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

Hexacima Hexaxim Hexyon

diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inact.) and Haemophilus type b conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/002702/P46/006

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Note

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



Table of contents

| | |
|---|-----------|
| 1. Introduction | 3 |
| 2. Scientific discussion | 3 |
| 2.1. Information on the development program | 3 |
| 2.2. Information on the pharmaceutical formulation used in the study..... | 3 |
| 2.3. Clinical aspects | 3 |
| 2.3.1. Introduction..... | 3 |
| 2.3.2. Clinical study | 3 |
| 2.3.3. Discussion on clinical aspects | 30 |
| 3. CHMP overall conclusion and recommendation..... | 31 |
| Fulfilled: | 31 |
| Not fulfilled: | 31 |
| 4. Additional clarification requested..... | 32 |

1. Introduction

On 16 November 2015, the MAH submitted the completed paediatric study **A3L39** for Hexaxim/Hexacima/Hexyon, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk balance for Hexaxim™/Hexacima™/Hexyon™ and that no consequential regulatory action is required.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A3L39 '*Immunogenicity and Safety Study of a Hexavalent DTaP-IPV-HB-Hib Combined Vaccine in a 3-dose Primary Series in Healthy Infants in Europe*' is a stand-alone study.

The MAH stated that the booster part of A3L39 (=A3L40) will end November 2015. A3L40 final clinical study report will be submitted in Q2 2016 (=MEA 006).

2.2. Information on the pharmaceutical formulation used in the study

Commercially available lots of Hexyon, Pentavac and Infanrix hexa as well as concomitant vaccines (Prevenar 13, RotaTeq, NeisVac-C) were used.

2.3. Clinical aspects

2.3.1. Introduction

Hexaxim™/Hexacima™/Hexyon™ is indicated for active immunisation (primary and booster vaccination) of infants and toddlers from six weeks to 24 months of age against diphtheria (D), tetanus (T), pertussis, Hepatitis B (Hep B), poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

The MAH submitted the final report for:

A3L39: Immunogenicity and Safety Study of a Hexavalent DTaP-IPV-HB-Hib Combined Vaccine in a 3-dose Primary Series in Healthy Infants in Europe.

To simplify matters, this report mentions only Hexyon as study vaccine. However, the information equally applies to Hexacima and Hexaxim.

2.3.2. Clinical study

Description

The purpose of the Phase III study A3L39 is to assess the immunogenicity and safety of Hexyon and compare it to the control Infanrix hexa in infants in a 3-dose regimen for primary immunization at 2, 3, and 4 months of age (MoA) in the Czech Republic and Germany. However, another immunization schedule in use in Europe, the mixed, so-called 'Hexa/Penta/Hexa' schedule, has still not been addressed in a clinical study; this schedule consists of the investigational hexavalent vaccine (containing Hep B) to be administered at 2 and 6 MoA and a pediatric combination pentavalent vaccine

(Pentavac®) containing all the antigens of the hexavalent vaccine except Hep B, at 4 MoA. For this purpose, the Phase III study A3L39 is also designed to assess, in an open-label manner, the immunogenicity and safety of the mixed schedule in Spain, in infants who had received a first dose of Hep B vaccine prior to the study.

The study is designed i) to test the non-inferiority against Hep B, Hib and pertussis toxoid (PT), filamentous hemagglutinin (FHA) of Hexyon compared to Infanrix hexa; ii) to descriptively evaluate the immunogenicity of Hexyon compared to Infanrix hexa; iii) to descriptively evaluate the immunogenicity of the mixed Hexa/Penta/Hexa schedule; iv) to descriptively evaluate the immunogenicity of concomitantly administered routine vaccines (Prevenar™ 13 [PCV13] in Czech Republic and Germany; and RotaTeq® in Czech Republic, Germany, and Spain); and v) to describe the safety profile of Hexyon when given in a 3-dose regimen or a mixed schedule and when administered with commonly licensed pediatric vaccines.

Methods

Objective(s)

a) Immunogenicity:

- **Primary – Groups 1 and 2 only:** To demonstrate the non-inferiority of Hexyon to Infanrix hexa, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates to PT, FHA, Hep B, and Hib polysaccharide (PRP) antigens, 1 month after a 3-dose primary series.

- **Secondary – Groups 1 and 2:**

To describe the immunogenicity parameters before the 1st dose for PT and FHA and 1 month after the 3rd dose for all antigens.

To describe the immune response to Prevenar 13 pneumococcal serotypes 1 month after the 3rd dose.

To describe the immune responses to RotaTeq before the 1st dose and 1 month after the 3rd dose.

- **Secondary – Group 3:**

To describe the immunogenicity parameters before the 1st dose and 1 month after the 3rd dose for all antigens contained in Hexyon and Pentavac.

To describe the immune responses to RotaTeq before the 1st dose and 1 month after the 3rd dose.

- **Observational :**

To describe the Hep B immune response after 3 doses of Hep B in the first year of life, given either at 2, 3, and 4 MoA (Group 1) or prior to the study, then at 2 and 6 MoA (Group 3).

b) Safety:

- **Secondary only** - To describe the safety profile after each and any injection for each study group.

Study design

This was a Phase III multi-centre study in the Czech Republic, Germany, and Spain in 795 infants of 2 months of age (MoA).

The subjects from the Czech Republic and Germany (total 530) were 1:1 randomized to receive in an observer-blinded manner at 2, 3, and 4 MoA

Group 1 - Hexyon, concomitantly with Prevenar 13 and RotaTeq

Group 2 - Infanrix hexa, concomitantly with Prevenar 13 and RotaTeq

The subjects were to be followed up for a total of 3 months.

Subjects from Spain (total 265) who had been administered a first dose of hepatitis B vaccine prior to study start were automatically assigned to **Group 3** (open-label). They received

- Hexyon at 2 and 6 MoA, and Pentavac at 4 MoA, concomitantly with
- Prevenar 13 at 2 and 4 MoA **or** at 2, 4 and 6 MoA, depending upon local use and the Investigator's judgment
- and NeisVac-C at 2 MoA,
- and RotaTeq at 2, 4 and 6 MoA.

The subjects were to be followed up for a total of 5 months.

There were 4 visits (V) scheduled with vaccinations at V01, V02, and V03 and blood samplings (5 mL each) at V01 and V04 (30 days after the 3rd vaccination).

Diary Cards (DCs) were provided at V01, V02, and V03. At 2 to 3 days, then 8 to 10 days following each vaccination, the subjects' parents/legally acceptable representatives were contacted by phone to ensure that the DCs were completed.

Solicited reactions were to be collected for Hexyon, Infanrix hexa, Pentavac and Prevenar 13.

Trial period: 21 Jan 2014 (FVFS) to 27 Nov 2014 (LVLS).

Table 1: Overview of study groups

| Visit | Visit 1 (V01) | Visit 2 (V02) | Visit 3 (V03) | Visit 4 |
|---|---|--------------------------------------|---|--------------------------------------|
| Groups 1 and 2 | | | | |
| Approximate age of subjects | 2 months | 3 months | 4 months | 5 months |
| Trial timelines (days) | D0 | D30 | D60 | D90 |
| Time windows/age interval (days) | 55 to 75 days of age | V01 + 30 days [-2 days; + 7 days] | V02 + 30 days [-2 days; + 7 days] | V03 + 30 days [-7 days; + 7 days] |
| Blood sampling (BL) | BL1 (5 mL) | | | BL2 (5 mL) |
| Vaccination | | | | |
| Group 1 | Hexyon + PCV13 +RotaTeq | Hexyon + PCV13 +RotaTeq | Hexyon + PCV13 +RotaTeq | |
| Group 2 | Infanrix hexa + PCV13 + RotaTeq | Infanrix hexa + PCV13 + RotaTeq | Infanrix hexa + PCV13 + RotaTeq | |
| Group 3 | | | | |
| Approximate age of subjects | 2 months | 4 months | 6 months | 7 months |
| Trial timelines (days) | D0 | D60 | D120 | D150 |
| Time windows/age interval (days) | 55 to 75 days of age | V01 + 60 days [-2 days; + 7 days] | V02 + 60 days [-2 days; + 7 days] | V03 + 30 days [-7 days; + 7 days] |
| Blood sampling (BL) | BL1 (5 mL) | | | BL2 (5 mL) |
| Vaccination, Group 3 | Hexyon + PCV13 + RotaTeq + NeisVac-C | Pentavac + PCV13 + RotaTeq | Hexyon + RotaTeq + PCV13 [†] | |

† According to local use and upon Investigator's judgment

Source: Extract from Tables 3.1 and 3.2 A3L39 CSR

Administration of vaccines:

Hexyon and Pentavac or Infanrix hexa - anterolateral area of the right thigh; IM

PCV 13 and NeisVac-C - anterolateral area of the left thigh; IM

Rotateq – oral application

CHMP comment:

Since Group 3 subjects were administered PCV-13 and NeisVac-C at 2 MoA at the same location, injection site reactions at this time point cannot be differentiated for these 2 vaccines.

Study population /Sample size

Inclusion criteria:

- Infants, aged between 55-75 days, born at full term (≥ 37 gestational weeks) and/or with a birth weight ≥ 2.5 kg
- Signed ICF and presence by health insurance, if applicable

- Group 3 only: previous dose of Hep B vaccine

Exclusion criteria

- receipt of any vaccine in the 4 weeks before first study dose or planned receipt of any vaccine in the 4 weeks following any study dose, except routine vaccines according to National Immunisation schedule or influenza vaccines
- Groups 1, 2, and 3: Previous vaccination against D, T, pertussis, poliomyelitis, Hib, pneumococcal infections, or rotavirus
- Group 1 and 2 only: Previous vaccination against Hep B

Other exclusion criteria were as usual, e.g., receipt of immunoglobulins or blood (products), congenital or acquired immunodeficiency, bleeding disorder, personal or maternal Hep B or Hep C seropositivity, known hypersensitivity against any vaccine or vaccine component, acute illness/ infection etc.

