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

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no: EMEA/H/C/001104/P46/057.1

Note

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

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1. Introduction

On April 29, 2015, the MAH submitted a completed paediatric study for Prevenar13, 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 B1851015 (6096A1-3019-CN): A Phase 3, Randomized, Active-Controlled Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared with a 7-Valent Pneumococcal Conjugate Vaccine in Healthy Infants in China is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- B1851015 (6096A1-3019-CN): A Phase 3, Randomized, Active-Controlled Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared with a 7-Valent Pneumococcal Conjugate Vaccine in Healthy Infants in China;

The Marketing Authorisation Holder (MAH) is submitting, in accordance with Article 46 of Regulation (EC) No1901/2006 (as amended) on medicinal products for pediatric use, the final results for the toddler dose and 6-month follow-up safety data from a 13-valent pneumococcal conjugate vaccine (13vPnC, Prevenar 13) Phase 3 pediatric study (Study, B1851015) conducted in China. The study was conducted to support registration of 13vPnC in China.

A clinical study report (CSR) with results from the infant phase of this study were submitted to the European Medicines Agency (EMA) in September 2014 (eCTD sequence 0282) and reviewed in procedure EMEA/H/C/1104/P46 057. The Committee for Human Medicinal Products (CHMP) concluded that no new findings were reported from this study that require further regulatory action.

2.3.2. Clinical study

B1851015 (6096A1-3019-CN): A Phase 3, Randomized, Active-Controlled Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared with a 7-Valent Pneumococcal Conjugate Vaccine in Healthy Infants in China

Description

This was a phase 3, parallel-group, randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of 13vPnC as compared with 7vPnC in healthy infants in China. This study comprised double-blind (Groups 1 and 2) and open-label (Groups 3 and 4) groups.

Methods

Objectives

Note: Results for all primary objectives for this study, and secondary objectives relating to the infant series doses, were presented in the infant series clinical study report (CSR). This report presents results of the secondary objectives relating to the toddler dose and the exploratory objective.

Primary Objectives:

- To demonstrate that the immune responses to the 13 pneumococcal serotypes induced by 13-valent pneumococcal conjugate vaccine (13vPnC) in a 3-, 4-, 5-, and 12-month schedule (Group 2) are noninferior to the immune responses induced by 7-valent pneumococcal conjugate vaccine (7vPnC) in a 3-, 4-, 5-, and 12-month schedule (Group 1) when measured 1 month after the infant series.
- To demonstrate that the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in a 2-, 4-, 6-, and 12-month schedule (Group 3) are noninferior to the immune responses induced by 7vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 1) when measured 1 month after the infant series.

Primary Safety Objective:

- To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

Secondary Objectives:

Groups 2 and 3

- To evaluate the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 2) compared to the immune responses induced by 7vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 1) when measured 1 month after the toddler dose.
- To evaluate the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in a 2-, 4-, 6-, and 12-month schedule (Group 3) compared to the immune responses induced by 7vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 1) when measured 1 month after the toddler dose.

Group 4

- To evaluate the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in a 3-, 5-, and 12-month schedule (Group 4) compared with the immune responses induced by 7vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 1) when measured 1 month after the infant series and 1 month after the toddler dose.

Groups 2, 3 and 4

- To describe the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in a 3-, 4-, 5-, and 12-month schedule (Group 2), 13vPnC in a 2-, 4-, 6-, and 12-month schedule (Group 3), and 13vPnC in a 3-, 5-, and 12-month schedule (Group 4) when measured;

- 1 month after the infant series
- 1 month after the toddler dose

Exploratory Objective:

- To describe the immune responses to the 13 pneumococcal serotypes during the period of the study.

Study design

This was a phase 3, parallel-group, randomized, active-controlled study to evaluate the safety, tolerability, and immunogenicity of 13vPnC as compared with 7vPnC in healthy infants in China. This study comprised double-blind (Groups 1 and 2) and open-label (Groups 3 and 4) groups. Approximately 1666 healthy Chinese infants (aged 42 to 77 days at the time of enrollmenta) were planned to be randomized to receive the study vaccines as follows:

- Group 1 (7vPnC) (vaccine administered at 3-, 4-, 5-, and 12 months)
- Group 2 (13vPnC) (vaccine administered at 3-, 4-, 5-, and 12 months)
- Group 3 (13vPnC) (vaccine administered at 2-, 4-, 6- and 12 months)
- Group 4 (13vPnC) (vaccine administered at 3-, 5-, and 12 months)

Study population /Sample size

Inclusion Criteria:

Subjects who satisfied the following inclusion criteria were eligible to participate in this study if all other qualifying criteria were met:

1. Evidence of a personally signed and dated informed consent document indicating that the subject's parent/legal guardian had been informed of all pertinent aspects of the study.
2. Subject whose caregiver was willing and able to comply with scheduled visits, laboratory tests, and other study procedures. The subject's caregiver must have been able to be reached by telephone for the duration of the study.
3. Male or female subject aged 42 to 77 days (approximately 2 months) at the time of enrollment.
4. Healthy infant as determined by medical history, physical examination, and judgment of the investigator.

Exclusion Criteria:

Subjects with any of the following criteria were not eligible to participate in the study:

1. Previous vaccination with licensed or investigational pneumococcal vaccine.
2. A previous anaphylactic reaction to any vaccine or vaccine-related component.
3. Contraindication to vaccination with pneumococcal vaccines.
4. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.
5. Known or suspected immune deficiency or suppression.

6. History of culture-proven invasive disease caused by *S. pneumoniae*.
7. Major known congenital malformation or serious chronic disorder.
8. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorder such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorder. Did not include resolving syndromes due to birth trauma such as Erb palsy.
9. Receipt of blood products or gamma globulin. Hepatitis B immunoglobulin may have been given.
10. Participation in another investigational study within 28 days before the current study begins and during study participation. Participation in purely observational studies was acceptable.
11. Subjects whose parents or legal guardian were investigational site staff members or subjects whose parents or legal guardian were Pfizer employees directly involved in the conduct of the study.
12. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational produced administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study.
13. Known or suspected allergy to 13vPnC, 7vPnC, or other compounds related to these classes of medication.

Treatments

Vaccines Administered:

Subjects were randomized to 1 of 4 groups and were vaccinated with 7vPnC or 13vPnC according to the vaccination schedules detailed for each group under ‘Study Design’. On each vaccination day, a single dose (0.5 mL) of 13vPnC or 7vPnC was administered intramuscularly into the anterolateral muscle of the left thigh.

Outcomes/endpoints

Immunogenicity Evaluations:

Blood samples for analyses included in this study report were collected at 1 month (28 to 42 days) after the toddler dose. Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were determined in all subjects for each blood sample and expressed as micrograms per milliliter (μg/mL). A randomly selected subset was to be analyzed for serum opsonophagocytic activity (OPA) elicited by the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) at the time indicated above. Subjects were randomly assigned by an independent statistician.

Safety Evaluations:

The safety of 13vPnC in this study was determined based on incidence rates of local reactions (redness, swelling and tenderness at the site of study vaccine injection), systemic events (decreased appetite, irritability, increased sleep, decreased sleep, fever, and use of antipyretic medication to treat or prevent symptoms), and AEs. Subjects were observed for at least 30 minutes after each vaccination for any significant acute reactions. Observations after vaccination were to be performed according to local immunization practice.

Statistical Methods

Seven (7) analysis populations were planned for the study overall; 6 immunogenicity analysis populations and the safety population. Data for infant series 2 immunogenicity populations were included in the infant CSR (see P046 57 AR).

Data for the following 4 remaining immunogenicity populations are included in this report:

Pre-toddler Dose Evaluable Infant Pneumococcal Immunogenicity Population

This population is referred throughout the CSR as the 'evaluable pre-toddler dose immunogenicity population', and included subjects who met all of the following criteria:

1. Eligible for the study;
2. 41 to 78 days of age, inclusive, on the day of randomization (this was also the day of first vaccination for Group 3);
3. Received the vaccine to which they were randomly assigned at all infant doses (when vaccinated);
4. Received all 3 study vaccinations for Group 1, 2, 3, and both study vaccinations for Group 4, during the infant series;
5. Received no prohibited vaccines;
6. Had no major protocol violations as determined by the clinical lead or clinicians for the immunogenicity evaluable population;
7. Were 364 to 469 days of age, inclusive, at the pre-toddler dose blood draw;
8. Had at least 1 valid and determinate pneumococcal assay result before the toddler dose that would contribute to the planned analysis; and,
9. Note: the above condition was considered met if the subject had a valid and determinate pre-toddler dose assay result for any pneumococcal serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).
10. Had the blood draw before the toddler dose within the required time frame (within 1 day before or on the day of the toddler dose).

