Amsterdam, 30 March 2023
EMA/CHMP/107799/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

## Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no.: EMEA/H/C/001104/P46/070

Note

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

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# 1. Introduction

On 10 January 2023, the MAH submitted a completed paediatric study for Prevenar 13, 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 Cohort Study to Evaluate Immunogenicity for Children Aged 5 Months to ≤60 Months at the Time of Clinical Pneumonia Diagnosis": B1851196: is a stand-alone study.

## *2.2. Information on the pharmaceutical formulation used in the study*

Not applicable as no study intervention was given. Participants were vaccinated as part of their paediatric health care, not as part of this study.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- B1851196: A Cohort Study to Evaluate Immunogenicity for Children Aged 5 Months to ≤60 Months at the Time of Clinical Pneumonia Diagnosis.

### 2.3.2. Clinical study

B1851196: A Cohort Study to Evaluate Immunogenicity for Children Aged 5 Months to ≤60 Months at the Time of Clinical Pneumonia Diagnosis.

#### Description

This cohort study was designed to describe serotype specific antibody levels among children, 5 months to ≤60 months of age, with the diagnosis of clinical pneumonia (per local standards). Participants were characterized by 13vPnC vaccination status cohort (in children who completed at least 2 doses of 13vPnC versus children that did not receive any 13vPnC dose) and by pneumococcal VT carriage status. This was an epidemiology study (no study intervention was given).

#### Methods

*Study Design and Study Participants*

This cohort study was designed to describe vaccine serotype (VT) specific antibody levels and deep upper respiratory aspirate pneumococcal VT carriage statuses among children who were 5 months to ⩽60 months of age and hospitalized with clinical pneumonia at SCH.

Participants were assigned to a cohort based on their 13vPnC vaccination status ("13vPnC cohort" or "Non-13vPnC cohort"). The 13vPnC cohort included those children who had received at least 2 doses of 13vPnC, and the Non-13vPnC cohort included those children that did not receive any 13vPnC dose as

part of their paediatric care. Participants were also characterized by deep upper respiratory aspirate pneumococcal VT carriage status ("VT carriage+" or "VT carriage- or *Streptococcus pneumoniae*-, Sp-"). The four 13vPnC vaccination cohort / pneumococcal VT carriage status subgroups are presented in Table 1.

Table 1. Study Subgroups

| | | Vaccination cohort | |
|---|---|---|---|
| | | 13vPnC Cohort | Non-13vPnC Cohort |
| Deep upper respiratory aspirate pneumococcal VT carriage status | VT Carriage+ | 13vPnC vaccinated cohort with 13vPnC VT strain isolated | 13vPnC unvaccinated cohort with 13vPnC VT strain isolated |
| | VT Carriage- or Sp- | 13vPnC vaccinated cohort with no 13vPnC VT strain isolated or with negative *S pneumoniae* | 13vPnC unvaccinated cohort with no 13vPnC VT strain isolated or with negative *S pneumoniae* |

Note: VT - or Sp - includes participants with serotypes not included in 13vPnC orparticipants without *S pneumoniae.*

*Treatments*

No treatment was given in this study.

*Objective, estimands and endpoint*

| Type | Objective | Endpoint | Estimand |
|---|---|---|---|
| Primary | | | |
| Immunogenicity | To describe the antibody levels, as measured by IgG and MOPA, by 13vPnC vaccination cohort and by VT carriage status, among children 5 months to ≤60 months of age with a diagnosis of clinical pneumonia per local standards. | The serotype specific IgG GMC and MOPA GMT for each of the pneumococcal vaccine serotypes measured at the time of diagnosis of clinical pneumonia. | The serotype specific IgG GMC and MOPA GMT for each of the pneumococcal vaccine serotypes measured at the time of diagnosis of clinical pneumonia |

*Sample size*

The study enrolled 300 participants, 276 (92.0%) of whom were evaluable for immunogenicity analyses (IgG for all; MOPA in a subset): 92 in the 13vPnC cohort and 184 in the non-13vPnC cohort.

Of the 276 in the evaluable population, 259 participants completed the study. 17 (5.7%) evaluable participants discontinued the study due to protocol deviations during the follow-up phase, but they were still considered evaluable.

*Randomisation and blinding (masking)*

Randomization and blinding were not applicable to the present study as participants were assigned to a cohort according to their 13vPnC vaccination status.

*Statistical Methods*

The multiple regression model used the log concentration or log titers as the dependent variable. Independent variables included vaccination cohort (13vPnC or non-13vPnC), carriage status ("VT Carriage+" or "VT Carriage- or Sp-"), and the interaction of the vaccination cohort and carriage status, as well as the confounding variables (age at enrollment, sex, and season of enrollment).

## Results

*Participant flow*

Participants were in the study for 1 day. After the blood draw (obtained from all participants) and the deep upper respiratory aspirate (if collected as a study procedure), participants were followed for 12 hours. Two non-13vPnC participants were planned to be included in the unvaccinated cohort for every participant enrolled in the 13vPnC cohort. Non-13vPnC cohort participants' enrollment dates were within 6 months of those of the 13vPnC cohort participants. The standard guidance for the diagnosis of pneumonia at SCH was followed for entry into the study. Pneumonia diagnosis was made by the clinical judgment of treating doctors based on the "Clinical Diagnosis and Treatment Guidelines for Pediatric Internal Medicine", issued by the Chinese Medical Association.