A total of 795 subjects were to be included (265 each in Groups 1, 2 and 3, respectively). Of the 795 subjects, 530 subjects (Groups 1 and 2) were to be included in the primary immunogenicity analysis in order to obtain 424 evaluable subjects (attrition rate of approximately 20%). The sample size for the primary analysis was calculated using Farrington and Manning formula and based on a type 1 error of 2.5% (one sided hypothesis) to obtain an overall power of 90%:

Table 2: Calculation of sample size and power calculation

| Endpoints | Expected reference seroprotection/ vaccine response | Clinically acceptable margin for non-inferiority | Power achieved with N=212 |
|---------------------------------|--|---|----------------------------------|
| Anti-Hep B \geq 10 mIU/mL | 95% | 10% | 99.0% |
| Anti-PRP \geq 0.15 μ g/mL | 90% | 10% | 91.1% |
| Anti-PT vaccine response | 98% | 10% | 99.9% |
| Anti-FHA vaccine response | 98% | 10% | 99.9% |
| Overall power | | | > 90% |

The sample size of Group 3 (265 subjects) was arbitrarily defined since the data for Group 3 were used for descriptive purposes only.

A sample size of 265 subjects allowed detecting with 0.95 probability, an AE occurring with a true frequency of at least 1.12%.

Treatments

Groups 1 and 2:

Subjects were to receive 3 doses of either Hexyon or Infanrix hexa, respectively, both co-administered with Prevenar 13 and RotaTeq at 2, 3, and 4 MoA.

Group 3:

Subjects were to receive 2 doses of Hexyon at 2 MoA and 6 MoA and 1 dose of Pentavac at 4 MoA. Prevenar 13 was co-administered at 2 and 4 MoA or at 2, 4, and 6 MoA depending upon local use and the Investigator's judgment, NeisVac-C was co-administered at 2 MoA, and RotaTeq at 2, 4, and 6 MoA.

Outcomes/endpoints

a) Primary endpoints (Groups 1 and 2) - immunogenicity:

Seroprotection for Hep B and PRP at 1 month-post 3rd dose:

- Anti-Hep B antibody (Ab) concentrations ≥ 10 mIU/mL
- Anti-PRP Ab concentrations ≥ 0.15 μ g/mL

Vaccine response for PT and FHA:

- Post-Dose 3 Ab concentrations ≥ 4 x lower level of quantification (LLOQ), if baseline (pre-Dose 1) Ab level < 4 x LLOQ or
- Post-Dose 3 Ab concentrations \geq baseline, if baseline ≥ 4 x LLOQ

b) Secondary and observational endpoints - immunogenicity (descriptive only):

Groups 1 and 2 at baseline (at 2 MoA)

- Ab concentrations for PT and FHA
- Ab concentrations above a cut-off:
 - Anti-PT and anti-FHA Ab concentrations \geq LLOQ (=2 EU/mL);
 - anti-rotavirus (RV) IgA ≥ 20 U/mL

Groups 1 and 2 at 1 m-post 3rd vaccination (at 5 MoA)

- Ab concentrations/ titers for each valence
- Ab concentrations/ titers above a cut-off:
 - Anti-D and anti-T Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
 - Anti-PT and anti-FHA Ab concentrations ≥ 4 EU/mL
 - Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
 - Anti-Hep B Ab concentrations ≥ 100 mIU/mL

- Anti-PRP Ab concentrations $\geq 1.0 \mu\text{g/mL}$
- Anti-RV IgA $\geq 20 \text{ U/mL}$
- Anti-pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F concentrations $\geq 0.35 \mu\text{g/mL}$
- Ab concentration ratios for anti-PT and FHA (1 m-post 3rd dose in relation to baseline)
- Seroconversion for anti-PT and anti-FHA, defined as anti-PT and anti-FHA ≥ 4 -fold Ab concentration increase from baseline to 1m-post 3rd dose
- Seroconversion for anti-RV IgA defined as anti-RV IgA $\geq 20 \text{ U/mL}$, in subjects seronegative at baseline

Group 3 at baseline (at 2 MoA)

- Ab concentrations/titers for each valence (except Prevenar 13)
- Ab concentrations/titers above a cut-off:
 - Anti-D and anti-T Ab concentrations $\geq 0.01 \text{ IU/mL}$ and $\geq 0.1 \text{ IU/mL}$
 - Anti-PT and anti-FHA Ab concentrations $\geq \text{LLOQ}$
 - Anti-poliovirus 1, 2, and 3 Ab titers $\geq 8 \text{ (1/dil)}$
 - Anti-Hep B Ab concentrations $\geq 10 \text{ mIU/mL}$
 - Anti-PRP Ab concentrations $\geq 0.15 \mu\text{g/mL}$
 - Anti-RV IgA $\geq 20 \text{ U/mL}$

Group 3 at 1 m-post 3rd vaccination (at 7 MoA):

- Ab concentrations/titers for each valence (except Prevenar 13)
- Ab concentrations/titers above a cut-off:
 - Anti-D and anti-T Ab concentrations $\geq 0.01 \text{ IU/mL}$, $\geq 0.1 \text{ IU/mL}$ and $\geq 1.0 \text{ IU/mL}$
 - Anti-PT and anti-FHA Ab concentrations $\geq 4 \text{ EU/mL}$
 - Anti-poliovirus 1, 2, and 3 Ab titers $\geq 8 \text{ (1/dil)}$
 - Anti-Hep B Ab concentrations $\geq 10 \text{ mIU/mL}$ and $\geq 100 \text{ mIU/mL}$
 - Anti-PRP Ab concentrations $\geq 0.15 \mu\text{g/mL}$ and $\geq 1.0 \mu\text{g/mL}$
 - Anti-RV IgA $\geq 20 \text{ U/mL}$
- Ab concentration/titer ratios for all antigens except Prevenar 13 (1 m-post 3rd dose in relation to baseline)
- Seroconversion for anti-PT and anti-FHA, defined as anti-PT and anti-FHA ≥ 4 -fold Ab concentration increase from baseline to 1m-post 3rd dose
- Seroconversion for anti-RV IgA defined as anti-RV IgA $\geq 20 \text{ U/mL}$, in subjects seronegative at baseline
- Vaccine response for PT and FHA:
 - Post-Dose 3 Ab concentrations $\geq 4 \times \text{LLOQ}$, if baseline $< 4 \times \text{LLOQ}$ or
 - Post-Dose 3 Ab concentrations at least baseline, if baseline $\geq 4 \times \text{LLOQ}$

c) Secondary endpoints - safety (descriptive only):

Occurrence of

- any immediate unsolicited systemic AEs reported in the 30 minutes after each and any dose
- solicited, i.e., prelisted in the subject's DC and CRF, injection site and systemic reactions occurring up to 7 days after each and any dose
- unsolicited (spontaneously reported) AEs up to 30 days after each and any dose
- SAEs, including AESIs (adverse events of special interest), throughout the trial period

Pre-defined AESIs:

Extensive limb swelling (ELS), hypotonic hyporesponsive episode (HHE) and convulsions (whether febrile or not), anaphylactic reactions, apnea, severe neurological conditions were considered important identified or potential risks. In addition, sudden infant death syndrome (SIDS) or sudden unexpected death (SUD) were closely monitored although not associated with multivalent pediatric vaccines.

Immunoassays applied:

All immunological assays were carried out at the Sponsor's laboratory in Swiftwater, Pennsylvania, USA, or at qualified contract laboratories. Results thus correlated to results obtained in previous studies with Hexyon /Hexacima /Hexaxim.

Priority of determinations was as follows: anti-Hep B, anti-PRP, anti-PT, and anti-FHA, anti-D, anti-T, anti-poliovirus type 1, 2, 3, pneumococcal serotypes 1, 3, 5, 6A, 7F, 19A, 4, 6B, 9V, 14, 18C, 19F and 23F and anti-RV IgA.

Table 3 Immunoassays Applied in the Study

| Endpoint | Assay | Reference serum |
|---|--|--|
| Anti-D | Micrometabolic inhibition test (MIT, using Vero cells) | WHO Int. Standard for D-antitoxin |
| Anti-T | ELISA | WHO human ref. standard lot TE3 |
| Anti-PT | ELISA | Reference standard serum |
| Anti-FHA | ELISA | Reference standard serum |
| Anti-Polio | Micrometabolic inhibition test (MIT, using Vero cells) | - |
| Anti-HepB | VITROS ECi/ECiQ enhanced chemiluminescence detection | Comparison to calibrator previously calibrated to the WHO 1 st Int. Reference Preparation for Antibody to HBsAg |
| Anti-PRP | Farr-type RIA | CBER reference standard Lot 1983 |
| Anti-pneumococcal polysaccharides (PS) | ELISA | Reference standard serum |
| Anti-RV (IgA) | ELISA | Reference standard serum |

Table 4 Correlates and Surrogates of Protection

| Antigen | Serum Antibody (Ab) Titer as Level of Protection | Assessment |
|----------------------------|--|-----------------------|
| Diphtheria | ≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term) | Established correlate |
| Tetanus | ≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term) | Established correlate |
| Polio 1, 2, 3 | ≥ 8 (1/dil) | Established correlate |
| PRP-T | ≥ 0.15 µg/mL (short-term) ≥ 1 µg/mL (long-term) | Established correlate |
| Hepatitis B | ≥ 10 mIU/mL (short-term) ≥ 100 mIU/mL (long-term) | Established correlate |
| PT, FHA (Pertussis) | <p>Vaccine Response:</p> <ul style="list-style-type: none"> - If pre-vaccination antibody concentration was <4xLLOQ, then the post-vaccination antibody concentration was to be ≥4xLLOQ; - If pre-vaccination antibody concentration was ≥4xLLOQ, then the post-vaccination antibody concentration was to be ≥pre-immunisation levels. <p>Remark: LLOQ = 2 EU/ml, i.e., 4 x LLOQ = 8 EU/mL for PT and FHA</p> | Accepted surrogate |
| Pneumococcal PS | ≥ 0.35 µg/mL | Established correlate |
| Rotavirus (RV) | ≥ 20 U/mL (serum IgA) | Accepted surrogate |

CHMP comment:

Established correlates and accepted surrogates of protection were applied to calculate seroprotection rates (D, T, IPV, HepB, PRP, pneumococcal PS, RV) and vaccine response rates (PT, FHA). The serological assays were in accordance to those used in previous studies with Hexyon and concomitant vaccines.