Evaluable Toddler Dose Pneumococcal Immunogenicity Population

This population is referred throughout the CSR as the 'evaluable toddler dose immunogenicity population', and included subjects who met all of the following criteria:

1. Eligible for the study;
2. 41 to 78 days of age, inclusive, on the day of randomization (this was also the day of first vaccinations for Group 3);
3. 364 to 469 days of age, inclusive, on the day of toddler dose;
4. Received the vaccine to which they were randomly assigned at all infant doses and toddler dose (when vaccinated);
5. Received all 4 study vaccinations (3 infant doses and 1 toddler dose) for Groups 1, 2 and 3, and all 3 study vaccinations (2 infant doses and 1 toddler dose) for Group 4;

6. Had at least 1 valid and determinate pneumococcal assay result after the toddler dose that would contribute to the planned analysis;
7. Note: the above condition was considered met if the subject had a valid and determinate pre-toddler dose assay result for any pneumococcal serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).
8. Had blood draw after the toddler dose within the required time frame (27 to 56 days after the toddler dose);
9. Received no prohibited vaccines before blood draw after the toddler dose; and,
10. Had no major protocol violations as determined by the clinical lead or clinicians for the immunogenicity evaluable population.

Pre-toddler Dose All-Available Infant Pneumococcal Immunogenicity Population

This population is referred to throughout this CSR as the 'all-available pre-toddler dose immunogenicity population', and included subjects who had at least 1 valid and determinate pneumococcal assay result from the pre-toddler dose blood draw for each group.

All-Available Toddler Dose Pneumococcal Immunogenicity Population

This population is referred to throughout this CSR as the 'all-available toddler dose immunogenicity population', and included subjects who had at least 1 valid and determinate pneumococcal assay result from the blood draw after the toddler dose for each group.

Safety Population:

The safety population included all subjects who received at least 1 dose of study vaccine.

Immunogenicity Analysis:

Statistical procedures similar to those used for the primary endpoints above were performed for the secondary immunogenicity endpoints, 95% CIs (instead of 97.5% CIs) were calculated for the differences in proportions for responders, both for IgG concentrations and OPA titers.

The immunogenicity analyses were described in general terms first, and by analysis type second. Missing values were excluded from the immunogenicity analyses; no imputation or estimation of missing values was attempted.

Primary Endpoints:

- The proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 µg/mL for each of the pneumococcal serotypes measured 1 month after the infant series.
- The serotype-specific IgG geometric mean concentrations (GMCs) for each of the pneumococcal serotypes measured 1 month after the infant series.

Secondary Endpoints:

- The proportion of subjects in a subset achieving a serotype-specific OPA titer ≥lower limit of quantitation (LLOQ) for each of the pneumococcal serotypes measured 1 month after the infant series.
- The serotype-specific OPA geometric mean titer (GMT) for each of the pneumococcal serotypes measured 1 month after the infant series.

Proportions of Subjects Achieving Defined Levels

Within each vaccine group and for each pneumococcal serotype, the proportion of subjects achieving an antibody concentration or titer at a prespecified level, i.e. ≥0.35 µg/mL for IgG antibody concentration and LLOQ for OPA titer were computed at proposed analysis endpoints. In addition, exact, unconditional, 2-sided, 95% confidence intervals (CIs) on the proportion were calculated.

For primary immunogenicity endpoints responses for 13vPnC in Group 2 and in 13vPnC Group 3, to assess the difference for each serotype separately in the observed proportion responses for 13vPnC in Group 2 and in Group 3 compared with the 7vPnC in Group 1, exact, unconditional, 2-sided, 97.5% CIs on the difference in proportions were to be calculated. The noninferiority criterion for primary endpoint with regard to the proportion of subjects achieving IgG antibody concentration ≥0.35 µg/mL only applies to the 7 common serotypes. For both the primary (percentage of subjects achieving serotype-specific IgG concentration ≥0.35 µg/mL) and the secondary endpoint (percentage of subjects achieving an OPA titer ≥LLOQ), analysis for the additional 6 serotypes in 13vPnC (which are not in 7vPnC), based on the actual response rates, were to be performed for comparisons of vaccine groups. In addition, for the primary responder endpoint (percentage of subjects achieving serotype-specific IgG concentration ≥0.35 µg/mL), the analyses for the additional 6 serotypes in 13vPnC were also performed based on the lowest response rate among the 7 common serotypes (from the 7vPnC vaccine group). This analysis was performed to bridge antibody response for serotypes not in 7vPnC to 7vPnC efficacy.

Geometric Means

Geometric Mean (Analysis of a Single Population Mean):

For the toddler dose analysis, two-sided 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

Ratio of the Geometric Means (Analysis of Two Population Means):

For the toddler dose analysis, two-sided 95% CIs for the ratio of two geometric means (13vPnC Groups -7vPnC Group 1 reference) were constructed by back transformation of the CIs for the difference of the two logarithmically transformed assay results computed using the Student t distribution. The mean difference of the logarithmically transformed results was equivalent to the ratio of the two geometric means on the logarithmic scale: log (x/y) =(log x) - (log y).

Safety Analyses:

The safety of 7vPnC and 13vPnC in this study was determined based on observation of local reactions (including redness, swelling, and tenderness) at the pneumococcal injection site, systemic events (including fever, decreased appetite, irritability, increased sleep, and decreased sleep), use of antipyretic medication to treat or prevent symptoms, and other AEs reported.

Adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized by vaccine group.

Differences in incidence rates of local reactions and systemic events after administration of each dose of study vaccine in the 13vPnC groups relative to the incidence rates in the 7vPnC group were reported.

CHMP's comment: It is noted that for the two primary objectives 97.5% CI were calculated, while 95% CI were used for all secondary analyses. This is acceptable but should be kept in mind when interpreting results.

Results

Recruitment/ Number analysed

Of the 1674 subjects randomized in the study, 1556 (93.0%) subjects were vaccinated with the toddler dose. The majority of subjects (>87.2%) in each vaccine group completed the toddler dose and 6-month follow up. A total of 51 (3.0%) subjects who received the toddler dose were withdrawn before the post-toddler dose blood draw. The disposition of subjects was similar across vaccine groups.

In total, 830 (53.3%) male subjects and 726 (46.7%) female subjects were included in the safety population at the time of the toddler dose. The mean ages of subjects in each group were similar at the toddler dose.

Efficacy results

Pre-toddler dose:

Before the toddler dose, the proportion of subjects with IgG concentrations ≥0.35 µg/mL remained high (≥82.5%) in Groups 1, 2 and 3 for the common serotypes (Table 2), although slightly lower than that observed after the infant series (Data not shown in this AR).

For the additional serotypes, the proportions of responders in 13vPnC Groups 2 and 3 (>93.7% all serotypes, except serotype 3 [73.6% in Group 2 and 60.4 in Group 3]) were somewhat lower than after the infant series, but remained higher than in 7vPnC Group 1 before the toddler dose. In the 7vPnC group the proportions of responders for each additional serotype was higher before the toddler dose than after the infant series, and were particularly high for serotypes 19A (90.2%), 5 (77.9%), and 6A (74.0%).

IgG GMCs for the common and additional serotypes before the toddler dose were consistent with these results (Table 4), and in the 13vPnC groups were lower than after the infant series (Data not shown in this AR). As with the proportion of responders, IgG GMCs for serotype 3 were lower than for other additional serotypes.

Post-toddler dose:

Common serotypes: One month after the toddler dose, the proportions of responders were generally similar or higher (≥98.3%) than after the infant series for each common serotype in Groups 1, 2, and 3 (Table 3, Infant data not shown in this AR).

One month after the toddler dose, IgG GMCs were higher than after the infant series for each common serotype in 13vPnC Groups 2 and 3 and 7vPnC Group 1 (Table 5, Infant data not shown in this AR). Based on statistical comparisons between the 13vPnC and 7vPnC groups, IgG GMCs for the common serotypes in Group 2 were noninferior to those in Group 1 (ie, lower limit of the 95% confidence interval [CI] for the ratio >0.5); for serotype 19F the GMC was statistically significantly greater in 13vPnC Group 2 (ie, lower bound of 95% CI for the ratio >1, Table 6). In addition, the non-inferiority criterion was met for all 7 common serotypes in 13vPnC Group 3 relative to 7vPnC Group 1, and IgG GMCs were statistically significantly greater in Group 3 for serotypes 18C and 19 F (Table 7).