Table 2. Analysis Population and Subject Disposition

| | Cohort | | |
|---|---|---|---|
| | 13vPnC (N[a]=101) n[b] (%) | Non-13vPnC (N[a]=199) n[b] (%) | Total (N[a]=300) n[b] (%) |
| Enrolled Population[c] | 101 (100.0) | 199 (100.0) | 300 (100.0) |
| Excluded from Enrolled Population | 9 (8.9) | 15 (7.5) | 24 (8.0) |
| Not meeting Inclusion Criteria 1 | 0 | 2 (1.0) | 2 (0.7) |
| Not meeting Inclusion Criteria 2 | 0 | 0 | 0 |
| Not meeting Inclusion Criteria 3 | 1 (1.0) | 3 (1.5) | 4 (1.3) |
| Not meeting Inclusion Criteria 4 | 5 (5.0) | 5 (2.5) | 10 (3.3) |
| Not meeting Inclusion Criteria 5 | 1 (1.0) | 0 | 1 (0.3) |
| Not meeting Inclusion Criteria 6 | 0 | 1 (0.5) | 1 (0.3) |
| Meeting Exclusion Criteria 1 | 0 | 0 | 0 |
| Meeting Exclusion Criteria 2 | 0 | 0 | 0 |
| Meeting Exclusion Criteria 3 | 0 | 0 | 0 |
| Meeting Exclusion Criteria 4 | 0 | 1 (0.5) | 1 (0.3) |
| Meeting Exclusion Criteria 5 | 1 (1.0) | 5 (2.5) | 6 (2.0) |
| Meeting Exclusion Criteria 6 | 0 | 0 | 0 |
| Meeting Exclusion Criteria 7 | 0 | 0 | 0 |
| No immunogenicity assay available | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Blood collection time was earlier than the ICD time[d] | 1 (1.0) | 0 | 1 (0.3) |
| Discontinued[e] | 7 (6.9) | 16 (8.0) | 23 (7.7) |
| Completed study | 89 (88.1) | 170 (85.4) | 259 (86.3) |
| Discontinued but Evaluable[f] | 3 (3.0) | 14 (7.0) | 17 (5.7) |
| Adverse event | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Study terminated by sponsor | 0 | 0 | 0 |
| Withdrawal by parent/guardian | 0 | 0 | 0 |
| Protocol deviation | 3 (3.0) | 14 (7.0) | 17 (5.7) |
| Global deterioration of health status | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Evaluable Population[g] | 92 (91.1) | 184 (92.5) | 276 (92.0) |

a. N = number of subjects in the specified cohort or total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Enrolled: Signed the informed consent document.
d. The information was from study medical records.
e. Discontinued subjects (7 in 13vPnC and 16 in Non-13vPnC) have been listed in Listing of Subjects Withdrawn From the Study After Enrollment.
f. Discontinued but Evaluable subjects (3 in 13vPnC and 14 in Non-13vPnC) were included in the Evaluable population if they met the 3 conditions (Signed the informed consent document, met all inclusion/exclusion criteria and had at least one immunogenicity assay value).
g. Evaluable subjects included Completed and Discontinued but Evaluable.

*Recruitment*

Participants of the study were 5-60 months of age at the time of consent with a diagnosis of clinical pneumonia per SCH standard of care. Participants (or their legally authorized representatives) were informed that their participation was voluntary. Participants (or their legally authorized representatives) signed a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements (where applicable), and the IEC or study center.

*Baseline data/ Number analysed*

A total of 300 participants were enrolled in this study, of whom 276 (92.0%) were included in the evaluable population: 92 in the 13vPnC cohort and 184 in the non-13vPnC cohort. The evaluable population consisted of 135 female and 141 male participants aged 5 to 59 months, with a mean (SD) age of 24.5 (14.24) months. In the 13vPnC cohort, the mean (SD) age of participants was 20.6 (10.86) months, and the majority were enrolled in summer and fall (68 [73.9%] participants). In the non-13vPnC cohort, the mean (SD) age of participants was older, 26.4 (15.32) months, and the majority were enrolled in fall and winter (164 [89.1%] participants; Table 3). Of the 276 in the evaluable population, 259 participants completed the study. Although 17 (5.7%) evaluable participants discontinued the study due to PDs during the follow-up phase, they were still evaluable. The culture results of deep upper respiratory aspirates (labeled in the Tables as “VT Carriage +” or “VT Carriage - or Sp -”) were available for 259 participants, and 52 of the aspirates grew *S. pneumoniae*. A serotype could be identified for 39 of the *S. pneumoniae* samples.