Furthermore, the safety observations were in accordance to those applied in previous vaccine studies conducted in the EU.

Statistical Methods

Hypotheses and Statistical Methods for Primary Objective

The objective was to demonstrate that the immune response to Hexyon was non-inferior to that to the Infanrix hexa, both co-administered with Prevenar 13, in terms of seroprotection/vaccine response rates for Hep B, PT, FHA and PRP antigens 1 month after a 3-dose schedule (2, 4, 6 MoA).

The individual tested hypotheses for the valence i were as follows:

$$H_0^i : P_{\text{Tested}}^i - P_{\text{Reference}}^i \leq -\delta^i$$
$$H_1^i : P_{\text{Tested}}^i - P_{\text{Reference}}^i > -\delta^i$$

With P = seroprotection or vaccine response rate
tested = tested study vaccine
reference = reference vaccine
 δ = clinically acceptable limit to conclude to non-inferiority (10%)

Non-inferiority was demonstrated if the hypothesis H_0 was rejected.

For each antigen, a non-inferiority test was performed using the 95% 2-sided CI of the difference $P_{\text{Tested}} - P_{\text{Reference}}$ between the seroprotection/vaccine response rates ($\alpha=2.5\%$). The 95% CI was calculated based on the Wilson score method without continuity correction as quoted by Newcombe.

For each antigen, non-inferiority was demonstrated if the lower bound of the 2-sided 95% CI of the difference of proportions was greater than $-\delta_i\%$. The primary objective was reached if the non-inferiority was proven for all the antigens. The hypothesis of non-inferiority was tested on the per-protocol (PP) analysis set and was to be confirmed using the full analysis set (FAS).

Statistical Methods for Secondary and Observational Objectives

Only descriptive statistics were provided.

The 95% CI was calculated:

- Using the exact binomial method (Clopper-Pearson method) for single proportions
- Using the normal approximation of the Log10 titers, followed by a back transformation for GMCs/GMTs

Reverse Cumulative Distribution Curves (RCDCs) of individual concentrations/titers were also presented.

Results

Recruitment/ Number analysed

A total of 794 subjects (266, 263 and 265 subjects in Groups 1, 2, and 3, respectively) were randomized, all but 1 (in Group 1) were vaccinated at V01.

Adherence to vaccination schedule was high; there were 4 subjects with early termination, none of which was due to an AE or SAE.

There were 791 subjects included in the FAS (264 in Group 1, 262 in Group 2 and 265 in Group 3). Besides the 1 subject not vaccinated at V01 two additional subjects with improper unblinding were excluded from the FAS.

None of the subjects discontinued the study due to an SAE. However, an SAE (convulsions) related to Hexyon observed for one subject in Group 1 led to the subject's discontinuation for the subsequent dose (see safety section).

A total of 712 subjects were included in the PP analysis set. The 82 subjects (10.3%) excluded from the PP analysis set had at least one protocol deviation. The most prevalent violation types were vaccination at an improper time window (51 subjects/ 6.4%) and either no provision of 2nd blood sample or 2nd blood drawn at an improper time window (24 subjects/ 3%; for details refer to Table 4.3, A3L39 CSR).

Overall, 791 subjects were included in the safety analysis set (SafAS): 265 (99.6%) in Group 1, 261 (99.6%) in Group 2 and 265 (100%) in Group 3.

The mean age of the subjects at baseline was between 62 days in Group 3 and 63 days in Groups 1 and 2, with an age range between 55 and 75 days. **For German subjects from Groups 1 and 2, the age was not calculated as the date of birth was not collected.**

Within the FAS of the various groups, between 48 and 52% of subjects were female; the mean weight at baseline was 5.2 kg (range 2.7 – 8.5 kg). Most of the subjects (96 to 98% in Groups 1, 2 and 3) were White (**Table 5**).

CHMP comment:

It is not clear why 2 subjects were excluded from the FAS due to improper unblinding. The MAH is asked to comment on this.

Table 5: Baseline demographics – Full analysis set

| Demographic Attribute | Group 1 (N=264) n (%) | Group 2 (N=262) n (%) | Group 1+2 (N=526) n (%) | Group 3 (N=265) n (%) | Group 1+3 (N=529) n (%) |
|---|-----------------------------|-----------------------------|-------------------------------|-----------------------------|-------------------------------|
| Sex n (%) | | | | | |
| Male | 138 (52.3) | 126 (48.1) | 264 (50.2) | 140 (52.8) | 278 (52.6) |
| Female | 126 (47.7) | 136 (51.9) | 262 (49.8) | 125 (47.2) | 251 (47.4) |
| Sex ratio: Male/Female | 1.10 | 0.93 | 1.01 | 1.12 | 1.11 |
| Age (Days) | | | | | |
| M | 140 | 136 | 276 | 265 | 405 |
| Mean (SD) | 63.0 (5.6) | 62.7 (5.4) | 62.8 (5.5) | 62.0 (4.7) | 62.4 (5.1) |
| Median | 62.0 | 62.0 | 62.0 | 61.0 | 62.0 |
| Min; Max | 55.0; 75.0 | 55.0; 74.0 | 55.0; 75.0 | 55.0; 75.0 | 55.0; 75.0 |
| Q1; Q3 | 58.0; 67.5 | 58.0; 66.5 | 58.0; 67.0 | 58.0; 65.0 | 58.0; 66.0 |
| Weight (Kg) | | | | | |
| M | 264 | 262 | 526 | 265 | 529 |
| Mean (SD) | 5.2 (0.7) | 5.3 (0.7) | 5.2 (0.7) | 5.2 (0.6) | 5.2 (0.6) |
| Median | 5.2 | 5.2 | 5.2 | 5.1 | 5.2 |
| Min; Max | 2.7; 7.2 | 3.4; 8.5 | 2.7; 8.5 | 3.8; 7.2 | 2.7; 7.2 |
| Q1; Q3 | 4.8; 5.6 | 4.8; 5.7 | 4.8; 5.6 | 4.8; 5.6 | 4.8; 5.6 |
| Racial origin: n (%) | | | | | |
| White | 259 (98.1) | 254 (96.9) | 513 (97.5) | 254 (95.8) | 513 (97.0) |
| Asian | 1 (0.4) | 3 (1.1) | 4 (0.8) | 1 (0.4) | 2 (0.4) |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (1.5) | 4 (0.8) |
| Black or African American | 1 (0.4) | 3 (1.1) | 4 (0.8) | 1 (0.4) | 2 (0.4) |
| Mixed Origin | 3 (1.1) | 2 (0.8) | 5 (1.0) | 5 (1.9) | 8 (1.5) |

N; M: number of subjects with available data for the relevant endpoint

n/%: number/percentage of subjects fulfilling the item listed

Q1; Q3: first and third quartile

Remark: for subjects from Germany, the birthdate was not collected

Group 3: Hep B at birth

Source: Table 4.5 A3L39 CSR

Immunogenicity results

Primary

The primary immunogenicity objective was to demonstrate the non-inferiority of Hexyon to the control, Infanrix hexa, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates to PT, FHA, Hep B and PRP antigens, 1 month after a 3-dose primary series (**Table 6**).

Table 6: Non-inferiority of seroprotection, vaccine response rates of Hexyon vs. Infanrix hexa at one month post-Dose 3 – PP analysis set

| Component | Criteria | Group 1 (N=237) | | | Group 2 (N=239) | | | Group 1 minus Group 2 (i.e. Test - Reference) | | | |
|---------------------|-------------------|--------------------|------|--------------|--------------------|------|--------------|--|--------------------|---------------------|--------------|
| | | n/M | % | (95% CI) | n/M | % | (95% CI) | % observed | 2-sided (95% CI) † | Clinical delta (δ%) | Conclusion ‡ |
| Anti-PT (EU/mL) | Vaccine response* | 225/229 | 98.3 | (95.6; 99.5) | 225/230 | 97.8 | (95.0; 99.3) | 0.4 | (-2.51; 3.44) | 10 | Reject H0 |
| Anti-FHA (EU/mL) | Vaccine response* | 229/231 | 99.1 | (96.9; 99.9) | 217/229 | 94.8 | (91.0; 97.3) | 4.4 | (1.23; 8.12) | 10 | Reject H0 |
| Anti-Hep B (mIU/mL) | ≥ 10 mIU/mL | 221/231 | 95.7 | (92.2; 97.9) | 228/231 | 98.7 | (96.3; 99.7) | -3.0 | (-6.59; 0.11) | 10 | Reject H0 |
| Anti-PRP (µg/mL) | ≥ 0.15 µg/mL | 204/224 | 91.1 | (86.5; 94.5) | 195/226 | 86.3 | (81.1; 90.5) | 4.8 | (-1.12; 10.74) | 10 | Reject H0 |

N: number of subjects in the PP analysis set

n: number of subjects

M: number of subjects available for the endpoint

*Vaccine response for PT and FHA defined as follows: Post-Dose 3 Ab concentrations ≥ 4 x LLOQ, if baseline < 4 x LLOQ ; Post-Dose 3 Ab concentrations ≥ baseline, if baseline ≥ 4 x LLOQ

† The 95% CI was calculated based on the Wilson score method without continuity correction as described by Newcombe R.G.