Additional serotypes: For each additional serotype, including serotype 3, the proportions of responders in Groups 1, 2 and 3 were higher after the toddler dose than after the infant series (Table 3, Infant data not shown in this AR). In 13vPnC Groups 2 and 3 the proportions of responders were ≥98.8% for each additional serotype. In 7vPnC Group 1, the proportion responders was ≥84.9% for serotypes 5, 6A, and 19A, and ranged from 16.5% to 18.8% for serotypes 1, 3, and 7F.

IgG GMCs for each additional serotype in Groups 1, 2 and 3 were numerically higher after the toddler dose than after the infant series, except for serotype 3 in Groups 2 and 3 (Table 4, Infant data not shown in this AR).

When compared with GMCs in 7vPnC Group 1, the IgG GMCs for each additional serotype in 13vPnC Groups 2 and 3 were statistically significantly higher (lower bound of the 95% CI for the GMC ratios was >1, Table 5 and Table 6).

Table 1. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL Before the Toddler Dose - Evaluable Pre-toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)															
	7vPnC Group 1				13vPnC Group 2				13vPnC Group 3				13vPnC Group 4			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
7vPnC																
4	430	425	98.8	(97.3, 99.6)	436	427	97.9	(96.1, 99.1)	442	418	94.6	(92.0, 96.5)	223	209	93.7	(89.7, 96.5)
6B	430	398	92.6	(89.7, 94.9)	436	392	89.9	(86.7, 92.6)	442	410	92.8	(89.9, 95.0)	223	188	84.3	(78.9, 88.8)
9V	430	408	94.9	(92.4, 96.8)	435	388	89.2	(85.9, 92.0)	442	376	85.1	(81.4, 88.3)	223	183	82.1	(76.4, 86.9)
14	430	427	99.3	(98.0, 99.9)	435	430	98.9	(97.3, 99.6)	442	434	98.2	(96.5, 99.2)	223	220	98.7	(96.1, 99.7)
18C	430	397	92.3	(89.4, 94.7)	435	409	94.0	(91.4, 96.1)	442	409	92.5	(89.7, 94.8)	223	197	88.3	(83.4, 92.2)
19F	429	424	98.8	(97.3, 99.6)	433	428	98.8	(97.3, 99.6)	441	437	99.1	(97.7, 99.8)	223	222	99.6	(97.5, 100.0)
23F	430	364	84.7	(80.9, 87.9)	435	359	82.5	(78.6, 86.0)	442	379	85.7	(82.1, 88.9)	223	162	72.6	(66.3, 78.4)
Additional																
1	398	50	12.6	(9.5, 16.2)	435	411	94.5	(91.9, 96.4)	441	420	95.2	(92.8, 97.0)	223	213	95.5	(91.9, 97.8)
3	401	53	13.2	(10.1, 16.9)	428	315	73.6	(69.2, 77.7)	437	264	60.4	(55.7, 65.0)	217	138	63.6	(56.8, 70.0)
5	430	335	77.9	(73.7, 81.7)	435	423	97.2	(95.2, 98.6)	442	436	98.6	(97.1, 99.5)	223	215	96.4	(93.1, 98.4)
6A	430	318	74.0	(69.5, 78.0)	436	414	95.0	(92.5, 96.8)	442	429	97.1	(95.0, 98.4)	223	209	93.7	(89.7, 96.5)
7F	423	62	14.7	(11.4, 18.4)	434	425	97.9	(96.1, 99.0)	441	434	98.4	(96.8, 99.4)	223	215	96.4	(93.1, 98.4)
19A	429	387	90.2	(87.0, 92.9)	435	428	98.4	(96.7, 99.4)	442	439	99.3	(98.0, 99.9)	222	217	97.7	(94.8, 99.3)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
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Table 2. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL After the Toddler Dose - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)															
	7vPnC Group 1				13vPnC Group 2				13vPnC Group 3				13vPnC Group 4			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
7vPnC																
4	399	399	100.0	(99.1, 100.0)	409	409	100.0	(99.1, 100.0)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)
6B	399	397	99.5	(98.2, 99.9)	409	407	99.5	(98.2, 99.9)	423	422	99.8	(98.7, 100.0)	215	213	99.1	(96.7, 99.9)
9V	399	398	99.7	(98.6, 100.0)	409	406	99.3	(97.9, 99.8)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)
14	399	399	100.0	(99.1, 100.0)	409	409	100.0	(99.1, 100.0)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)
18C	399	398	99.7	(98.6, 100.0)	409	407	99.5	(98.2, 99.9)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)
19F	399	398	99.7	(98.6, 100.0)	409	409	100.0	(99.1, 100.0)	423	422	99.8	(98.7, 100.0)	215	215	100.0	(98.3, 100.0)
23F	399	393	98.5	(96.8, 99.4)	409	402	98.3	(96.5, 99.3)	423	417	98.6	(96.9, 99.5)	215	210	97.7	(94.7, 99.2)
Additional																
1	347	59	17.0	(13.2, 21.4)	409	406	99.3	(97.9, 99.8)	423	422	99.8	(98.7, 100.0)	215	214	99.5	(97.4, 100.0)
3	370	61	16.5	(12.9, 20.7)	409	405	99.0	(97.5, 99.7)	421	416	98.8	(97.3, 99.6)	213	210	98.6	(95.9, 99.7)
5	398	338	84.9	(81.0, 88.3)	409	407	99.5	(98.2, 99.9)	423	422	99.8	(98.7, 100.0)	215	215	100.0	(98.3, 100.0)
6A	399	385	96.5	(94.2, 98.1)	409	407	99.5	(98.2, 99.9)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)
7F	394	74	18.8	(15.0, 23.0)	409	405	99.0	(97.5, 99.7)	423	421	99.5	(98.3, 99.9)	215	214	99.5	(97.4, 100.0)
19A	399	398	99.7	(98.6, 100.0)	409	409	100.0	(99.1, 100.0)	423	423	100.0	(99.1, 100.0)	215	215	100.0	(98.3, 100.0)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
Source: Program ID: Study B1851015/t_imm_igg_desc_t.SAS. Runtime ID: 04NOV14 14:09

Table 3. Pneumococcal IgG GMCs (µg/mL) Before the Toddler Dose - Evaluable Pre-Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)											
	7vPnC Group 1			13vPnC Group 2			13vPnC Group 3			13vPnC Group 4		
Serotype	**n[a]**	**GMC[b]**	**(95% CI[c])**	**n[a]**	**GMC[b]**	**(95% CI[c])**	**n[a]**	**GMC[b]**	**(95% CI[c])**	**n[a]**	**GMC[b]**	**(95% CI[c])**
7vPnC												
4	430	1.48	(1.38, 1.57)	436	1.21	(1.13, 1.30)	442	1.26	(1.17, 1.37)	223	1.04	(0.93, 1.17)
6B	430	1.08	(0.99, 1.17)	436	0.97	(0.89, 1.05)	442	1.12	(1.03, 1.22)	223	0.77	(0.67, 0.88)
9V	430	1.00	(0.93, 1.08)	435	0.80	(0.74, 0.86)	442	0.76	(0.71, 0.81)	223	0.68	(0.61, 0.77)
14	430	5.26	(4.86, 5.68)	435	4.47	(4.11, 4.86)	442	4.20	(3.85, 4.59)	223	3.89	(3.45, 4.40)
18C	430	0.86	(0.81, 0.93)	435	0.83	(0.78, 0.88)	442	1.00	(0.94, 1.07)	223	0.71	(0.63, 0.79)
19F	429	1.70	(1.54, 1.88)	433	2.19	(1.99, 2.42)	441	2.10	(1.91, 2.30)	223	2.11	(1.88, 2.37)
23F	430	0.83	(0.76, 0.90)	435	0.80	(0.73, 0.88)	442	0.97	(0.89, 1.06)	223	0.59	(0.52, 0.68)
Additional												
1	398	0.04	(0.03, 0.05)	435	1.11	(1.02, 1.21)	441	1.23	(1.13, 1.32)	223	1.08	(0.97, 1.19)
3	401	0.12	(0.11, 0.14)	428	0.49	(0.46, 0.52)	437	0.40	(0.37, 0.42)	217	0.44	(0.40, 0.48)
5	430	0.59	(0.54, 0.64)	435	1.23	(1.16, 1.30)	442	1.35	(1.28, 1.44)	223	1.21	(1.10, 1.33)
6A	430	0.57	(0.53, 0.62)	436	1.18	(1.10, 1.28)	442	1.40	(1.30, 1.52)	223	1.09	(0.98, 1.23)
7F	423	0.07	(0.06, 0.09)	434	1.37	(1.27, 1.47)	441	1.57	(1.47, 1.69)	223	1.23	(1.10, 1.36)
19A	429	0.77	(0.71, 0.84)	435	1.65	(1.51, 1.79)	442	1.41	(1.30, 1.54)	222	1.48	(1.31, 1.68)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Program ID: Study B1851015/t_imm_gmc_desc_t.SAS. Runtime ID: 04NOV14 14:08

