	(31.0, 198.5)	30	1.47	(0.87, 2.49)

Abbreviations: BLQ = below the limit of quantitation; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.

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

c. GMTs were calculated for all subjects with available data from both the prevaccination and postvaccination blood draws. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.

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

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

f. GMFRs were calculated using all subjects with available data from both the prevaccination and postvaccination blood draws.

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Table 18. Comparison of Pneumococcal OPA GMTs, 1 Month After Study Vaccination for Cohort 4 vs 1 Month After the Infant Series for Cohort 1 – Evaluable Immunogenicity Population

	Sampling Time Point[a] and Cohort							
	1 Month After Study Vaccination (Cohort 4)			1 Month After Infant Series (Cohort 1)			1 Month After Study Vaccination (Cohort 4) vs 1 Month After Infant Series (Cohort 1)	
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	GMR[e]	(95% CI[d])
1	60	35.2	(27.4, 45.3)	37	201.7	(134.8, 301.8)	0.17	(0.11, 0.27)
3	60	216.2	(166.0, 281.7)	37	112.9	(82.5, 154.4)	1.92	(1.27, 2.89)
4	60	4095.1	(3361.8, 4988.3)	37	1857.8	(1264.8, 2728.8)	2.20	(1.44, 3.38)
5	60	74.7	(52.9, 105.6)	37	645.9	(452.6, 921.8)	0.12	(0.07, 0.19)
6A	60	6098.5	(4635.4, 8023.4)	37	5996.2	(4337.5, 8289.3)	1.02	(0.66, 1.56)
6B	60	3430.3	(2573.0, 4573.3)	37	2331.6	(1481.3, 3670.0)	1.47	(0.89, 2.43)
7F	60	15989.3	(12614.2, 20267.4)	37	10413.4	(7373.1, 14707.3)	1.54	(1.03, 2.29)
9V	60	14040.7	(11283.8, 17471.1)	37	5386.5	(3634.0, 7984.3)	2.61	(1.67, 4.07)
14	60	6927.4	(5080.3, 9445.9)	37	2859.4	(1668.9, 4899.3)	2.42	(1.31, 4.48)
18C	60	2138.1	(1619.4, 2822.9)	37	2677.9	(2000.3, 3585.0)	0.80	(0.53, 1.21)
19A	60	2956.0	(1986.8, 4397.9)	37	1677.3	(1159.9, 2425.5)	1.76	(1.03, 3.01)
19F	60	1763.3	(1414.2, 2198.6)	37	744.4	(506.7, 1093.6)	2.37	(1.53, 3.67)
23F	60	3938.8	(2555.5, 6070.9)	37	3833.2	(2216.2, 6630.1)	1.03	(0.52, 2.05)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NIFDC = National Institutes for Food and Drug Control; OPA = opsonophagocytic activity; SAP = statistical analysis plan.

a. SAP-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.
c. GMTs were calculated for all subjects in the 13vPnC group with available data from the specified postvaccination blood draw. The NIFDC's OPA LLOQ for all serotypes was 8. For titers below the LLOQ, or denoted as BLQ, 0.5 × LLOQ was assigned for analysis.
d. CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or ratios.
e. GMR is the ratio of GMTs: 1 month after study vaccination for Cohort 4/1 month after infant series for Cohort 1. GMRs were calculated for all subjects with available data from postvaccination blood draws.

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Safety results

- Most local reactions were mild to moderate in severity. In Cohorts 2 and 3, no severe or significant local reactions were reported. In Cohort 4, no severe redness or swelling was reported. Compared with the 13vPnC group, local reactions were reported by a lower proportion of participants in the Hib vaccine group in Cohorts 2 and 3 after Dose 1 and were reported by a higher proportion of participants in the Hib vaccine group in Cohort 2 after Dose 2. Local reactions were reported by a similar proportion of participants in the 13vPnC and Hib vaccine groups in Cohort 4.
- Most systemic events were mild to moderate in severity. The proportion of participants with fever or any other systemic events was low following each dose of 13vPnC or Hib vaccine. Compared with the 13vPnC group, systemic events were reported by a lower proportion of participants in the Hib vaccine group in Cohorts 2 and 3 and were reported by a slightly higher proportion of participants in the Hib vaccine group in Cohort 4.

- No deaths, life-threatening AEs, severe AEs, safety-related withdrawals, or NDCMCs were reported during the study.
- The proportion of participants reporting any AEs was low, and most of the AEs reported were mild in severity.
- The proportion of participants reporting SAEs was low. No SAEs were considered related to the investigational product by the investigator.
- There were no deviation from what was noted in the SmPC.
- The safety population was not large enough to detect unusual AE:s.

2.3.2. Discussion on clinical aspects

These data support a conclusion that 13vPnC given as a catch up regimen in different age groups (7 months to <12 months, ≥1 year to <2 years, and ≥2 years to <6 years of age) will be effective in preventing pneumococcal disease.

The vaccine was well tolerated in infants and children in the different age groups and AEs reported in the study were consistent with medical events or conditions that are common to these age groups. There were no new safety signals identified during the study period covered in this report.

These data support a conclusion that 13vPnC will be safe and effective at preventing pneumococcal disease in Chinese infants and children through <6 years of age and has a positive risk benefit.

In addition, the 5 year antibody persistence data demonstrated that 13vPnC given according to the currently licensed infant schedule (2, 4, 6, and 12 to 15 months) in infants enrolled at approximately 2 months of age induces a robust immune response to the 13 serotypes in 13vPnC, and the immune response induced by 13vPnC when measured at 1, 2, 3, and 4 years after the toddler dose demonstrates overall persistence of IgG and OPA antibodies.

Safety and immunogenicity results from this study are consistent with the known profile of 13vPnC as reflected in the EU SmPC and support the continued use of 13vPnC. No changes are being proposed to the Prevenar 13 label in this submission.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.