‡ If lower bound of 95% CI was greater than - δ then the null hypothesis H0 was rejected and we could conclude for the non-inferiority Group 1 vs. Group 2

Group 1: Hexyon + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Group 2: Infanrix hexa + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Source: Table 5.1 A3L39 CSR

Non-inferiority of Hexyon compared to Infanrix hexa in terms of seroprotection rates (for Hep B and PRP) and vaccine response rates (for PT and FHA) was demonstrated as the lower bound of the 2-sided 95% CI of the difference in response rates between groups was greater than -10% for each of the 4 vaccine components.

High proportions of subjects in each group showed immunoprotection against the 4 antigens following a 3-dose primary vaccination: 96% and 99% of vaccinees, respectively, in Groups 1 (Hexyon) and 2 (Infanrix hexa) were protected against Hep B at ≥ 10 mIU/mL and 91% and 86%, respectively, were protected against HiB PRP at ≥ 0.15 μ g/mL. In addition, for 98% of subjects in both groups vaccine response against PT was shown and for 99% and 95% of subjects in Groups 1 and 2, respectively, vaccine response against FHA was demonstrated.

Similar results were obtained for the FAS.

CHMP comment:

Non-inferiority of Hexyon compared to Infanrix hexa was demonstrated with regard to seroprotection against Hep B and PRP and vaccine response against the pertussis antigens PT and FHA at 1 month post-dose 3 following primary vaccination at 2, 3 and 4 MoA with hexavalent vaccine administered concomitantly with PCV13 and RotaTeq.

Regarding PRP, in the present study the seroprotection rate was somewhat lower than that observed in previous studies following a 3-dose primary vaccination, i.e., in the SmPC 96% seroprotection at ≥ 0.15 μ g/mL has been documented whereas in the present study 91% of subjects in the Hexyon group were protected at ≥ 0.15 μ g/mL.

Secondary Immunogenicity Objectives

Hexyon vs. Infanrix hexa (Groups 1 and 2); primary vaccination at 2, 3, 4 MoA:

Following the 3-dose primary vaccination at 2, 3 and 4 MoA all subjects in the Hexyon and Infanrix hexa groups reached the short-term protection levels of ≥ 0.01 IU/mL against diphtheria (**Table 7**). 62% and 58% of subjects, respectively, showed long-term protective Ab levels of ≥ 0.1 IU/mL.

Every subject in the Hexyon and Infanrix hexa groups reached the long-term protective Ab level of ≥ 0.1 IU/mL against tetanus at 1 month-post Dose 3. Furthermore, every subject showed anti-polio type 1, 2, and 3 titers ≥ 8 (1/dil).

90% of subjects in both groups showed an at least 4-fold increase in anti-PT antibody levels from baseline to 1-month post-Dose 3 (defined as 'seroconversion'). For 89% of subjects in the Hexyon group and 76% in the Infanrix hexa group, seroconversion for FHA following the 3-dose primary vaccination was shown.

Regarding Hep B, in the Hexyon group 72% of subjects reached long-term protective Ab levels of ≥ 100 mIU/mL. This proportion is lower than that for the Infanrix hexa group (87% of subjects, with non-overlapping 95% CI). This has already been observed in previous comparative studies with Hexyon and Infanrix hexa. Regarding PRP, 59% of subjects in the Hexyon group and 37% in the Infanrix hexa group reached long-term protective Ab levels at ≥ 1 μ g/mL. These effects are reflected by higher Ab concentrations against PRP but lower Ab levels against Hep B in the Hexyon group following the 3-dose primary vaccination at 2, 3 and 4 MoA compared to the Infanrix hexa group (**Table 8**).

Overall, immunogenicity data for each of the Hexyon antigens are in accordance to respective data in the SmPC except for PRP for which somewhat lower seroprotection rates were detected in the present study.

Immune response against concomitant vaccines:

At least 90% of subjects in both groups reached protective anti-rotavirus (RV) IgA levels of ≥ 20 U/mL at 1 month-post 3rd dose. At least 87% of subjects showed seroconversion defined as anti-RV IgA levels ≥ 20 U/mL in infants seronegative at baseline (< 20 U/mL) (**Table 9**).

At least 93% of subjects in both groups were protected at ≥ 0.35 $\mu\text{g/mL}$ against each of the PCV13 pneumococcal serotypes at 1 month-post-3rd vaccination. Exceptions were serotype 6B for which seroprotection rates of 77% and 86% in Group 1 and Group 2, respectively, were found and serotype 5 with a protection rate of 87% in Group 1 (**Table 9**). Overall, anti-pneumococcal GMCs tended to be lower in Group 1 compared to Group 2 (**Table 10**).

Hexyon (Group 3); primary vaccination at 2, 4, 6 MoA:

Following the 3 dose vaccination at 2, 4 and 6 MoA, all subjects were seroprotected against diphtheria at ≥ 0.01 IU/mL; and for even 98% of vaccinees long-term seroprotection at ≥ 0.1 IU/mL was shown 1 month after the 3rd Hexyon dose. In addition, all subjects had long-term protective anti-tetanus Ab levels of ≥ 0.1 IU/mL at this timepoint. All but one subjects showed vaccine response against PT and FHA (99.5% and 100%, respectively) and 90% and 96% of subjects had an at least 4-fold Ab increase ('seroconversion') against PT and FHA, respectively, from baseline to 1 month-post 3rd dose (**Table 11**).

All subjects in this group showed seroprotection against poliovirus types 1, 2, and 3 at ≥ 8 (1/dil.), except for one subject that missed this titre for type 2.

All but 2 subjects (99%) reached the short-term seroprotective anti-Hep B Ab level of ≥ 10 mIU/mL and even 97% showed seroprotection at the more conservative long-term level of ≥ 100 mIU/mL. Furthermore, all subjects were protected against HiB PRP at ≥ 0.15 $\mu\text{g/mL}$ and 92% were protected at the long-term level of ≥ 1 $\mu\text{g/mL}$.

In general, much higher GMCs/GMTs for each of the valences were measured following the 2, 4, 6 months vaccination schedule than after the condensed 2, 3, 4 months schedule (**Table 12**). Only for PT and FHA, the differences between Group 1 and Group 3 were much lower.

Please note that Group 3 subjects received a monovalent Hep B vaccine at birth. Subjects, however, were only twice vaccinated with Hexyon at 2 and 6 MoA. At 4 MoA, Pentavac (without Hep B) was given.

RV seroprotection rates following the 2, 4, 6 months vaccination schedule were in the range of those following the condensed schedule (2, 3, 4 months). At 1 month-post 3rd dose, 91% of subjects reached serum IgA levels of ≥ 20 U/mL, and 88% of subjects seronegative at baseline were seroprotected at ≥ 20 U/mL one month after the 3rd dose (**Table 13**).

Similar immunogenicity results were obtained in the FAS.

CHMP comment:

Seroprotection and vaccine response rates following the 3-dose primary vaccination at 2, 3 and 4 months were in accordance to those of previous studies with Hexyon/ Hexacima/ Hexaxim except for PRP, for which a somewhat lower seroprotection rate at ≥ 0.15 $\mu\text{g/mL}$ was observed (91% compared to 96% mentioned in the SmPC).

Seroprotection rates against the 13 serotypes contained in PCV13 were in the range of those previously obtained with PCV13.

Furthermore, immunogenicity results obtained for Group 3 with the 3-dose vaccination schedule at 2, 4, and 6 MoA were concordant to those obtained in previous studies with Hexyon. The high Hep B GMCs obtained in this group very probably result from the extended Hep B vaccination schedule, i.e., 1 monovalent Hep B dose at birth, then 2 doses Hexyon at 2 and at 6 MoA. However, the GMCs / GMTs for the other valences of Hexyon were also generally higher than after the condensed 2, 3, 4 months-vaccination schedule. This is also known from other studies with hexavalent DTaP-IPV-HepB-HiB vaccines administered at 2, 4, and 6 MoA.