Table 4. Pneumococcal IgG GMCs (µg/mL) After the Toddler Dose - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)											
	7vPnC Group 1			13vPnC Group 2			13vPnC Group 3			13vPnC Group 4		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
7vPnC												
4	399	14.88	(13.64, 16.25)	409	12.75	(11.64, 13.96)	423	13.25	(12.19, 14.40)	215	12.15	(10.80, 13.67)
6B	399	11.94	(10.82, 13.18)	409	11.64	(10.46, 12.95)	423	13.05	(11.88, 14.35)	215	11.92	(10.28, 13.81)
9V	399	8.36	(7.70, 9.08)	409	6.79	(6.24, 7.38)	423	7.04	(6.48, 7.65)	215	7.23	(6.49, 8.06)
14	399	24.55	(22.71, 26.55)	409	21.79	(20.13, 23.60)	423	20.61	(19.04, 22.31)	215	23.45	(21.08, 26.09)
18C	399	9.02	(8.29, 9.82)	409	8.96	(8.22, 9.76)	423	11.38	(10.49, 12.34)	215	8.79	(7.73, 9.99)
19F	399	11.36	(10.36, 12.46)	409	18.02	(16.48, 19.70)	423	15.96	(14.57, 17.47)	215	22.13	(19.63, 24.95)
23F	399	12.61	(11.34, 14.03)	409	12.15	(10.82, 13.65)	423	13.90	(12.42, 15.55)	215	9.81	(8.40, 11.45)
Additional												
1	347	0.06	(0.05, 0.07)	409	11.77	(10.62, 13.03)	423	11.86	(10.84, 12.98)	215	12.55	(11.15, 14.12)
3	370	0.14	(0.12, 0.16)	409	1.73	(1.62, 1.85)	421	1.41	(1.33, 1.50)	213	1.63	(1.49, 1.79)
5	398	0.67	(0.61, 0.74)	409	8.05	(7.40, 8.75)	423	8.27	(7.62, 8.97)	215	7.90	(7.15, 8.72)
6A	399	3.02	(2.68, 3.40)	409	11.21	(10.18, 12.35)	423	14.08	(12.83, 15.45)	215	14.18	(12.57, 16.01)
7F	394	0.10	(0.08, 0.12)	409	9.73	(8.92, 10.61)	423	13.11	(11.99, 14.33)	215	10.11	(9.06, 11.28)
19A	399	2.48	(2.27, 2.70)	409	15.27	(13.99, 16.67)	423	14.19	(13.11, 15.35)	215	16.71	(14.86, 18.78)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Source: Program ID: Study B1851015/t_imm_gmc_desc_t.SAS. Runtime ID: 04NOV14 14:08

Table 5. Comparison of Pneumococcal IgG GMCs After the Toddler Dose, 13vPnC Group 2 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 2			7vPnC Group 1				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	409	12.75	(11.64, 13.96)	399	14.88	(13.64, 16.25)	0.86	(0.75, 0.97)
6B	409	11.64	(10.46, 12.95)	399	11.94	(10.82, 13.18)	0.97	(0.84, 1.13)
9V	409	6.79	(6.24, 7.38)	399	8.36	(7.70, 9.08)	0.81	(0.72, 0.91)
14	409	21.79	(20.13, 23.60)	399	24.55	(22.71, 26.55)	0.89	(0.79, 0.99)
18C	409	8.96	(8.22, 9.76)	399	9.02	(8.29, 9.82)	0.99	(0.88, 1.12)
19F	409	18.02	(16.48, 19.70)	399	11.36	(10.36, 12.46)	1.59	(1.39, 1.80)
23F	409	12.15	(10.82, 13.65)	399	12.61	(11.34, 14.03)	0.96	(0.82, 1.13)
Additional								
1	409	11.77	(10.62, 13.03)	347	0.06	(0.05, 0.07)	200.98	(160.75, 251.28)
3	409	1.73	(1.62, 1.85)	370	0.14	(0.12, 0.16)	12.22	(10.58, 14.12)
5	409	8.05	(7.40, 8.75)	398	0.67	(0.61, 0.74)	11.98	(10.54, 13.62)
6A	409	11.21	(10.18, 12.35)	399	3.02	(2.68, 3.40)	3.71	(3.19, 4.32)
7F	409	9.73	(8.92, 10.61)	394	0.10	(0.08, 0.12)	96.93	(80.28, 117.04)
19A	409	15.27	(13.99, 16.67)	399	2.48	(2.27, 2.70)	6.17	(5.46, 6.97)

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 13vPnC to 7vPnC reference value.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmc_inf_t.SAS. Runtime ID: 25NOV14 11:50

Table 6. Comparison of Pneumococcal IgG GMCs After the Toddler Dose, 13vPnC Group 3 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 3			7vPnC Group 1				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	423	13.25	(12.19, 14.40)	399	14.88	(13.64, 16.25)	0.89	(0.79, 1.00)
6B	423	13.05	(11.88, 14.35)	399	11.94	(10.82, 13.18)	1.09	(0.95, 1.25)
9V	423	7.04	(6.48, 7.65)	399	8.36	(7.70, 9.08)	0.84	(0.75, 0.95)
14	423	20.61	(19.04, 22.31)	399	24.55	(22.71, 26.55)	0.84	(0.75, 0.94)
18C	423	11.38	(10.49, 12.34)	399	9.02	(8.29, 9.82)	1.26	(1.12, 1.42)
19F	423	15.96	(14.57, 17.47)	399	11.36	(10.36, 12.46)	1.40	(1.23, 1.60)
23F	423	13.90	(12.42, 15.55)	399	12.61	(11.34, 14.03)	1.10	(0.94, 1.29)
Additional								
1	423	11.86	(10.84, 12.98)	347	0.06	(0.05, 0.07)	202.59	(163.40, 251.18)
3	421	1.41	(1.33, 1.50)	370	0.14	(0.12, 0.16)	9.96	(8.67, 11.46)
5	423	8.27	(7.62, 8.97)	398	0.67	(0.61, 0.74)	12.32	(10.86, 13.98)
6A	423	14.08	(12.83, 15.45)	399	3.02	(2.68, 3.40)	4.66	(4.01, 5.41)
7F	423	13.11	(11.99, 14.33)	394	0.10	(0.08, 0.12)	130.55	(108.16, 157.58)
19A	423	14.19	(13.11, 15.35)	399	2.48	(2.27, 2.70)	5.73	(5.10, 6.44)

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 13vPnC to 7vPnC reference value.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmc_inf_t.SAS. Runtime ID: 25NOV14 11:50

CHMP's comment: The IgG results are well in agreement with previously presented results, and do not cause further concern.

OPA GMTs for the toddler dose after a 3-dose infant series

Pre-toddler:

Before the toddler dose, OPA GMTs for the common serotypes were lower than GMTs after the infant series in Groups 1, 2 and 3, and were generally lower in 13vPnC Groups 2 and 3 than in 7vPnC Group 1. For the additional serotypes, GMTs in 13vPnC Groups 2 and 3 were lower, and in 7vPnC Group 1 were similar or lower, before the toddler dose than after the infant series (Table 7, Infant data not shown in this AR).

Post-toddler dose:

Common serotypes: One month after the toddler dose, OPA GMTs were higher than after the infant series for each common serotype in Groups 1, 2, and 3, with the exception of serotype 14 in Groups 1 and 2 (Table 8 Infant data not shown in this AR).

Based on statistical comparisons between the 13vPnC and 7vPnC groups, OPA GMTs for all common serotypes in Group 2 or Group 3 were noninferior to those in Group 1 (ie, lower limit of the 95% CI for the ratio >0.5); the GMT for serotype 19F was statistically significantly greater in 13vPnC Group 2 and Group 3 each relative to 7vPnC Group 1 (ie, lower bound of 95% CI for the ratio >1, Table 9 and Table 10).

Additional serotypes: OPA GMTs for each additional serotype in Groups 2 and 3 were numerically higher after the toddler dose than after the infant series, except for serotype 3 in Group 2 (Table 8 Infant data not shown in this AR).

When compared with GMTs in 7vPnC Group 1, the OPA GMTs for each additional serotype in 13vPnC Groups 2 and 3 were statistically significantly higher (lower bound of the 95% CI for the GMT ratios was >1, Table 9 and Table 10).