Table 3. Subject Demographic and Medical history – Evaluable Population

| | Cohort | | |
|---|---|---|---|
| | 13vPnC (N[a]=92) | Non-13vPnC (N[a]=184) | Total (N[a]=276) |
| Age category, nb (%) | | | |
| 5-≤12 Months | 25 (27.2) | 46 (25.0) | 71 (25.7) |
| With 2 doses | 6 (6.5) | N/A | 6 (2.2) |
| With 3 doses | 19 (20.7) | N/A | 19 (6.9) |
| 13-≤24 Months | 36 (39.1) | 46 (25.0) | 82 (29.7) |
| With 2 doses | 2 (2.2) | N/A | 2 (0.7) |
| With 3 doses | 8 (8.7) | N/A | 8 (2.9) |
| With 4 doses | 26 (28.3) | N/A | 26 (9.4) |
| 25-≤60 Months | 31 (33.7) | 92 (50.0) | 123 (44.6) |
| With 2 doses | 2 (2.2) | N/A | 2 (0.7) |
| With 3 doses | 1 (1.1) | N/A | 1 (0.4) |
| With 4 doses | 28 (30.4) | N/A | 28 (10.1) |
| Age at enrollment (in months) | | | |
| Mean (SD) | 20.6 (10.86) | 26.4 (15.32) | 24.5 (14.24) |
| Median (Q1, Q3) | 17.5 (12.0, 30.0) | 24.5 (12.5, 40.0) | 21.5 (12.0, 37.0) |
| Min, Max | (5, 46) | (5, 59) | (5, 59) |
| Sex, n[b] (%) | | | |
| Female | 45 (48.9) | 90 (48.9) | 135 (48.9) |
| Male | 47 (51.1) | 94 (51.1) | 141 (51.1) |
| Race, n[b] (%) | | | |
| Asian | 92 (100.0) | 184 (100.0) | 276 (100.0) |
| Ethnicity, n[b] (%) | | | |
| Non-Hispanic/non-Latino | 92 (100.0) | 184 (100.0) | 276 (100.0) |
| Number of siblings living in the same household, n[b] (%) | | | |
| 0 | 55 (59.8) | 82 (44.6) | 137 (49.6) |
| 1 | 34 (37.0) | 91 (49.5) | 125 (45.3) |
| 2 | 3 (3.3) | 11 (6.0) | 14 (5.1) |
| Enrollment season, n[b] (%) | | | |
| Spring (March-May) | 11 (12.0) | 2 (1.1) | 13 (4.7) |
| Summer (June-August) | 31 (33.7) | 18 (9.8) | 49 (17.8) |
| Fall (September-November) | 37 (40.2) | 110 (59.8) | 147 (53.3) |
| Winter (December-February) | 13 (14.1) | 54 (29.3) | 67 (24.3) |
| Significant medical history, n[b] (%) | | | |
| Ventricular septal defect | 0 | 1 (0.5) | 1 (0.4) |

Abbreviation: N/A = not applicable.

Note: MedDRA v25.0 coding dictionary applied.

a. N = number of subjects in the specified cohort or total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences of the same preferred term are counted only once.

*Efficacy results*

Immunogenicity results

IgG Assessment:

All 276 (100%) evaluable participants were included for IgG assessment.

Crude results by 13vPnC vaccination cohort:

- In the 13vPnC cohort, the GMCs ranged from 0.42 µg/mL (serotype 3) to 4.67 µg/mL (serotype 14). In the non-13vPnC cohort, the GMCs ranged from 0.06 µg/mL (serotype 18C) to 0.75 µg/mL (serotype 19A). The GMR values, 13vPnC cohort / non-13vPnC cohort, ranged from 2.42 (serotype 5) to 62.13 (serotype 14).

Model based adjusted results by 13vPnC vaccination cohort (Table 8):

- In the 13vPnC cohort, the adjusted GMCs ranged from 0.36 µg/mL (serotype 3) to 4.36 µg/ml (serotype 14). In the non-13vPnC cohort, the adjusted GMCs ranged from 0.04 µg/mL (serotype 18C) to 0.64 µg/mL (serotype 19A). The adjusted GMR values, 13vPnC cohort / non-13vPnC cohort, ranged from 2.61 (serotype 5) to 74.66 (serotype 14).

**Table 8. Model Adjusted Pneumococcal IgG GMCs (µg/mL) by Cohort – Evaluable Population**

| | 13vPnC Cohort (N[a]=92) | | Non-13vPnC Cohort (N[a]=184) | | Ratio: 13vPnC / Non-13vPnC | |
|---|---|---|---|---|---|---|
| Serotype | Adj GMC[b] | (95% CI[b]) | Adj GMC[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) |
| 1 | 1.11 | (0.60, 2.05) | 0.08 | (0.05, 0.13) | 13.27 | (6.57, 26.83) |
| 3 | 0.36 | (0.22, 0.58) | 0.06 | (0.04, 0.09) | 5.76 | (3.26, 10.18) |
| 4 | 1.23 | (0.64, 2.34) | 0.06 | (0.04, 0.10) | 20.23 | (9.65, 42.37) |
| 5 | 1.58 | (1.07, 2.34) | 0.61 | (0.46, 0.80) | 2.61 | (1.66, 4.09) |
| 6A | 2.19 | (1.39, 3.45) | 0.33 | (0.24, 0.46) | 6.58 | (3.92, 11.05) |
| 6B | 2.35 | (1.51, 3.65) | 0.41 | (0.30, 0.56) | 5.78 | (3.49, 9.58) |
| 7F | 1.28 | (0.77, 2.11) | 0.15 | (0.11, 0.22) | 8.36 | (4.72, 14.83) |
| 9V | 1.11 | (0.71, 1.74) | 0.25 | (0.18, 0.34) | 4.47 | (2.67, 7.48) |
| 14 | 4.36 | (2.03, 9.34) | 0.06 | (0.03, 0.10) | 74.66 | (30.98, 179.97) |
| 18C | 0.78 | (0.40, 1.52) | 0.04 | (0.03, 0.07) | 18.73 | (8.75, 40.08) |
| 19A | 4.00 | (2.64, 6.05) | 0.64 | (0.48, 0.86) | 6.24 | (3.89, 10.01) |
| 19F | 4.33 | (2.51, 7.49) | 0.33 | (0.22, 0.49) | 13.16 | (7.04, 24.59) |
| 23F | 1.50 | (0.96, 2.35) | 0.22 | (0.16, 0.30) | 6.98 | (4.19, 11.63) |