Table 7: Seroprotection/seroconversion rates for study vaccines (Groups 1 and 2)- PP analysis set

| | | | Group 1 (N=237) | | | Group 2 (N=239) | | |
|-------------------------|-------------------|------------------|--------------------|-------|--------------|--------------------|-------|--------------|
| | | | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Anti-D (IU/mL) | Pre-Dose 1 (V01) | ≥ 0.01 IU/mL | - | - | - | - | - | - |
| | | ≥ 0.1 IU/mL | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 0.01 IU/mL | 220/220 | 100.0 | (98.3; 100) | 219/219 | 100.0 | (98.3; 100) |
| | | ≥ 0.1 IU/mL | 136/220 | 61.8 | (55.0; 68.3) | 127/219 | 58.0 | (51.2; 64.6) |
| | | ≥ 1.0 IU/mL | 12/220 | 5.5 | (2.85; 9.33) | 11/219 | 5.0 | (2.53; 8.81) |
| Anti-T (IU/mL) | Pre-Dose 1 (V01) | ≥ 0.01 IU/mL | - | - | - | - | - | - |
| | | ≥ 0.1 IU/mL | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 0.01 IU/mL | 226/226 | 100.0 | (98.4; 100) | 223/223 | 100.0 | (98.4; 100) |
| | | ≥ 0.1 IU/mL | 226/226 | 100.0 | (98.4; 100) | 223/223 | 100.0 | (98.4; 100) |
| | | ≥ 1.0 IU/mL | 79/226 | 35.0 | (28.8; 41.6) | 97/223 | 43.5 | (36.9; 50.3) |
| Anti-PT (EU/mL) | Pre-Dose 1 (V01) | ≥ 2 EU/mL (LLOQ) | 147/233 | 63.1 | (56.5; 69.3) | 156/236 | 66.1 | (59.7; 72.1) |
| | Post-Dose 3 (V04) | ≥ 4 EU/mL | 233/233 | 100.0 | (98.4; 100) | 233/233 | 100.0 | (98.4; 100) |
| | Seroconversion † | | 207/229 | 90.4 | (85.8; 93.9) | 209/230 | 90.9 | (86.4; 94.3) |
| Anti-FHA (EU/mL) | Pre-Dose 1 (V01) | ≥ 2 EU/mL (LLOQ) | 216/235 | 91.9 | (87.7; 95.1) | 211/235 | 89.8 | (85.2; 93.3) |
| | Post-Dose 3 (V04) | ≥ 4 EU/mL | 233/233 | 100.0 | (98.4; 100) | 233/233 | 100.0 | (98.4; 100) |
| | Seroconversion † | | 206/231 | 89.2 | (84.4; 92.9) | 175/229 | 76.4 | (70.4; 81.8) |
| Anti-Polio 1 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 221/221 | 100.0 | (98.3; 100) | 224/224 | 100.0 | (98.4; 100) |
| Anti-Polio 2 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 228/228 | 100.0 | (98.4; 100) | 225/225 | 100.0 | (98.4; 100) |
| Anti-Polio 3 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 229/229 | 100.0 | (98.4; 100) | 227/227 | 100.0 | (98.4; 100) |
| Anti-Hep B (mIU/mL) | Pre-Dose 1 (V01) | ≥ 10 mIU/mL | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 10 mIU/mL | 221/231 | 95.7 | (92.2; 97.9) | 228/231 | 98.7 | (96.3; 99.7) |
| | | ≥ 100 mIU/mL | 166/231 | 71.9 | (65.6; 77.6) | 200/231 | 86.6 | (81.5; 90.7) |
| Anti-PRP (µg/mL) | Pre-Dose 1 (V01) | ≥ 0.15 µg/mL | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | ≥ 0.15 µg/mL | 204/224 | 91.1 | (86.5; 94.5) | 195/226 | 86.3 | (81.1; 90.5) |
| | | ≥ 1 µg/mL | 132/224 | 58.9 | (52.2; 65.4) | 84/226 | 37.2 | (30.9; 43.8) |

N: number of subjects analyzed in the PP analysis set

n: number of subjects experiencing the endpoint listed

M : number of subjects with available data for the relevant endpoint

-: not assessed

† Seroconversion defined as anti-PT and anti-FHA \geq 4 fold Ab concentrations increase from baseline to 1 month-post Dose 3

Group 1: Hexyon + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Group 2: Infanrix hexa + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Source: Table 5.2 A3L39 CSR

Table 8: Geometric mean titers/ concentrations for study vaccines (Groups 1 and 2) - PP analysis set

| | | Group 1 (N=237) | | | Group 2 (N=239) | | |
|---------------------------|------------------------------------|--------------------|-------|----------------|--------------------|-------|----------------|
| | | M | GM | (95% CI) | M | GM | (95% CI) |
| Anti-D (IU/mL) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 220 | 0.163 | (0.142; 0.187) | 219 | 0.148 | (0.130; 0.169) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-T (IU/mL) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 226 | 0.759 | (0.689; 0.836) | 223 | 0.874 | (0.791; 0.965) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-PT (EU/mL) | Pre-Dose 1 (V01) | 233 | 3.55 | (3.01; 4.18) | 236 | 3.97 | (3.36; 4.69) |
| | Post-Dose 3 (V04) | 233 | 116 | (108; 124) | 233 | 131 | (121; 141) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 229 | 33.9 | (27.9; 41.2) | 230 | 34.2 | (28.0; 41.8) |
| Anti-FHA (EU/mL) | Pre-Dose 1 (V01) | 235 | 6.17 | (5.37; 7.10) | 235 | 7.04 | (6.03; 8.22) |
| | Post-Dose 3 (V04) | 233 | 141 | (131; 151) | 233 | 84.3 | (78.0; 91.0) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 231 | 23.0 | (19.5; 27.2) | 229 | 12.3 | (10.0; 15.0) |
| Anti-Polio 1 (1/dil) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 221 | 113 | (96.7; 133) | 224 | 268 | (226; 317) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-Polio 2 (1/dil) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 228 | 191 | (163; 225) | 225 | 365 | (305; 437) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-Polio 3 (1/dil) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 229 | 302 | (261; 351) | 227 | 662 | (552; 793) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-Hep B (mIU/mL) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 231 | 207 | (170; 253) | 231 | 382 | (324; 450) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |
| Anti-PRP (μ g/mL) | Pre-Dose 1 (V01) | - | - | - | - | - | - |
| | Post-Dose 3 (V04) | 224 | 1.19 | (0.978; 1.45) | 226 | 0.600 | (0.505; 0.713) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | - | - | - | - | - | - |

N: number of subjects analyzed in the PP analysis set
M : number of subjects with available data for the relevant endpoint
GM : geometric mean
-: not assessed
Group 1: Hexyon + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA
Group 2: Infanrix hexa + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Source: Table 5.3 A3L39 CSR

Table 9: Seroprotection/seroconversion rates for concomitant vaccines (Groups 1 and 2) - PP analysis set

| | | | Group 1 (N=237) | | | Group 2 (N=239) | | |
|--------------------------------|--|------------------|--------------------|-------|--------------|--------------------|-------|--------------|
| | | | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Anti-RV IgA (U/mL) | Pre-Dose 1 (V01) | ≥ 20 U/mL | 2/234 | 0.9 | (0.1; 3.1) | 6/237 | 2.5 | (0.9; 5.4) |
| | Post-Dose 3 (V04) | ≥ 20 U/mL | 184/199 | 92.5 | (87.9; 95.7) | 179/200 | 89.5 | (84.4; 93.4) |
| | Post-Dose 3 (V04)/ Pre-Dose 1 (V01) | Seroconversion * | 180/197 | 91.4 | (86.5; 94.9) | 174/199 | 87.4 | (82.0; 91.7) |
| Pneumococcal serotypes: | | | | | | | | |
| Serotype 1 (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 215/217 | 99.1 | (96.7; 99.9) | 218/220 | 99.1 | (96.8; 99.9) |
| Serotype 3 (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 200/210 | 95.2 | (91.4; 97.7) | 212/219 | 96.8 | (93.5; 98.7) |
| Serotype 4 (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 214/217 | 98.6 | (96.0; 99.7) | 217/219 | 99.1 | (96.7; 99.9) |
| Serotype 5 (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 188/216 | 87.0 | (81.8; 91.2) | 209/219 | 95.4 | (91.8; 97.8) |
| Serotype 6A (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 201/216 | 93.1 | (88.8; 96.1) | 204/219 | 93.2 | (89.0; 96.1) |
| Serotype 6B (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 167/217 | 77.0 | (70.8; 82.4) | 190/220 | 86.4 | (81.1; 90.6) |
| Serotype 7F (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 216/216 | 100.0 | (98.3; 100) | 219/219 | 100.0 | (98.3; 100) |
| Serotype 9V (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 207/216 | 95.8 | (92.2; 98.1) | 214/219 | 97.7 | (94.8; 99.3) |
| Serotype 14 (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 215/216 | 99.5 | (97.4; 100) | 220/220 | 100.0 | (98.3; 100) |
| Serotype 18C (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 212/215 | 98.6 | (96.0; 99.7) | 215/220 | 97.7 | (94.8; 99.3) |
| Serotype 19A (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 214/216 | 99.1 | (96.7; 99.9) | 218/219 | 99.5 | (97.5; 100) |
| Serotype 19F (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 215/215 | 100.0 | (98.3; 100) | 220/220 | 100.0 | (98.3; 100) |
| Serotype 23F (µg/mL) | Post-Dose 3 (V04) | ≥ 0.35 µg/mL | 199/215 | 92.6 | (88.2; 95.7) | 209/220 | 95.0 | (91.2; 97.5) |

N: number of subjects analyzed in the PP analysis set
n: number of subjects experiencing respective endpoint
M : number of subjects with available data for the relevant endpoint
* Seroconversion defined as anti-RV IgA ≥ 20 U/mL in subjects seronegative at baseline (< 20 U/mL)
Group 1: Hexyon + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA
Group 2: Infanrix hexa + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Source: Table 5.4 A3L39 CSR