Table 7. Pneumococcal OPA GMTs Before the Toddler Dose - Evaluable Pre-toddler Immunogenicity Population

	Vaccine Group (as Randomized)											
	7vPnC Group 1			13vPnC Group 2			13vPnC Group 3			13vPnC Group 4		
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])
7vPnC												
4	117	446	(312.3, 636.7)	116	177	(110.2, 284.3)	110	314	(208.0, 473.7)	110	220	(135.2, 357.1)
6B	112	64	(38.2, 107.1)	110	39	(23.6, 63.9)	106	69	(41.2, 116.1)	108	17	(10.5, 27.0)
9V	116	224	(133.7, 377.0)	113	170	(100.5, 286.6)	107	202	(119.7, 340.8)	117	143	(84.9, 242.4)
14	119	814	(630.0, 1052.5)	117	619	(476.0, 804.3)	107	520	(384.7, 702.3)	119	559	(418.1, 747.4)
18C	112	449	(281.7, 717.2)	111	241	(142.9, 406.9)	105	411	(255.8, 661.4)	114	183	(104.6, 318.9)
19F	113	12	(8.0, 17.2)	114	16	(10.3, 24.4)	109	20	(12.9, 30.9)	114	20	(12.8, 32.0)
23F	115	231	(148.2, 360.5)	112	199	(127.4, 312.2)	107	402	(264.7, 612.0)	116	108	(65.0, 179.6)
Additional												
1	119	4	(3.9, 4.4)	117	7	(5.8, 8.8)	110	9	(6.7, 10.8)	125	7	(6.2, 8.9)
3	118	7	(5.5, 8.0)	117	27	(21.8, 32.7)	111	32	(25.7, 40.6)	125	30	(24.1, 36.7)
5	119	4	(3.9, 4.4)	117	9	(7.2, 11.4)	111	13	(10.1, 17.4)	124	12	(9.3, 15.6)
6A	118	33	(20.4, 53.2)	117	393	(266.6, 580.3)	111	503	(354.9, 711.7)	106	184	(112.6, 301.1)
7F	97	15	(9.2, 23.3)	116	546	(407.3, 733.1)	110	903	(712.8, 1143.8)	123	569	(427.0, 758.2)
19A	118	5	(4.2, 5.5)	115	21	(14.7, 30.3)	109	24	(16.0, 34.9)	123	26	(18.2, 37.3)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
Source: Program ID: Study B1851015/t_imm_gmt_desc_t.SAS. Runtime ID: 04NOV14 14:09

Table 8. Pneumococcal OPA GMTs After the Toddler Dose - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)											
	7vPnC Group 1			13vPnC Group 2			13vPnC Group 3			13vPnC Group 4		
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])
7vPnC												
4	113	7662	(6171.2, 9513.2)	109	6915	(5700.3, 8389.1)	105	7319	(5960.5, 8988.0)	108	7193	(5716.6, 9049.6)
6B	111	4958	(3931.7, 6251.5)	109	4894	(3695.5, 6481.9)	103	5740	(4723.9, 6975.2)	103	2713	(1973.3, 3729.5)
9V	113	7825	(6469.6, 9463.4)	109	7679	(6251.4, 9433.6)	105	8892	(7563.3, 10452.9)	107	7861	(6237.6, 9907.1)
14	112	3269	(2773.0, 3854.4)	109	2694	(2248.9, 3226.7)	106	2776	(2268.6, 3396.8)	107	2928	(2481.8, 3453.7)
18C	111	22011	(18687.5, 25925.5)	110	20661	(16762.4, 25467.0)	106	20098	(17265.9, 23393.5)	113	18425	(15495.1, 21909.0)
19F	112	1410	(1066.7, 1864.3)	106	3860	(2897.1, 5144.0)	101	4513	(3685.1, 5528.1)	106	3636	(3046.5, 4340.0)
23F	112	13098	(10963.1, 15648.6)	108	11141	(8895.2, 13953.7)	103	9845	(7137.2, 13578.9)	104	6255	(4289.5, 9120.3)
Additional												
1	113	4	(3.9, 4.8)	108	372	(299.8, 460.7)	105	424	(349.0, 516.1)	117	391	(317.7, 480.4)
3	113	7	(5.8, 8.8)	110	289	(246.8, 338.5)	107	309	(269.0, 354.8)	118	351	(305.5, 402.9)
5	113	4	(3.9, 4.3)	111	656	(527.7, 816.5)	105	727	(592.6, 891.6)	118	661	(547.7, 797.8)
6A	111	2569	(1879.1, 3511.4)	108	10013	(7740.8, 12952.0)	105	11347	(9501.1, 13551.5)	108	7755	(6548.9, 9184.0)
7F	92	17	(10.5, 28.8)	108	5141	(4373.1, 6044.1)	104	7123	(6163.8, 8230.9)	115	5700	(4741.5, 6853.3)
19A	106	48	(32.4, 70.4)	106	1713	(1382.2, 2124.0)	105	2041	(1753.6, 2376.4)	113	1503	(1209.3, 1868.5)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
Source: Program ID: Study B1851015/t_imm_gmt_desc_t.SAS. Runtime ID: 04NOV14 14:09

Table 9. Comparison of Pneumococcal OPA GMTs After the Toddler Dose, 13vPnC Group 2 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 2			7vPnC Group 1				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	109	6915	(5700.3, 8389.1)	113	7662	(6171.2, 9513.2)	0.9	(0.68, 1.21)
6B	109	4894	(3695.5, 6481.9)	111	4958	(3931.7, 6251.5)	1.0	(0.69, 1.42)
9V	109	7679	(6251.4, 9433.6)	113	7825	(6469.6, 9463.4)	1.0	(0.74, 1.30)
14	109	2694	(2248.9, 3226.7)	112	3269	(2773.0, 3854.4)	0.8	(0.65, 1.05)
18C	110	20661	(16762.4, 25467.0)	111	22011	(18687.5, 25925.5)	0.9	(0.72, 1.22)
19F	106	3860	(2897.1, 5144.0)	112	1410	(1066.7, 1864.3)	2.7	(1.84, 4.08)
23F	108	11141	(8895.2, 13953.7)	112	13098	(10963.1, 15648.6)	0.9	(0.64, 1.13)
Additional								
1	108	372	(299.8, 460.7)	113	4	(3.9, 4.8)	85.9	(68.25, 108.01)
3	110	289	(246.8, 338.5)	113	7	(5.8, 8.8)	40.6	(31.26, 52.74)
5	111	656	(527.7, 816.5)	113	4	(3.9, 4.3)	160.3	(128.62, 199.75)
6A	108	10013	(7740.8, 12952.0)	111	2569	(1879.1, 3511.4)	3.9	(2.60, 5.84)
7F	108	5141	(4373.1, 6044.1)	92	17	(10.5, 28.8)	296.1	(180.45, 485.91)
19A	106	1713	(1382.2, 2124.0)	106	48	(32.4, 70.4)	35.9	(23.09, 55.68)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs: 13vPnC to 7vPnC reference.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmt_inf_t.SAS. Runtime ID: 12NOV14 15:20

Table 10. Comparison of Pneumococcal OPA GMTs After the Toddler Dose, 13vPnC Group 3 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 3			7vPnC Group 1				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	105	7319	(5960.5, 8988.0)	113	7662	(6171.2, 9513.2)	1.0	(0.71, 1.29)
6B	103	5740	(4723.9, 6975.2)	111	4958	(3931.7, 6251.5)	1.2	(0.85, 1.57)
9V	105	8892	(7563.3, 10452.9)	113	7825	(6469.6, 9463.4)	1.1	(0.88, 1.46)
14	106	2776	(2268.6, 3396.8)	112	3269	(2773.0, 3854.4)	0.8	(0.66, 1.10)
18C	106	20098	(17265.9, 23393.5)	111	22011	(18687.5, 25925.5)	0.9	(0.73, 1.14)
19F	101	4513	(3685.1, 5528.1)	112	1410	(1066.7, 1864.3)	3.2	(2.26, 4.54)
23F	103	9845	(7137.2, 13578.9)	112	13098	(10963.1, 15648.6)	0.8	(0.53, 1.07)
Additional								
1	105	424	(349.0, 516.1)	113	4	(3.9, 4.8)	98.1	(79.41, 121.08)
3	107	309	(269.0, 354.8)	113	7	(5.8, 8.8)	43.4	(33.73, 55.85)
5	105	727	(592.6, 891.6)	113	4	(3.9, 4.3)	177.5	(145.12, 217.11)
6A	105	11347	(9501.1, 13551.5)	111	2569	(1879.1, 3511.4)	4.4	(3.07, 6.35)
7F	104	7123	(6163.8, 8230.9)	92	17	(10.5, 28.8)	410.2	(249.67, 674.10)
19A	105	2041	(1753.6, 2376.4)	106	48	(32.4, 70.4)	42.7	(28.22, 64.69)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs: 13vPnC to 7vPnC reference.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmt_inf_t.SAS. Runtime ID: 12NOV14 15:20

CHMP's comment: The OPA GMTs in the Prevenar 13 groups were differed more compared to the IgG results. However, the responses to the toddler dose were consistent, and in agreement with previously reported results. The data do not cause further concern.