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G.
Note: Blood draw taken at time of enrollment.
a. N = number of subjects in the specified cohort.
b. Adjusted GMC and CIs are back transforms of adjusted mean and CIs based on a multiple regression model. A multiple regression model uses log assay value as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, sex, season of enrollment).
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Crude results of GMC comparison between VT carriage status by 13vPnC vaccination cohort:

- In the 13vPnC cohort, the pneumococcal IgG GMCs for VT carriage+ participants ranged from 0.32 µg/mL (serotype 3) to 5.80 µg/mL (serotype 19F), while the GMCs for the VT carriage- or Sp- participants ranged from 0.44 µg/mL (serotype 3) to 4.96 µg/ml (serotype 14). In the 13vPnC cohort, the GMR values, VT carriage+ / VT carriage- or Sp-, ranged from 0.42 (serotype 7F) to 1.80 (serotype 19F).

- In the non-13vPnC cohort, the pneumococcal IgG GMCs for VT carriage+ participants ranged from 0.04 µg/mL (serotypes 14 and 18C) to 0.58 µg/mL (serotypes 5 and 19A), and the GMCs for the VT carriage- or Sp- participants ranged from 0.06 µg/mL (serotype 18C) to 0.74 µg/mL

(serotype 19A). In the non-13vPnC cohort, the GMR values, VT carriage+ / VT carriage- or Sp-, ranged from 0.44 (serotype 14) to 1.53 (serotype 6B).

Model based adjusted results of GMC comparison between VT carriage status by 13vPnC vaccination cohort (Table 10):

- In the 13vPnC cohort, the pneumococcal IgG adjusted GMCs for VT carriage+ participants ranged from 0.30 µg/mL (serotype 3) to 5.71 µg/mL (serotype 19F). The adjusted GMCs for the VT carriage- or Sp- participants ranged from 0.41 µg/mL (serotype 3) to 4.97 µg/mL (serotype 14). The adjusted GMRs, VT carriage+/ VT carriage- or Sp-, ranged from 0.42 (serotype 7F) to 1.73 (serotype 19F).
- In the non-13vPnC cohort, the adjusted GMCs for VT carriage+ participants ranged from 0.03 µg/mL (serotype 18C) to 0.57 µg/mL (serotype 19A). The adjusted GMCs for the VT carriage- or Sp- participants ranged from 0.05 µg/mL (serotype 18C) to 0.72 µg/mL (serotype 19A). The adjusted GMRs, VT carriage+/ VT carriage- or Sp- ranged from 0.49 (serotype 14) to 1.50 (serotype 6B).

**Table 10. Model Adjusted Pneumococcal IgG GMCs (µg/mL) Ratios: VT+ vs VT- or Sp- within Each Cohort – Evaluable Population**