Table 10: Geometric mean concentrations for concomitant vaccines (Groups 1 and 2) - PP analysis set

| | | Group 1 (N=237) | | | Group 2 (N=239) | | |
|-------------------------------|------------------------------------|--------------------|-------|----------------|--------------------|-------|---------------|
| | | M | GMC | (95% CI) | M | GMC | (95% CI) |
| Anti-RV (U/mL) | Pre-Dose 1 (V01) | 234 | 3.87 | (3.77; 3.98) | 237 | 4.24 | (3.94; 4.55) |
| | Post-Dose 3 (V04) | 199 | 455 | (350; 593) | 200 | 322 | (250; 415) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 197 | 118 | (90.4; 154) | 199 | 77.1 | (59.6; 99.6) |
| Pneumococcal serotypes | | | | | | | |
| Serotype 1 (µg/mL) | Post-Dose 3 (V04) | 217 | 1.84 | (1.67; 2.03) | 220 | 2.33 | (2.12; 2.57) |
| Serotype 3 (µg/mL) | Post-Dose 3 (V04) | 210 | 1.09 | (0.995; 1.19) | 219 | 1.33 | (1.22; 1.44) |
| Serotype 4 (µg/mL) | Post-Dose 3 (V04) | 217 | 2.06 | (1.90; 2.25) | 219 | 2.76 | (2.52; 3.03) |
| Serotype 5 (µg/mL) | Post-Dose 3 (V04) | 216 | 0.777 | (0.704; 0.858) | 219 | 0.996 | (0.913; 1.09) |
| Serotype 6A (µg/mL) | Post-Dose 3 (V04) | 216 | 1.40 | (1.24; 1.58) | 219 | 1.67 | (1.49; 1.88) |
| Serotype 6B (µg/mL) | Post-Dose 3 (V04) | 217 | 0.762 | (0.662; 0.877) | 220 | 1.09 | (0.948; 1.26) |
| Serotype 7F (µg/mL) | Post-Dose 3 (V04) | 216 | 2.46 | (2.26; 2.69) | 219 | 2.89 | (2.65; 3.16) |
| Serotype 9V (µg/mL) | Post-Dose 3 (V04) | 216 | 1.16 | (1.06; 1.27) | 219 | 1.46 | (1.34; 1.59) |
| Serotype 14 (µg/mL) | Post-Dose 3 (V04) | 216 | 6.78 | (5.91; 7.77) | 220 | 9.34 | (8.36; 10.4) |
| Serotype 18C (µg/mL) | Post-Dose 3 (V04) | 215 | 1.62 | (1.47; 1.78) | 220 | 2.03 | (1.84; 2.24) |
| Serotype 19A (µg/mL) | Post-Dose 3 (V04) | 216 | 3.30 | (2.99; 3.64) | 219 | 4.01 | (3.63; 4.43) |
| Serotype 19F (µg/mL) | Post-Dose 3 (V04) | 215 | 3.19 | (2.95; 3.45) | 220 | 4.05 | (3.74; 4.39) |
| Serotype 23F (µg/mL) | Post-Dose 3 (V04) | 215 | 1.33 | (1.18; 1.52) | 220 | 1.61 | (1.42; 1.83) |

N: number of subjects analyzed in the PP analysis set

M : number of subjects with available data for the relevant endpoint

GMC : geometric mean concentration

Group 1: Hexyon + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Group 2: Infanrix hexa + Prevenar 13 + RotaTeq at 2, 3 and 4 MoA

Source: Table 5.5 A3L39 CSR

Table 11: Seroprotection/seroconversion/vaccine response rates for study vaccine (Group 3) - PP analysis set

| | | | Group 3 (N=236) | | |
|----------------------|--|-------------------|--------------------|-------|--------------|
| | | | n/M | % | (95% CI) |
| Anti-D (IU/mL) | Pre-Dose 1 (V01) | ≥ 0.01 IU/mL | 115/189 | 60.8 | (53.5; 67.8) |
| | | ≥ 0.1 IU/mL | 21/189 | 11.1 | (7.01; 16.5) |
| | Post-Dose 3 (V04) | ≥ 0.01 IU/mL | 211/211 | 100.0 | (98.3; 100) |
| | | ≥ 0.1 IU/mL | 206/211 | 97.6 | (94.6; 99.2) |
| | | ≥ 1.0 IU/mL | 100/211 | 47.4 | (40.5; 54.4) |
| Anti-T (IU/mL) | Pre-Dose 1 (V01) | ≥ 0.01 IU/mL | 186/193 | 96.4 | (92.7; 98.5) |
| | | ≥ 0.1 IU/mL | 165/193 | 85.5 | (79.7; 90.1) |
| | Post-Dose 3 (V04) | ≥ 0.01 IU/mL | 205/205 | 100.0 | (98.2; 100) |
| | | ≥ 0.1 IU/mL | 205/205 | 100.0 | (98.2; 100) |
| | | ≥ 1.0 IU/mL | 178/205 | 86.8 | (81.4; 91.1) |
| Anti-PT (EU/mL) | Pre-Dose 1 (V01) | ≥ 2 EU/mL (LLOQ) | 123/195 | 63.1 | (55.9; 69.9) |
| | Post-Dose 3 (V04) | ≥ 4 EU/mL | 218/218 | 100.0 | (98.3; 100) |
| | Post-Dose 3 (V04)/ Pre-Dose 1 (V01) | Vaccine response* | 183/184 | 99.5 | (97.0; 100) |
| | | Seroconversion † | 165/184 | 89.7 | (84.3; 93.7) |
| Anti-FHA (EU/mL) | Pre-Dose 1 (V01) | ≥ 2 EU/mL (LLOQ) | 173/194 | 89.2 | (83.9; 93.2) |
| | Post-Dose 3 (V04) | ≥ 4 EU/mL | 214/214 | 100.0 | (98.3; 100) |
| | Post-Dose 3 (V04)/ Pre-Dose 1 (V01) | Vaccine response* | 178/178 | 100.0 | (97.9; 100) |
| | | Seroconversion † | 170/178 | 95.5 | (91.3; 98.0) |
| Anti-Polio 1 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | 96/205 | 46.8 | (39.8; 53.9) |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 196/196 | 100.0 | (98.1; 100) |
| Anti-Polio 2 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | 115/203 | 56.7 | (49.5; 63.6) |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 202/203 | 99.5 | (97.3; 100) |
| Anti-Polio 3 (1/dil) | Pre-Dose 1 (V01) | ≥ 8 (1/dil) | 44/208 | 21.2 | (15.8; 27.3) |
| | Post-Dose 3 (V04) | ≥ 8 (1/dil) | 205/205 | 100.0 | (98.2; 100) |
| Anti-Hep B (mIU/mL) | Pre-Dose 1 (V01) | ≥ 10 mIU/mL | 90/231 | 39.0 | (32.6; 45.6) |
| | Post-Dose 3 (V04) | ≥ 10 mIU/mL | 223/225 | 99.1 | (96.8; 99.9) |
| | | ≥ 100 mIU/mL | 218/225 | 96.9 | (93.7; 98.7) |
| Anti-PRP (µg/mL) | Pre-Dose 1 (V01) | ≥ 0.15 µg/mL | 73/227 | 32.2 | (26.1; 38.7) |
| | Post-Dose 3 (V04) | ≥ 0.15 µg/mL | 226/226 | 100.0 | (98.4; 100) |
| | | ≥ 1 µg/mL | 208/226 | 92.0 | (87.7; 95.2) |

N: number of subjects analyzed in the PP analysis set

n: number of subjects experiencing respective endpoint

M : number of subjects with available data for the relevant endpoint

M : number of subjects with available data for the relevant endpoint

* Vaccine response defined as follows: Post-Dose 3 Ab concentrations ≥ 4 x LLOQ, if baseline < 4 x LLOQ or post-Dose 3 Ab concentrations ≥ baseline, if baseline ≥ 4 x LLOQ

† Seroconversion defined as ≥ 4 fold Ab concentration increase from baseline to 1 month-post Dose 3

Group 3: (Hep B at birth) Hexyon + PCV13 + RotaTeq at 2 and 6 MoA and Pentavac +/- PCV13 + RotaTeq at 4 MoA and NeisVac-C at 2 MoA

Source: Table 5.6 A3L39 CSR

Table 12: Geometric mean titers/ concentrations for study vaccine (Group 3) - PP analysis set

| | | Group 3 (N=236) | | |
|-----------------------------|---|----------------------------|-----------|-----------------|
| | | M | GM | (95% CI) |
| Anti-D (IU/mL) | Pre-Dose 1 (V01) | 189 | 0.015 | (0.012; 0.019) |
| | Post-Dose 3 (V04) | 211 | 0.790 | (0.694; 0.898) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 176 | 49.2 | (35.4; 68.2) |
| Anti-T (IU/mL) | Pre-Dose 1 (V01) | 193 | 0.300 | (0.249; 0.360) |
| | Post-Dose 3 (V04) | 205 | 2.21 | (2.00; 2.44) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 173 | 7.29 | (5.70; 9.32) |
| Anti-PT (EU/mL) | Pre-Dose 1 (V01) | 195 | 3.21 | (2.74; 3.75) |
| | Post-Dose 3 (V04) | 218 | 97.1 | (89.9; 105) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 184 | 30.4 | (24.6; 37.5) |
| Anti-FHA (EU/mL) | Pre-Dose 1 (V01) | 194 | 4.94 | (4.33; 5.65) |
| | Post-Dose 3 (V04) | 214 | 165 | (153; 178) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 178 | 32.7 | (27.5; 38.9) |
| Anti-Polio 1 (1/dil) | Pre-Dose 1 (V01) | 205 | 7.22 | (6.04; 8.62) |
| | Post-Dose 3 (V04) | 196 | 891 | (760; 1044) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 174 | 128 | (95.8; 171) |
| Anti-Polio 2 (1/dil) | Pre-Dose 1 (V01) | 203 | 10.2 | (8.41; 12.3) |
| | Post-Dose 3 (V04) | 203 | 2027 | (1669; 2462) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 179 | 228 | (165; 316) |
| Anti-Polio 3 (1/dil) | Pre-Dose 1 (V01) | 208 | 4.58 | (4.08; 5.13) |
| | Post-Dose 3 (V04) | 205 | 1485 | (1243; 1775) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 186 | 323 | (257; 404) |
| Anti-Hep B (mIU/mL) | Pre-Dose 1 (V01) | 231 | 10.0 | (7.92; 12.7) |
| | Post-Dose 3 (V04) | 225 | 2719 | (2272; 3255) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 221 | 286 | (217; 378) |
| Anti-PRP (µg/mL) | Pre-Dose 1 (V01) | 227 | 0.083 | (0.070; 0.098) |
| | Post-Dose 3 (V04) | 226 | 7.91 | (6.75; 9.27) |
| | Post-Dose 3 (V04)/Pre-Dose 1 (V01) | 217 | 94.7 | (73.2; 122) |