IgG results for the toddler dose administered after a 2-dose infant series

Pre-toddler dose:

Common serotypes: Before the toddler dose, the proportion of subjects with IgG concentrations ≥0.35 µg/mL ranged from 72.6% to 99.6% in 13vPnC Group 4 for the common serotypes (for most serotypes somewhat lower than after the infant series, Table 1 Infant data not shown in this AR). IgG GMCs for the common serotypes were consistent with these results (Table 3, Infant data not shown in this AR).

Additional serotypes: Before the toddler dose, the proportion of responders in 13vPnC Group 4 (≥93.7% all additional serotypes, except serotype 3 [63.6%]) were somewhat lower than after the infant series, but remained higher than in 7vPnC Group 1 before the toddler dose (Table 1 Infant data not shown in this AR).

IgG GMCs before the toddler dose were lower than after the infant series in Group 4; however, GMCs at the pretoddler time point remained higher in 13vPnC Group 4 than in 7vPnC Group 1 (Table 3 Infant data not shown in this AR). As noted for the other 13vPnC groups, IgG GMCs for serotype 3 in Group 4 were lower than for other additional serotypes.

Post-toddler dose:

Common serotypes: The proportion of responders in Group 4 was higher (≥97.7%) 1 month after the toddler dose than after the infant series for each common serotype (Table 2 Infant data not shown in this AR). IgG GMCs were also higher after the toddler dose than after the infant series and were generally similar to GMCs for the other study groups (Table 4 Infant data not shown in this AR).

Based on statistical comparisons between the 13vPnC Group 4 and 7vPnC Group 1, IgG GMCs for all common serotypes in Group 4 were noninferior to those in Group 1 (ie, lower limit of the 95% CI for the ratio >0.5 [although noninferiority was not prespecified for this analysis]); for serotype 19F the GMC was statistically significantly greater in 13vPnC Group 4 (ie, lower bound of 95% CI for the ratio >1, Table 11).

Additional serotypes: The proportions of responders to the additional serotypes in Group 4 (≥98.6%) were similar or higher than observed after the infant series and were generally similar to those of 13vPnC Groups 2 and 3 (Table 2 Infant data not shown in this AR). IgG GMCs for each additional serotype in Groups 4 were numerically higher after the toddler dose than after the infant series, except for serotype 3 (Table 4 Infant data not shown in this AR).

When compared with GMCs in 7vPnC Group 1, the IgG GMCs for each additional serotype in 13vPnC Group 4 was statistically significantly higher (lower bound of the 95% CI for the GMC ratios was >1, Table 11).

Table 11. Comparison of Pneumococcal IgG GMCs After the Toddler Dose, 13vPnC Group 4 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 4			7vPnC Group 1				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	215	12.15	(10.80, 13.67)	399	14.88	(13.64, 16.25)	0.82	(0.70, 0.95)
6B	215	11.92	(10.28, 13.81)	399	11.94	(10.82, 13.18)	1.00	(0.84, 1.19)
9V	215	7.23	(6.49, 8.06)	399	8.36	(7.70, 9.08)	0.86	(0.75, 0.99)
14	215	23.45	(21.08, 26.09)	399	24.55	(22.71, 26.55)	0.96	(0.84, 1.09)
18C	215	8.79	(7.73, 9.99)	399	9.02	(8.29, 9.82)	0.97	(0.84, 1.13)
19F	215	22.13	(19.63, 24.95)	399	11.36	(10.36, 12.46)	1.95	(1.67, 2.27)
23F	215	9.81	(8.40, 11.45)	399	12.61	(11.34, 14.03)	0.78	(0.65, 0.93)
Additional								
1	215	12.55	(11.15, 14.12)	347	0.06	(0.05, 0.07)	214.29	(161.43, 284.47)
3	213	1.63	(1.49, 1.79)	370	0.14	(0.12, 0.16)	11.53	(9.55, 13.93)
5	215	7.90	(7.15, 8.72)	398	0.67	(0.61, 0.74)	11.76	(10.11, 13.68)
6A	215	14.18	(12.57, 16.01)	399	3.02	(2.68, 3.40)	4.69	(3.90, 5.64)
7F	215	10.11	(9.06, 11.28)	394	0.10	(0.08, 0.12)	100.66	(78.88, 128.45)
19A	215	16.71	(14.86, 18.78)	399	2.48	(2.27, 2.70)	6.75	(5.84, 7.80)

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 13vPnC to 7vPnC reference value.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmc_inf_t.SAS. Runtime ID: 25NOV14 11:50

OPA GMTs for the toddler dose administered after a 2-dose infant series

Pre-toddler:

Before the toddler dose, OPA GMTs for the common serotypes were lower in 13vPnC Group 4 than in 7vPnC Group 1, except for serotype 19F. For the additional serotypes, GMTs in 13vPnC Group 4 were higher than in 7vPnC Group 1 (Table 7). OPA GMTs in Group 4 were generally similar or lower than titers in the other 13vPnC groups. OPA GMTs for all serotypes were lower before the toddler dose than after the infant series (Table 7, Infant data not shown in this AR).

Post-toddler dose:

Common serotypes: One month after the toddler dose, OPA GMTs were numerically higher than after the infant series for each common serotype in Group 4, with the exception of serotype 14 (Table 8,

Infant data not shown in this AR). OPA GMTs in Group 4 were generally similar to those in the other groups for most common serotypes.

Although noninferiority was not predefined for the toddler dose, OPA GMTs in Group 4 met the noninferiority criterion when compared to those in Group 1 (ie, lower limit of the 95% CI for the ratio >0.5) for all common serotypes, except serotypes 6B and 23F; the GMT for serotype 19F was statistically significantly greater in 13vPnC Group 4 relative to 7vPnC Group 1 (ie, lower bound of 95% CI for the ratio >1, Table 12).

Additional serotypes: OPA GMTs for each additional serotype in Group 4, including serotype 3, were numerically higher after the toddler dose than after the infant series (Table 8 Infant data not shown in this AR).

The OPA GMTs for the additional serotypes in 13vPnC Group 4 were statistically significantly higher (lower bound of the 95% CI for the GMC ratios was >1, Table 12) than those in 7vPnC Group 1.

Table 12. Comparison of Pneumococcal OPA GMTs After the Toddler Dose, 13vPnC Group 4 vs 7vPnC Group 1 - Evaluable Toddler Dose Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC Group 4			7vPnC Group 1				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	108	7193	(5716.6, 9049.6)	113	7662	(6171.2, 9513.2)	0.9	(0.69, 1.28)
6B	103	2713	(1973.3, 3729.5)	111	4958	(3931.7, 6251.5)	0.5	(0.37, 0.81)
9V	107	7861	(6237.6, 9907.1)	113	7825	(6469.6, 9463.4)	1.0	(0.75, 1.35)
14	107	2928	(2481.8, 3453.7)	112	3269	(2773.0, 3854.4)	0.9	(0.71, 1.13)
18C	113	18425	(15495.1, 21909.0)	111	22011	(18687.5, 25925.5)	0.8	(0.66, 1.06)
19F	106	3636	(3046.5, 4340.0)	112	1410	(1066.7, 1864.3)	2.6	(1.85, 3.60)
23F	104	6255	(4289.5, 9120.3)	112	13098	(10963.1, 15648.6)	0.5	(0.32, 0.72)
Additional								
1	117	391	(317.7, 480.4)	113	4	(3.9, 4.8)	90.3	(71.82, 113.42)
3	118	351	(305.5, 402.9)	113	7	(5.8, 8.8)	49.3	(38.49, 63.12)
5	118	661	(547.7, 797.8)	113	4	(3.9, 4.3)	161.4	(132.63, 196.46)
6A	108	7755	(6548.9, 9184.0)	111	2569	(1879.1, 3511.4)	3.0	(2.11, 4.31)
7F	115	5700	(4741.5, 6853.3)	92	17	(10.5, 28.8)	328.3	(200.40, 537.89)
19A	113	1503	(1209.3, 1868.5)	106	48	(32.4, 70.4)	31.5	(20.37, 48.58)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs: 13vPnC to 7vPnC reference.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC -7vPnC reference).
Source: Program ID: Study B1851015/t_imm_gmt_inf_t.SAS. Runtime ID: 12NOV14 15:20

CHMP's comment: The results for the toddler dose given after 2-dose primary schedule (group 4) were in agreement with the other results (tables 2-5), and do not raise further concern.