| | 13vPnC Cohort (N[a]=92) | | | | | | Non-13vPnC Cohort (N[a]=184) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VT+ (N1 = 7) | | VT- or Sp- (N1 = 79) | | Ratio: VT+ / VT- or Sp- | | VT+ (N1 = 20) | | VT- or Sp- (N1 = 140) | | Ratio: VT+ / VT- or Sp- | |
| Serotype | Adj GMC[b] | (95% CI[b]) | Adj GMC[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) | Adj GMC[b] | (95% CI[b]) | Adj GMC[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) |
| 1 | 0.74 | (0.23, 2.34) | 1.66 | (1.15, 2.40) | 0.44 | (0.13, 1.46) | 0.07 | (0.03, 0.14) | 0.10 | (0.07, 0.15) | 0.66 | (0.32, 1.36) |
| 3 | 0.30 | (0.12, 0.78) | 0.41 | (0.31, 0.55) | 0.74 | (0.28, 1.93) | 0.05 | (0.03, 0.09) | 0.07 | (0.05, 0.10) | 0.70 | (0.39, 1.26) |
| 4 | 1.02 | (0.30, 3.44) | 1.48 | (1.01, 2.17) | 0.69 | (0.20, 2.42) | 0.05 | (0.02, 0.11) | 0.07 | (0.05, 0.10) | 0.75 | (0.35, 1.60) |
| 5 | 1.39 | (0.66, 2.91) | 1.80 | (1.43, 2.27) | 0.77 | (0.36, 1.66) | 0.54 | (0.34, 0.86) | 0.68 | (0.54, 0.86) | 0.80 | (0.50, 1.27) |
| 6A | 1.77 | (0.76, 4.16) | 2.71 | (2.07, 3.54) | 0.65 | (0.27, 1.58) | 0.32 | (0.19, 0.55) | 0.34 | (0.26, 0.45) | 0.94 | (0.55, 1.60) |
| 6B | 1.97 | (0.86, 4.52) | 2.80 | (2.15, 3.63) | 0.71 | (0.30, 1.66) | 0.50 | (0.30, 0.83) | 0.33 | (0.26, 0.43) | 1.50 | (0.89, 2.51) |
| 7F | 0.83 | (0.32, 2.13) | 1.96 | (1.46, 2.64) | 0.42 | (0.16, 1.12) | 0.13 | (0.07, 0.24) | 0.17 | (0.13, 0.23) | 0.77 | (0.43, 1.38) |
| 9V | 0.99 | (0.42, 2.30) | 1.25 | (0.96, 1.63) | 0.79 | (0.33, 1.89) | 0.21 | (0.13, 0.36) | 0.29 | (0.22, 0.37) | 0.74 | (0.44, 1.26) |
| 14 | 3.82 | (0.91, 16.02) | 4.97 | (3.16, 7.80) | 0.77 | (0.18, 3.38) | 0.04 | (0.02, 0.10) | 0.08 | (0.05, 0.13) | 0.49 | (0.20, 1.22) |
| 18C | 0.58 | (0.17, 2.03) | 1.06 | (0.71, 1.57) | 0.55 | (0.15, 2.00) | 0.03 | (0.01, 0.07) | 0.05 | (0.04, 0.08) | 0.59 | (0.27, 1.28) |
| 19A | 4.97 | (2.28, 10.80) | 3.22 | (2.52, 4.11) | 1.54 | (0.69, 3.44) | 0.57 | (0.35, 0.93) | 0.72 | (0.56, 0.92) | 0.80 | (0.49, 1.29) |
| 19F | 5.71 | (2.04, 15.93) | 3.29 | (2.38, 4.55) | 1.73 | (0.60, 5.00) | 0.35 | (0.19, 0.67) | 0.31 | (0.22, 0.42) | 1.16 | (0.61, 2.20) |
| 23F | 1.01 | (0.44, 2.35) | 2.23 | (1.71, 2.90) | 0.46 | (0.19, 1.08) | 0.23 | (0.13, 0.38) | 0.20 | (0.16, 0.26) | 1.12 | (0.66, 1.88) |

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G.
Note: Blood draw taken at time of enrollment.
Note: 3 subjects in 13vPnC cohort and 10 subjects in non-13vPnC cohort were "Untypable" (*S. pneumoniae* isolates detected but bacterium quantity insufficient for culture or unable to grow) and deep upper respiratory aspirates culture results were not available for 3 subjects in 13vPnC cohort and 14 subjects in non-13vPnC cohort, thus those subjects were excluded in the analysis.
Note: VT- or Sp- includes subjects with serotypes not included in 13vPnC and subjects with *S. pneumoniae* -.
a. N = number of subjects in the specified cohort.
b. Adjusted GMC and CIs are back transforms of adjusted mean and CIs based on a multiple regression model. A multiple regression model uses log assay value as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, sex, season of enrollment).
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### Multiplex Opsonophagocytic Activity (MOPA) Results

For MOPA assessment, 69 participants with adequate blood volumes from the non-13vPnC cohort were used, which was approximately equal to the number of 13vPnC participants (Table 13). Crude results by 13vPnC vaccination cohort:

- In the 13vPnC cohort, the GMTs ranged from 70.9 (serotype 1) to 3791.4 (serotype 7F). In the non-13vPnC cohort, the GMTs ranged from 14.8 (serotype 1) to 223.2 (serotype 7F). The GMR values, 13vPnC cohort / non-13vPnC cohort, ranged from 4.78 (serotype 1) to 44.46 (serotype 23F).

Model based adjusted results by 13vPnC vaccination cohort (Table 14):

- In the 13vPnC cohort, the adjusted GMTs ranged from 50.4 (serotype 1) to 4247.1 (serotype 7F). In the non-13vPnC cohort, the adjusted GMTs ranged from 13.1 (serotype 1) to 261.1 (serotype 14). The adjusted GMR values, 13vPnC cohort / non- 13vPnC cohort, ranged from 3.86 (serotype 1) to 38.46 (serotype 19F).