N: number of subjects analyzed in the PP analysis set

M : number of subjects with available data for the relevant endpoint

GM : geometric mean

Group 3: (Hep B at birth) Hexyon + PCV13 + RotaTeq at 2 and 6 MoA and Pentavac +/- PCV13 + RotaTeq at 4 MoA and NeisVac-C at 2 MoA

Source: Table 5.7 A3L39 CSR

Table 13: Seroprotection/ seroconversion rates and geometric mean concentration for concomitant vaccine RotaTeq (Group 3) - PP analysis set

| | | | Group 3 (N=236) | | |
|----------------|--------------------------|------------------|-----------------|------------|-----------------|
| | | | n/M | % | (95% CI) |
| Anti-RV (U/mL) | Pre-Dose 1 | ≥ 20 U/mL | 6/183 | 3.3 | (1.2; 7.0) |
| | Post-Dose 3 | ≥ 20 U/mL | 167/184 | 90.8 | (85.6; 94.5) |
| | Post-Dose 3 / Pre-Dose 1 | Seroconversion * | 130/147 | 88.4 | (82.1; 93.1) |
| | | | M | GMC | (95% CI) |
| Anti-RV (U/mL) | Pre-Dose 1 | | 183 | 4.47 | (4.08; 4.90) |
| | Post-Dose 3 | | 184 | 279 | (214; 362) |
| | Post-Dose 3 / Pre-Dose 1 | | 147 | 66.6 | (49.5; 89.8) |

N: number of subjects analyzed in the PP analysis set

n: number of subjects experiencing the endpoint

M: number of subjects with available data for the relevant endpoint

GMC: geometric mean concentration

Group 3: (Hep B at birth) Hexyon + PCV13 + RotaTeq at 2 and 6 MoA and Pentavac +/- PCV13 + RotaTeq at 4 MoA and NeisVac-C at 2 MoA

Source: Tables 5.8 and 5.9 A3L39 CSR

Safety results (Tables 14 to 18)

Within 30 minutes after any vaccine injection, 5 subjects (1.9%) in Group 1 and 2 subjects (0.8%) in Group 2 experienced at least 1 immediate unsolicited AE. For 3 subjects in Group 1 and both subjects in Group 2 these AEs were documented as immediate unsolicited adverse reactions (ARs) (flatulence, cough, abdominal pain and restlessness of various grades). None of the subjects in Group 3 experienced an immediate unsolicited AE/AR.

Within 7 days after any vaccine injection, a vast majority of subjects (98 – 99%) in all groups experienced at least 1 solicited reaction. Solicited injection site reactions were reported with similar frequencies in Groups 1 and 2 after each vaccine injection (83% and 82%, respectively) and with a somewhat lower frequency (77%) in Group 3. The frequencies of solicited injection site reactions were similar at the Hexyon, Pentavac or Infanrix hexa site as compared to Prevenar 13 site (contralateral application) in all groups. The most frequent injection site reactions were pain, erythema, and swelling. Grade 3 injection site reactions were experienced with a frequency of 10% and 9%, respectively, in Groups 1 and 2 and 6% in Group 3. Most of the injection site reactions were reported within 3 days after injection, were of Grade 1 or 2 in intensity and lasted up to maximum 3 days.

CHMP comment:

Since Group 3 subjects were administered at 2 MoA PCV-13 and NeisVac-C at the same location, injection site reactions at this time point cannot be differentiated for these 2 vaccines. However, in this group, injection site reactions at the PCV13 (+ NeisVac-C) site following the 1st injection were either in the same range as those in Group 1 and Group 2 (for injection site pain) or even recorded at a lower frequency than in the other groups (for injection site erythema and swelling).

Grade 3 systemic reactions were observed in 18%, 13% and 17% of subjects in Groups 1, 2, and 3, respectively. All subjects received a Prevenar 13 and RotaTeq dose concomitantly with the hexavalent study vaccines (plus a dose of NeisVac-C in Group 3 at 2 MoA). Therefore, it is not possible to discriminate if the systemic reactions reported were caused by the hexa-/ pentavalent vaccine or by

(one of the) concomitant vaccines. Overall, there were no notable differences in Groups 1, 2 and 3 in terms of proportions of subjects experiencing solicited systemic reactions within 7 days after any injection except for pyrexia which was reported at a higher frequency in Group 1 (73%) than in Group 2 and 3 (57 and 59%, respectively).

The most frequently reported solicited systemic reaction after any vaccine injection was irritability (up to 84% of subjects), followed by crying (up to 77%) and somnolence (up to 74%). The majority of solicited systemic reactions were of Grade 1 or Grade 2 intensity. Grade 3 solicited systemic reactions were infrequent. Most solicited systemic reactions occurred within 3 days after injection and resolved within 3 days, however, some were still ongoing at D8.

Within 30 days after any vaccine injection, unsolicited AEs were reported for a similar proportion of subjects in Group 1 (41%) and Group 2 (40%) but for a higher proportion (70%) of Group 3 subjects. The most frequent unsolicited AEs were in the SOC 'Infections and infestations', followed by 'Gastrointestinal disorders', 'Respiratory, thoracic and mediastinal disorders' and 'Skin and subcutaneous tissue disorders'.

Unsolicited ARs were reported for a low proportion of subjects in Group 1 (6%), Group 2 (3%) and Group 3 (2%). For all subjects, the unsolicited ARs were not serious, except for Subject [confidential information] in Group 1 who experienced convulsions after the second vaccine injection (see below). Most of these unsolicited ARs were of Grade 1 or Grade 2 intensity, emerged within 5 days after injection and lasted up to 5 days.

Within 30 days after any vaccine injection, 9, 8 and 7 subjects in Groups 1, 2 and 3, respectively, experienced at least 1 SAE. During the study, a total of 36 SAEs were reported for 32 subjects. 12 and 9 subjects in Groups 1 and 2, respectively, and 7 subjects in Group 3 experienced at least 1 SAE. None of the SAEs were related to treatment, except for Subject [confidential information] in Group 1 who experienced convulsions related to Hexyon according to the Investigator (also reported as AESI).

There was no AE leading to study discontinuation. However, the SAE (convulsions) for Subject [confidential information] related to Hexyon vaccination led to the subject's discontinuation for the subsequent dose.

No death was reported during the study.

Narrative of subject [confidential information]:

The subject had convulsions 10 days after the 2nd dose of Hexyon, Prevenar 13 and RotaTeq; the event led to hospitalization. The subject experienced 3 other episodes of convulsions on the day of hospitalization and another episode 3 days later. The subject recovered under treatment 7 days after the first episode and was discharged from the hospital 4 days later. Although the subject continued the trial, the SAE led to the subject's discontinuation for the subsequent dose. Therefore the subject did not receive the third Hexyon dose.

The event of convulsions was reported by the Investigator as related to Hexyon and RotaTeq and unrelated to Prevenar 13 or to trial procedure. However, the time to onset of 10 days is rather suggestive of a relationship with a live vaccine (RotaTeq) than with inactivated vaccines (Hexyon and Prevenar). Therefore, the event was reported by the company as unrelated to Hexyon or Prevenar 13 or to trial procedure, and related to RotaTeq.

After completion of the study and 4 months after the first episode, the subject experienced another episode of convulsions and was hospitalized. The subject recovered after 4 days under treatment. This new episode was reported by the Investigator as unrelated to vaccination.

Other SAEs (hemangioma, head injury, inguinal hernia, hematemesis, various infections, exanthema subitum, myoclonus, poor weight gain) were considered by the Investigator as unrelated to vaccination.

CHMP comment:

From the narrative of the affected subject a causative relationship between the SAE of convulsions and vaccination, particularly with Hexyon, was very unlikely.

The CHMP agrees that all other SAEs were unrelated to vaccination or study procedures.

No new safety issues evolved.