Safety results

Local Reactions:

Toddler dose:

Local reactions were reported infrequently within 7 days after the toddler dose, and the percentages of subjects with local reactions were generally similar across the 4 groups (5.8% to 7.9%, Table 33).

Redness and swelling were mostly mild or moderate in severity in all vaccine groups; the only severe cases were reported in Group 4 (1 event of severe redness [0.4%] and 1 event of severe swelling [0.4%]). Significant local tenderness, defined as interfering with limb movement, was reported in 2 subjects (0.4%) in Group 2 and in 3 subjects (0.7%) in Group 3; no significant tenderness was reported in Group 1 or Group 4.

Differences between groups in percentage of subjects with local reactions were small and not statistically significant for any comparison (Group 2 versus Group 1; Group 3 versus Group 1; Group 2 versus Group 3; and Group 4 versus Group 1.

Table 33 Subjects Reporting Local Reactions Within 7 Days After Toddler Dose - Safety Population

	Vaccine Group (as Administered)															
	7vPnC Group 1				13vPnC Group 2				13vPnC Group 3				13vPnC Group 4			
Local Reaction	N[a]	n[b]	%	(95% CI[e])	N[a]	n[b]	%	(95% CI[e])	N[a]	n[b]	%	(95% CI[e])	N[a]	n[b]	%	(95% CI[e])
Redness																
Any	432	9	2.1	(1.0, 3.9)	447	15	3.4	(1.9, 5.5)	446	16	3.6	(2.1, 5.8)	225	4	1.8	(0.5, 4.5)
Mild[d]	432	6	1.4	(0.5, 3.0)	447	11	2.5	(1.2, 4.4)	446	11	2.5	(1.2, 4.4)	225	1	0.4	(0.0, 2.5)
Moderate[d]	432	6	1.4	(0.5, 3.0)	447	7	1.6	(0.6, 3.2)	446	6	1.3	(0.5, 2.9)	225	3	1.3	(0.3, 3.8)
Severe[d]	432	0	0.0	(0.0, 0.9)	447	0	0.0	(0.0, 0.8)	446	0	0.0	(0.0, 0.8)	225	1	0.4	(0.0, 2.5)
Swelling																
Any	432	15	3.5	(2.0, 5.7)	447	16	3.6	(2.1, 5.7)	446	16	3.6	(2.1, 5.8)	225	7	3.1	(1.3, 6.3)
Mild[d]	432	10	2.3	(1.1, 4.2)	447	12	2.7	(1.4, 4.6)	446	12	2.7	(1.4, 4.7)	225	4	1.8	(0.5, 4.5)
Moderate[d]	432	7	1.6	(0.7, 3.3)	447	6	1.3	(0.5, 2.9)	446	6	1.3	(0.5, 2.9)	225	4	1.8	(0.5, 4.5)
Severe[d]	432	0	0.0	(0.0, 0.9)	447	0	0.0	(0.0, 0.8)	446	0	0.0	(0.0, 0.8)	225	1	0.4	(0.0, 2.5)
Tenderness																
Any	432	28	6.5	(4.3, 9.2)	447	22	4.9	(3.1, 7.4)	446	24	5.4	(3.5, 7.9)	225	12	5.3	(2.8, 9.1)
Present	432	28	6.5	(4.3, 9.2)	447	20	4.5	(2.8, 6.8)	446	21	4.7	(2.9, 7.1)	225	12	5.3	(2.8, 9.1)
Significant[c]	432	0	0.0	(0.0, 0.9)	447	2	0.4	(0.1, 1.6)	446	3	0.7	(0.1, 2.0)	225	0	0.0	(0.0, 1.6)
Any of the above	432	34	7.9	(5.5, 10.8)	447	29	6.5	(4.4, 9.2)	446	32	7.2	(5.0, 10.0)	225	13	5.8	(3.1, 9.7)

a. N = number of subjects reporting yes for at least 1 day or no for all 7 days.
b. n = Number of subjects reporting the specific characteristic.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5-2.0 cm; moderate, >2.0-7.0 cm; and severe, >7.0 cm.
e. Exact 2-sided confidence interval to a Single Population Proportion expressed as a percentage.

Systemic Events:

Toddler dose:

Systemic events were reported in <10% of subjects in any group within 7 days following the toddler dose, with comparable percentages across the 4 groups (Table 35). Fewer than 7.0% of subjects in each of the 4 groups experienced any fever after the toddler dose. Moderate fever (temperature >39ºC but ≤40ºC) was reported in <1.0% of subjects in any group. Severe fever (temperature >40ºC) was reported in only 1 subject (13vPnC Group 2) after the toddler dose. Within 7 days after the toddler dose ≤5.4% of subjects in any group used medication to prevent or treat fever. The statistically significant higher percentages of subjects with any fever or moderate fever observed in Group 2, Group 3, and Group 4 each relative to Group 1 were not likely to be clinically significant. No statistically significant difference was noted for fever of any severity for Group 2 relative to Group 3.

Among the other systemic events (decreased appetite, irritability, increased sleep, and decreased sleep) irritability was reported most frequently in each of the 4 groups (3.1% to 4.4%) within 7 days after the toddler dose (Table 35). No statistically significant differences between groups were observed for systemic events other than fever.

Table 35 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days After Toddler Dose - Safety Population

	Vaccine Group (as Administered)															
	7vPnC Group 1				13vPnC Group 2				13vPnC Group 3				13vPnC Group 4			
Systemic Event	N[a]	n[b]	%	(95% CI[d])	N[a]	n[b]	%	(95% CI[d])	N[a]	n[b]	%	(95% CI[d])	N[a]	n[b]	%	(95% CI[d])
Temperature ≥38ºC	432	14	3.2	(1.8, 5.4)	447	30	6.7	(4.6, 9.4)	446	30	6.7	(4.6, 9.5)	225	14	6.2	(3.4, 10.2)
Temperature ≥38ºC but ≤39ºC	432	14	3.2	(1.8, 5.4)	447	29	6.5	(4.4, 9.2)	446	28	6.3	(4.2, 8.9)	225	14	6.2	(3.4, 10.2)
Temperature >39ºC but ≤40ºC	432	1	0.2	(0.0, 1.3)	447	4	0.9	(0.2, 2.3)	446	2	0.4	(0.1, 1.6)	225	0	0.0	(0.0, 1.6)
Temperature >40ºC	432	0	0.0	(0.0, 0.9)	447	1	0.2	(0.0, 1.2)	446	0	0.0	(0.0, 0.8)	225	0	0.0	(0.0, 1.6)
Decreased appetite	433	15	3.5	(2.0, 5.6)	447	11	2.5	(1.2, 4.4)	446	11	2.5	(1.2, 4.4)	225	5	2.2	(0.7, 5.1)
Irritability	432	19	4.4	(2.7, 6.8)	447	15	3.4	(1.9, 5.5)	446	16	3.6	(2.1, 5.8)	225	7	3.1	(1.3, 6.3)
Increased sleep	432	3	0.7	(0.1, 2.0)	447	0	0.0	(0.0, 0.8)	446	0	0.0	(0.0, 0.8)	225	1	0.4	(0.0, 2.5)
Decreased sleep	432	7	1.6	(0.7, 3.3)	447	10	2.2	(1.1, 4.1)	446	7	1.6	(0.6, 3.2)	225	2	0.9	(0.1, 3.2)
Use of medication to prevent or treat symptoms	432	23	5.3	(3.4, 7.9)	447	24	5.4	(3.5, 7.9)	446	24	5.4	(3.5, 7.9)	225	10	4.4	(2.2, 8.0)
Any systemic event[c]	433	32	7.4	(5.1, 10.3)	447	41	9.2	(6.7, 12.2)	446	37	8.3	(5.9, 11.3)	225	20	8.9	(5.5, 13.4)

a. N = Number of subjects reporting yes for at least 1 day or no for all 7 days.
b. n = Number of subjects reporting the event.
c. Any systemic event includes temperature ≥38ºC, decreased appetite, irritability, increased sleep and decreased sleep.
d. Exact 2-sided confidence interval to a Single Popular Proportion expressed as a percentage.