**Table 14. Model Adjusted Pneumococcal MOPA GMTs by Cohort – Evaluable Population**

| | 13vPnC Cohort (N[a]=92) | | Non-13vPnC Cohort (N[a]=184) | | Ratio: 13vPnC / Non-13vPnC | |
|---|---|---|---|---|---|---|
| Serotype | Adj GMT[b] | (95% CI[b]) | Adj GMT[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) |
| 1 | 50.4 | (19.4, 130.6) | 13.1 | (5.9, 28.9) | 3.86 | (1.23, 12.13) |
| 3 | 219.0 | (88.4, 542.6) | 29.7 | (13.9, 63.3) | 7.39 | (2.48, 22.00) |
| 4 | 1055.5 | (319.6, 3486.6) | 77.8 | (28.7, 210.9) | 13.57 | (3.22, 57.14) |
| 5 | 435.3 | (165.8, 1142.8) | 15.2 | (6.8, 34.0) | 28.67 | (8.98, 91.53) |
| 6A | 957.4 | (274.5, 3339.7) | 46.1 | (16.3, 130.9) | 20.75 | (4.62, 93.27) |
| 6B | 363.1 | (112.3, 1173.9) | 80.3 | (30.1, 213.8) | 4.52 | (1.10, 18.55) |
| 7F | 4247.1 | (1338.1, 13480.4) | 250.9 | (95.6, 658.0) | 16.93 | (4.22, 67.92) |
| 9V | 608.5 | (208.1, 1779.4) | 69.7 | (28.4, 170.6) | 8.74 | (2.40, 31.76) |
| 14 | 1519.0 | (489.0, 4718.8) | 261.1 | (101.4, 672.7) | 5.82 | (1.49, 22.74) |
| 18C | 462.3 | (171.3, 1247.9) | 32.2 | (14.0, 73.7) | 14.37 | (4.35, 47.44) |
| 19A | 1619.7 | (534.0, 4913.3) | 59.3 | (23.5, 149.7) | 27.33 | (7.19, 103.83) |
| 19F | 954.1 | (348.7, 2610.1) | 24.8 | (10.7, 57.5) | 38.46 | (11.46, 129.04) |
| 23F | 2207.9 | (642.1, 7591.5) | 78.6 | (28.0, 220.5) | 28.07 | (6.36, 124.01) |

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; MOPA = multiplex opsonophagocytic activity.
Note: Blood draw taken at time of enrollment.
a. N = number of subjects in the specified cohort.
b. Adjusted GMT and CIs are back transforms of adjusted mean and CIs based on a multiple regression model. A multiple regression model uses log assay value as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, sex, season of enrollment).
PFIZER CONFIDENTIAL SDTM Creation: 27OCT2022 (04:00) Source Data: adva Table Generation: 07NOV2022 (11:29)
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Crude results of GMT comparison between VT carriage status by 13vPnC vaccination cohort:

- In the 13vPnC cohort, the pneumococcal MOPA GMTs for VT carriage+ participants ranged from 35.0 (serotype 1) to 4661.3 (serotype 7F). The GMTs for the VT carriage- or Sp- participants ranged from 71.1 (serotype 1) to 4111.0 (serotype 23F). The GMR values, VT carriage+/ VT carriage- or Sp-, ranged from 0.06 (serotype 6B) to 3.87 (serotype 19F).

- In the non-13vPnC cohort, the pneumococcal MOPA GMTs for VT carriage+ participants ranged from 11.1 (serotypes 1 and 5) to 442.5 (serotype 7F). The GMTs for the VT carriage- or Sp- participants ranged from 14.6 (serotype 1) to 180.8 (serotype 7F). The GMR values, VT carriage+/ VT carriage- or Sp-, ranged from 0.44 (serotype 4) to 2.45 (serotype 7F).

Model based adjusted results of GMT comparison between VT carriage status by 13vPnC vaccination cohort (Table 16):

- In the 13vPnC cohort, the pneumococcal MOPA adjusted GMTs for VT carriage+ participants ranged from 37.1 (serotype 1) to 4502.1 (serotype 7F). The adjusted GMTs for the VT carriage- or Sp- participants ranged from 68.3 (serotype 1) to 4160.0 (serotype 23F). The adjusted GMRs, VT carriage+/ VT carriage- or Sp-, ranged from 0.07 (serotype 6B) to 4.37 (serotype 19F).

- In the non-13vPnC cohort, the pneumococcal MOPA adjusted GMTs for VT carriage+ participants ranged from 10.1 (serotype 1) to 449.1 (serotype 14). The adjusted GMTs for the VT carriage- or Sp- participants ranged from 16.9 (serotype 1) to 153.2 (serotype 7F). The

adjusted GMRs, VT carriage+/ VT carriage- or Sp-, ranged from 0.47 (serotype 4) to 2.96 (serotype 14).

**Table 16. Model Adjusted Pneumococcal MOPA GMTs Ratios: VT+ vs VT- or Sp- within Each Cohort – Evaluable Population**

| | 13vPnC Cohort (N[a]=92) | | | | | | Non-13vPnC Cohort (N[a]=184) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VT+ (N1 = 7) | | VT- or Sp- (N1 = 79) | | Ratio: VT+ / VT- or Sp- | | VT+ (N1 = 20) | | VT- or Sp- (N1 = 140) | | Ratio: VT+ / VT- or Sp- | |
| Serotype | Adj GMT[b] | (95% CI[b]) | Adj GMT[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) | Adj GMT[b] | (95% CI[b]) | Adj GMT[b] | (95% CI[b]) | Adj GMR[b] | (95% CI[b]) |
| 1 | 37.1 | (6.4, 215.9) | 68.3 | (36.9, 126.5) | 0.54 | (0.09, 3.37) | 10.1 | (2.7, 38.0) | 16.9 | (8.4, 33.9) | 0.60 | (0.15, 2.42) |
| 3 | 159.7 | (29.9, 853.9) | 300.3 | (167.0, 539.9) | 0.53 | (0.09, 3.02) | 28.8 | (8.1, 102.1) | 30.5 | (15.7, 59.2) | 0.94 | (0.25, 3.59) |
| 4 | 853.3 | (93.8, 7759.4) | 1305.8 | (603.0, 2827.7) | 0.65 | (0.07, 6.43) | 53.3 | (10.1, 282.1) | 113.4 | (47.4, 271.4) | 0.47 | (0.08, 2.73) |
| 5 | 630.0 | (105.9, 3747.9) | 300.8 | (161.1, 561.5) | 2.09 | (0.33, 13.28) | 11.3 | (2.9, 43.5) | 20.3 | (10.1, 41.2) | 0.56 | (0.13, 2.31) |
| 6A | 502.3 | (49.9, 5052.4) | 1824.7 | (813.4, 4093.3) | 0.28 | (0.03, 3.01) | 41.8 | (7.3, 238.7) | 50.9 | (20.5, 126.7) | 0.82 | (0.13, 5.17) |
| 6B | 92.8 | (10.6, 811.4) | 1420.1 | (664.9, 3033.0) | 0.07 | (0.01, 0.62) | 126.5 | (24.6, 649.8) | 50.9 | (21.6, 120.0) | 2.48 | (0.44, 13.97) |
| 7F | 4502.1 | (532.9, 38033.5) | 4006.5 | (1898.4, 8455.5) | 1.12 | (0.12, 10.25) | 410.8 | (82.1, 2056.6) | 153.2 | (65.9, 356.0) | 2.68 | (0.49, 14.68) |
| 9V | 308.7 | (42.5, 2241.5) | 1199.4 | (599.2, 2400.5) | 0.26 | (0.03, 2.01) | 83.2 | (18.6, 371.8) | 58.3 | (26.6, 127.5) | 1.43 | (0.29, 6.93) |
| 14 | 964.7 | (118.8, 7831.8) | 2392.0 | (1149.3, 4978.4) | 0.40 | (0.05, 3.53) | 449.1 | (92.4, 2181.8) | 151.8 | (66.4, 347.3) | 2.96 | (0.56, 15.69) |
| 18C | 428.0 | (68.3, 2680.6) | 499.4 | (262.7, 949.0) | 0.86 | (0.13, 5.73) | 25.4 | (6.4, 101.3) | 40.8 | (19.8, 84.2) | 0.62 | (0.14, 2.68) |
| 19A | 1961.4 | (252.5, 15238.9) | 1337.6 | (652.6, 2741.4) | 1.47 | (0.18, 12.26) | 78.6 | (16.7, 369.4) | 44.7 | (19.9, 100.5) | 1.76 | (0.34, 9.01) |
| 19F | 1995.0 | (310.8, 12807.7) | 456.3 | (238.0, 874.7) | 4.37 | (0.64, 30.01) | 19.2 | (4.7, 78.1) | 32.1 | (15.4, 66.8) | 0.60 | (0.14, 2.64) |
| 23F | 1171.8 | (119.7, 11476.3) | 4160.0 | (1871.8, 9245.5) | 0.28 | (0.03, 2.99) | 101.0 | (18.0, 565.3) | 61.2 | (24.9, 150.9) | 1.65 | (0.27, 10.16) |

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; MOPA = multiplex opsonophagocytic activity.
Note: Blood draw taken at time of enrollment.
Note: 3 subjects in 13vPnC cohort and 10 subjects in non-13vPnC cohort were "Untypable" (*S. pneumoniae* isolates detected but bacterium quantity insufficient for culture or unable to grow) and deep upper respiratory aspirates culture results were not available for 3 subjects in 13vPnC cohort and 14 subjects in non-13vPnC cohort, thus those subjects were excluded in the analysis.
Note: VT- or Sp- includes subjects with serotypes not included in 13vPnC and subjects with *S. pneumoniae* -.
a. N = number of subjects in the specified cohort.
b. Adjusted GMT and CIs are back transforms of adjusted mean and CIs based on a multiple regression model. A multiple regression model uses log assay value as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, sex, season of enrollment).
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## Safety results

## Adverse Events

In the 13vPnC cohort, 5 participants reported AEs (Table 16.2.7.1). All the AEs were of mild severity. The most frequently reported AE was diarrhoea (2 participants); all other AEs (including enteritis, blood creatine phosphokinase MB increased, vomiting and gastroenteritis) were reported in single participants. In the non-13vPnC cohort, 12 participants had reported AEs. All the AEs were of mild severity. The most frequently reported AE was diarrhoea (3 participants). Other AEs included vomiting, pyrexia, gastroenteritis, enteritis, hepatic function abnormal, hypoglycaemia, oxygen saturation decreased, hypokalaemia, hypoglycaemia, and gastritis. The MAH considered that none of the AEs to be related to 13vPnC. None of the AEs caused study discontinuation.