Adverse Events:

Toddler dose: The percentages of subjects with AEs reported during the toddler dose (from day of toddler dose until the 1-month post-toddler blood draw) across the 4 groups ranged from 4.9% to 7.8%. The most frequently reported AEs were categorized (system organ class [SOC]) as Infections and infestations (≤6.3% across groups). The most frequently reported individual AE was nasopharyngitis, which was reported in 2.7 to 5.6% across all groups (Table 41). A total of 7 related AEs were reported in 7 subjects (<1% of subjects in any group).These included: injection site erythema in 1 subject in 7vPnC Group 1; vomiting in 1 subject in 13vPnC Group 2; and pyrexia in 2 subjects each in 13vPnC Groups 2 and 3 and in 1 subject in Group 4.

Most AEs were mild in severity. No severe or life-threatening AEs occurred in any vaccine group after the toddler dose (Table 44). One event of bronchitis was assessed by the investigator as moderate in severity and was judged to be an SAE that was not related to a study vaccine; no other SAEs were reported after the toddler dose. No deaths and no withdrawal from the study due to an AE were reported after the toddler dose.

6-month follow up: Only SAEs or newly diagnosed chronic medical conditions were collected during the 6-month follow up period after the toddler dose. Only 2 SAEs (0.2% each) were reported (enteritis and bronchopneumonia) and each occurred in the 7vPnC group. These events were considered by the investigator to be mild in severity and were assessed as not related to the study vaccine. No non-serious AEs (newly diagnosed chronic medical conditions) were reported during the 6-month follow-up period in 13vPnC recipients. No deaths or AE withdrawals from the study were reported during the 6-month follow-up.

The safety data provided in Study B1851015 for the infant series, after the infant series, after the toddler dose, and during the 6-month follow-up period presented no notable safety concerns, and were consistent with safety results in other infant studies of 13vPnC.

Table 41 All Adverse Events by System Organ Class and Preferred Term (All Causalities) , Toddler Dose - Safety Population

	Vaccine Group (as Administered)											
	7vPnC Group 1 (N[a]=436)			13vPnC Group 2 (N[a]=447)			13vPnC Group 3 (N[a]=448)			13vPnC Group 4 (N[a]=225)		
System Organ Class\ Preferred Term[b]	No. of Subjects[c]	(%)	No. of Events[d]	No. of Subjects[c]	(%)	No. of Events[d]	No. of Subjects[c]	(%)	No. of Events[d]	No. of Subjects[c]	(%)	No. of Events[d]
Any event	28	6.4	29	31	6.9	31	35	7.8	35	11	4.9	11
Gastrointestinal disorders	1	0.2	1	3	0.7	3	4	0.9	4	3	1.3	3
Diarrhoea	1	0.2	1	2	0.4	2	1	0.2	1	3	1.3	3
Enteritis	0	0.0	0	0	0.0	0	2	0.4	2	0	0.0	0
Mouth ulceration	0	0.0	0	0	0.0	0	1	0.2	1	0	0.0	0
Vomiting	0	0.0	0	1	0.2	1	0	0.0	0	0	0.0	0
General disorders and administration site conditions	3	0.7	4	2	0.4	2	3	0.7	3	2	0.9	2
Injection site erythema	1	0.2	1	0	0.0	0	0	0.0	0	0	0.0	0
Pyrexia	2	0.5	3	2	0.4	2	3	0.7	3	2	0.9	2
Infections and infestations	23	5.3	23	26	5.8	26	28	6.3	28	6	2.7	6
Bronchitis	0	0.0	0	1	0.2	1	1	0.2	1	0	0.0	0
Bronchopneumonia++	0	0.0	0	0	0.0	0	1	0.2	1	0	0.0	0
Gingivitis	0	0.0	0	0	0.0	0	1	0.2	1	0	0.0	0
Nasopharyngitis	23	5.3	23	23	5.1	23	25	5.6	25	6	2.7	6
Upper respiratory tract infection	0	0.0	0	2	0.4	2	0	0.0	0	0	0.0	0
Respiratory, thoracic and mediastinal disorders	1	0.2	1	0	0.0	0	0	0.0	0	0	0.0	0
Cough	1	0.2	1	0	0.0	0	0	0.0	0	0	0.0	0

a. The values in this row are used as the denominators for percentages.
b. MedDRA Version 17.0
c. Number of subjects reporting at least 1 event.
d. The total number of events. Multiple events may be reported by 1 subject.
++ Pathogen for these cases is unknown.

Table 44 Incidence and Severity (Grade) of All Adverse Events by System Organ Class and Preferred Term, Toddler Dose - Safety Population

	Vaccine Group (as Administered)																					
	7vPnC Group 1 (N[a]=436)						13vPnC Group 2 (N[a]=447)						13vPnC Group 3 (N[a]=448)						13vPnC Group 4 (N[a]=225)					
			Severity[d]						Severity[d]						Severity[d]						Severity[d]			
System Organ Class\ Preferred Term[b]	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT
Any event	28	6.4	25	3	0	0	31	6.9	28	3	0	0	35	7.8	32	3	0	0	11	4.9	10	1	0	0
Gastrointestinal disorders	1	0.2	1	0	0	0	3	0.7	2	1	0	0	4	0.9	4	0	0	0	3	1.3	3	0	0	0
Diarrhoea	1	0.2	1	0	0	0	2	0.4	1	1	0	0	1	0.2	1	0	0	0	3	1.3	3	0	0	0
Enteritis	0	0	0	0	0	0	0	0	0	0	0	0	2	0.4	2	0	0	0	0	0	0	0	0	0
Mouth ulceration	0	0	0	0	0	0	0	0	0	0	0	0	1	0.2	1	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	3	0.7	3	0	0	0	2	0.4	2	0	0	0	3	0.7	3	0	0	0	2	0.9	2	0	0	0
Injection site erythema	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pyrexia	2	0.5	2	0	0	0	2	0.4	2	0	0	0	3	0.7	3	0	0	0	2	0.9	2	0	0	0
Infections and infestations	23	5.3	20	3	0	0	26	5.8	24	2	0	0	28	6.3	25	3	0	0	6	2.7	5	1	0	0
Bronchitis	0	0	0	0	0	0	1	0.2	0	1	0	0	1	0.2	1	0	0	0	0	0	0	0	0	0
Bronchopneumonia[++]	0	0	0	0	0	0	0	0	0	0	0	0	1	0.2	0	1	0	0	0	0	0	0	0	0
Gingivitis	0	0	0	0	0	0	0	0	0	0	0	0	1	0.2	1	0	0	0	0	0	0	0	0	0
Nasopharyngitis	23	5.3	20	3	0	0	23	5.1	22	1	0	0	25	5.6	23	2	0	0	6	2.7	5	1	0	0
Upper respiratory tract infection	0	0	0	0	0	0	2	0.4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cough	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
Abbreviations: Mod = Moderate; Sev = Severe LT = Life Threatening.
a. The values in this row are used as the denominators for percentages.
b. MedDRA Version 17.0
c. Number of subjects reporting at least 1 event.
d. If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken.
++ Pathogen for these cases is unknown.

Table 45 Incidence and Severity (Grade) of All Adverse Events by System Organ Class and Preferred Term During the 6-Month Follow-up Period - Safety Population

	Vaccine Group (as Administered)																					
	7vPnC Group 1 (N[a]=462)						13vPnC Group 2 (N[a]=466)						13vPnC Group 3 (N[a]=462)						13vPnC Group 4 (N[a]=232)					
			Severity[d]						Severity[d]						Severity[d]						Severity[d]			
System Organ Class\ Preferred Term[b]	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT	No. of Subjects[c]	%	Mild	Mod	Sev	LT
Any event	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Enteritis	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infections and infestations	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bronchopneumonia[++]	1	0.2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only SAEs and newly diagnosed chronic medical conditions are collected between the blood draw after the toddler dose and the 6-month follow-up after the last dose of study vaccination.
Subjects are counted only once per treatment in each row.
Abbreviations: Mod = Moderate; Sev = Severe LT = Life Threatening.
a. The values in this row are used as the denominators for percentages.
b. MedDRA Version 17.0
c. Number of subjects reporting at least 1 event.
d. If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken.
++ Pathogen for these cases is unknown.

CHMP's comment: The safety results are in agreement with previously reported studies, if anything, lower frequencies of reactions. No new safety signal was detected in this study.

2.3.3. Discussion on clinical aspects

The current study was performed as a regulatory requirement in China. The infant part of the study has been submitted and assessed previously, in procedure P046 057. The results of the toddler dose do not cause any new concerns regarding efficacy or safety.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The procedure is considered fulfilled, as the study confirm previously assessed data.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.