**16.2.7.1 Listing of Adverse Events**

| Cohort | Subject | System Organ Class/ Preferred Term/ Investigator Entry | Start Date/Time | Severity/ Outcome | Research Related Injury | Treatment Given | Other Action Taken | Causality | Is the AE Still Ongoing | SAE/ Reference ID | Caused Study Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 13vPnC | B1851196 1001 10011027 | Gastrointestinal disorders/ Diarrhoea/ DIARRHEA | 03NOV2019 | MILD/ RECOVERING/RESOLVING | N | N | NO OTHER ACTION TAKEN | OTHER/ ENTERITIS | Yes | | N |
| | B1851196 1001 10011064 | Gastrointestinal disorders/ Enteritis/ CHILDREN ENTERITIS | 17JAN2020 | MILD/ NOT RECOVERED/NOT RESOLVED | N | Y | NO OTHER ACTION TAKEN | OTHER/ dyspepsia | Yes | | N |
| | | Gastrointestinal disorders/ Diarrhoea/ DIARRHEA | 18JAN2020 | MILD/ RECOVERING/RESOLVING | N | Y | NO OTHER ACTION TAKEN | OTHER/ PEDIATRIC ENTERITIS | Yes | | N |
| | B1851196 1001 10011103 | Investigations/ Blood creatine phosphokinase MB increased/ CKMB INCREASED | 26OCT2020 | MILD/ NOT RECOVERED/NOT RESOLVED | N | N | NO OTHER ACTION TAKEN | OTHER/ infection | Yes | | N |
| | B1851196 1001 10011208 | Gastrointestinal disorders/ Vomiting/ EMESIS | 12AUG2021 | MILD/ NOT RECOVERED/NOT RESOLVED | N | N | NO OTHER ACTION TAKEN | OTHER/ dyspepsia | Yes | | N |
| | B1851196 1001 10011287 | Infections and infestations/ Gastroenteritis/ ACUTE GASTROENTERITIS | 19NOV2021 | MILD/ RECOVERED/RESOLVED | N | Y | NO OTHER ACTION TAKEN | OTHER/ dyspepsia | No 21NOV2021 | | N |
| Non-13vPnC | B1851196 1001 10011017 | Gastrointestinal disorders/ Vomiting/ EMESIS | 24SEP2019 | MILD/ RECOVERING/RESOLVING | N | Y | NO OTHER ACTION TAKEN | OTHER/ GASTRITIS | Yes | | N |
| | 1001 10011176 | administration site conditions/ Pyrexia/ FEVER | | NOT RECOVERED/NOT RESOLVED | | | OTHER ACTION TAKEN | STUDY | | | |
| | B1851196 1001 10011240 | Investigations/ Oxygen saturation decreased/ OXYGEN SATURATION IS TOO LOW | 27SEP2021 | MILD/ RECOVERED/RESOLVED | N | N | OTHER ACTION TAKEN/ oxygen uptake | DISEASE UNDER STUDY | No 27SEP2021 | | N |
| | B1851196 1001 10011278 | Metabolism and nutrition disorders/ Hypokalaemia/ HYPOKALEMIA | 04NOV2021 | MILD/ NOT RECOVERED/NOT RESOLVED | N | Y | NO OTHER ACTION TAKEN | OTHER/ Poor food | Yes | | N |
| | B1851196 1001 10011282 | Metabolism and nutrition disorders/ Hypoglycaemia/ HYPOGLYCEMIA | 08NOV2021 | MILD/ RECOVERED/RESOLVED | N | Y | NO OTHER ACTION TAKEN | OTHER/ poor food | No 08NOV2021 | | N |
| | B1851196 1001 10011286 | Gastrointestinal disorders/ Gastritis/ ACUTE GASTRITIS | 17NOV2021 | MILD/ NOT RECOVERED/NOT RESOLVED | N | Y | NO OTHER ACTION TAKEN | OTHER/ dyspepsia | Yes | | N |

Abbreviation: SAE = Serious Adverse Event.
Note: MedDRA v25.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 27OCT2022 (03:59) Source Data: ae Table Generation: 07NOV2022 (11:28) (Snapshot date: 25OCT2022) Output File: ./nda1_cdisc/B1851196_CSR/adae_l002

### Discussion on clinical aspects

B1851196 was a cohort study to evaluate immunogenicity of 13PnC in children 5-60 months with the diagnosis (per local standards) of clinical pneumonia. No study intervention was given. Participants were vaccinated as part of their paediatric care, not as part of this study.

Participants were characterized by 13vPnC vaccination cohort (in children who completed at least 2 doses of 13vPnC versus children that did not receive any 13vPnC dose) and by pneumococcal carriage status (VT carriage positive versus VT carriage negative or *S pneumoniae* carriage negative). In general, IgG levels and MOPA titer values measured during an episode of pneumonia were greater among those who had been vaccinated with 13vPnC prior to study participation as part of their paediatric care (13vPnC cohort), as compared to those who were not (non-13vPnC cohort), which suggests that two or more doses of a 13vPnC infant series vaccination established long-term antibody responses.

The administration of 13PnC was well tolerated and the AEs reported in this group were consistent with medical events or conditions that are common in this age group. The findings in this study is 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. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.