Table 14: Summary of solicited reactions within 7 days after any vaccine injection - SafAS

| | Group 1 (N=265) | | | Group 2 (N=261) | | | Group 3 (N=265) | | |
|--|--------------------|------|--------------|--------------------|------|--------------|--------------------|------|--------------|
| | n/M | % | (95% CI) | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Subjects experiencing at least one: | | | | | | | | | |
| Solicited reaction | 261/265 | 98.5 | (96.2; 99.6) | 255/261 | 97.7 | (95.1; 99.2) | 261/265 | 98.5 | (96.2; 99.6) |
| Grade 3 solicited reaction | 63/265 | 23.8 | (18.8; 29.4) | 47/261 | 18.0 | (13.5; 23.2) | 56/265 | 21.1 | (16.4; 26.5) |
| Solicited injection site reaction | 220/265 | 83.0 | (77.9; 87.3) | 214/261 | 82.0 | (76.8; 86.5) | 203/265 | 76.6 | (71.0; 81.6) |
| Grade 3 injection site reaction | 27/265 | 10.2 | (6.8; 14.5) | 24/261 | 9.2 | (6.0; 13.4) | 17/265 | 6.4 | (3.8; 10.1) |
| Solicited systemic reaction | 257/265 | 97.0 | (94.1; 98.7) | 250/261 | 95.8 | (92.6; 97.9) | 258/265 | 97.4 | (94.6; 98.9) |
| Grade 3 systemic reaction | 47/265 | 17.7 | (13.3; 22.9) | 35/261 | 13.4 | (9.5; 18.2) | 46/265 | 17.4 | (13.0; 22.5) |

n: number of subjects experiencing the respective endpoint

N: number of subjects analyzed in the SafAS

M: number of subjects with available data for the relevant endpoint

Extract from Table 6.2, A3L39 CSR

Table 15: Solicited injection site reactions within 7 days following study vaccine or Prevenar 13 injection – SafAS, Group 3

| Subjects experiencing | Group 3 (N=265) | | | | | |
|--------------------------------|---------------------------------------|------|--------------|---------------------------------|------|--------------|
| | Hexyon / Pentavac administration site | | | Prevenar 13 administration site | | |
| at least one: | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Injection site pain | 166/265 | 62.6 | (56.5; 68.5) | 150/265 | 56.6 | (50.4; 62.7) |
| Post-injection 1 | 132/265 | 49.8 | (43.6; 56.0) | 123/265 | 46.4 | (40.3; 52.6) |
| Post-injection 2 | 83/264 | 31.4 | (25.9; 37.4) | 72/264 | 27.3 | (22.0; 33.1) |
| Post-injection 3 | 92/263 | 35.0 | (29.2; 41.1) | 81/255 | 31.8 | (26.1; 37.9) |
| Injection site erythema | 99/265 | 37.4 | (31.5; 43.5) | 70/265 | 26.4 | (21.2; 32.2) |
| Post-injection 1 | 39/265 | 14.7 | (10.7; 19.6) | 26/265 | 9.8 | (6.5; 14.0) |
| Post-injection 2 | 43/264 | 16.3 | (12.0; 21.3) | 32/264 | 12.1 | (8.4; 16.7) |
| Post-injection 3 | 55/263 | 20.9 | (16.2; 26.3) | 35/255 | 13.7 | (9.8; 18.6) |
| Injection site swelling | 71/265 | 26.8 | (21.6; 32.6) | 57/265 | 21.5 | (16.7; 27.0) |
| Post-injection 1 | 40/265 | 15.1 | (11.0; 20.0) | 31/265 | 11.7 | (8.1; 16.2) |
| Post-injection 2 | 29/264 | 11.0 | (7.5; 15.4) | 26/264 | 9.8 | (6.5; 14.1) |
| Post-injection 3 | 35/263 | 13.3 | (9.4; 18.0) | 23/255 | 9.0 | (5.8; 13.2) |

Table 16: Solicited injection site reactions within 7 days following study vaccine or Prevenar 13 injection – Groups 1 and 2

| Subjects experiencing at least one: | Group 1 (N=265) | | | | | | Group 2 (N=261) | | | | | |
|-------------------------------------|-------------------------------------|------|--------------|---------------------------------|------|--------------|-----------------------------------|------|--------------|---------------------------------|------|--------------|
| | DTaP-IPV-HB-Hib administration site | | | Prevenar 13 administration site | | | Infanrix hexa administration site | | | Prevenar 13 administration site | | |
| | n/M | % | (95% CI) | n/M | % | (95% CI) | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Injection site pain | 169/265 | 63.8 | (57.7; 69.6) | 163/265 | 61.5 | (55.4; 67.4) | 162/261 | 62.1 | (55.9; 68.0) | 158/261 | 60.5 | (54.3; 66.5) |
| Post-injection 1 | 118/265 | 44.5 | (38.4; 50.7) | 112/265 | 42.3 | (36.2; 48.5) | 121/261 | 46.4 | (40.2; 52.6) | 119/261 | 45.6 | (39.4; 51.8) |
| Post-injection 2 | 121/265 | 45.7 | (39.6; 51.9) | 115/265 | 43.4 | (37.3; 49.6) | 104/261 | 39.8 | (33.9; 46.1) | 102/261 | 39.1 | (33.1; 45.3) |
| Post-injection 3 | 89/264 | 33.7 | (28.0; 39.8) | 85/264 | 32.2 | (26.6; 38.2) | 98/261 | 37.5 | (31.7; 43.7) | 85/261 | 32.6 | (26.9; 38.6) |
| Injection site erythema | 146/265 | 55.1 | (48.9; 61.2) | 133/265 | 50.2 | (44.0; 56.4) | 126/261 | 48.3 | (42.1; 54.5) | 122/261 | 46.7 | (40.6; 53.0) |
| Post-injection 1 | 75/265 | 28.3 | (23.0; 34.1) | 73/265 | 27.5 | (22.3; 33.3) | 63/261 | 24.1 | (19.1; 29.8) | 62/261 | 23.8 | (18.7; 29.4) |
| Post-injection 2 | 105/265 | 39.6 | (33.7; 45.8) | 80/265 | 30.2 | (24.7; 36.1) | 88/261 | 33.7 | (28.0; 39.8) | 77/261 | 29.5 | (24.0; 35.4) |
| Post-injection 3 | 101/264 | 38.3 | (32.4; 44.4) | 82/264 | 31.1 | (25.5; 37.0) | 81/261 | 31.0 | (25.5; 37.0) | 74/261 | 28.4 | (23.0; 34.2) |
| Injection site swelling | 113/265 | 42.6 | (36.6; 48.8) | 103/265 | 38.9 | (33.0; 45.0) | 100/261 | 38.3 | (32.4; 44.5) | 94/261 | 36.0 | (30.2; 42.2) |
| Post-injection 1 | 57/265 | 21.5 | (16.7; 27.0) | 59/265 | 22.3 | (17.4; 27.8) | 46/261 | 17.6 | (13.2; 22.8) | 48/261 | 18.4 | (13.9; 23.6) |
| Post-injection 2 | 68/265 | 25.7 | (20.5; 31.4) | 58/265 | 21.9 | (17.1; 27.4) | 52/261 | 19.9 | (15.3; 25.3) | 56/261 | 21.5 | (16.6; 26.9) |
| Post-injection 3 | 68/264 | 25.8 | (20.6; 31.5) | 53/264 | 20.1 | (15.4; 25.4) | 67/261 | 25.7 | (20.5; 31.4) | 60/261 | 23.0 | (18.0; 28.6) |

n: number of subjects experiencing the respective endpoint

N: number of subjects analyzed in the SafAS

M: number of subjects with available data for the relevant endpoint

Source: Table 6.3 A3L39 CSR

Table 17: Solicited systemic reactions within 7 days after each vaccine injection - SafAS

| | Group 1 (N=265) | | | Group 2 (N=261) | | | Group 3 (N=265) | | |
|--|--------------------|------|--------------|--------------------|------|--------------|--------------------|------|--------------|
| | n/M | % | (95% CI) | n/M | % | (95% CI) | n/M | % | (95% CI) |
| Subjects experiencing at least one: | | | | | | | | | |
| Pyrexia | 193/265 | 72.8 | (67.0; 78.1) | 148/261 | 56.7 | (50.5; 62.8) | 156/265 | 58.9 | (52.7; 64.9) |
| Post-Injection 1 | 143/265 | 54.0 | (47.8; 60.1) | 77/260 | 29.6 | (24.1; 35.6) | 90/264 | 34.1 | (28.4; 40.2) |
| Post-Injection 2 | 137/265 | 51.7 | (45.5; 57.9) | 103/261 | 39.5 | (33.5; 45.7) | 65/264 | 24.6 | (19.5; 30.3) |
| Post-Injection 3 | 79/263 | 30.0 | (24.6; 36.0) | 69/261 | 26.4 | (21.2; 32.2) | 105/262 | 40.1 | (34.1; 46.3) |
| Vomiting | 94/265 | 35.5 | (29.7; 41.6) | 72/261 | 27.6 | (22.3; 33.4) | 94/265 | 35.5 | (29.7; 41.6) |
| Post-Injection 1 | 61/265 | 23.0 | (18.1; 28.6) | 35/261 | 13.4 | (9.5; 18.2) | 53/265 | 20.0 | (15.4; 25.3) |
| Post-Injection 2 | 49/265 | 18.5 | (14.0; 23.7) | 39/261 | 14.9 | (10.8; 19.9) | 33/264 | 12.5 | (8.8; 17.1) |
| Post-Injection 3 | 39/264 | 14.8 | (10.7; 19.6) | 25/261 | 9.6 | (6.3; 13.8) | 45/263 | 17.1 | (12.8; 22.2) |
| Crying | 203/265 | 76.6 | (71.0; 81.6) | 194/261 | 74.3 | (68.6; 79.5) | 203/265 | 76.6 | (71.0; 81.6) |
| Post-Injection 1 | 158/265 | 59.6 | (53.4; 65.6) | 137/261 | 52.5 | (46.2; 58.7) | 152/265 | 57.4 | (51.2; 63.4) |
| Post-Injection 2 | 160/265 | 60.4 | (54.2; 66.3) | 138/261 | 52.9 | (46.6; 59.1) | 135/264 | 51.1 | (44.9; 57.3) |
| Post-Injection 3 | 105/264 | 39.8 | (33.8; 46.0) | 100/261 | 38.3 | (32.4; 44.5) | 131/263 | 49.8 | (43.6; 56.0) |
| Somnolence | 195/265 | 73.6 | (67.8; 78.8) | 183/261 | 70.1 | (64.2; 75.6) | 193/265 | 72.8 | (67.0; 78.1) |
| Post-Injection 1 | 160/265 | 60.4 | (54.2; 66.3) | 143/261 | 54.8 | (48.5; 60.9) | 149/265 | 56.2 | (50.0; 62.3) |
| Post-Injection 2 | 130/265 | 49.1 | (42.9; 55.2) | 119/261 | 45.6 | (39.4; 51.8) | 116/264 | 43.9 | (37.9; 50.2) |
| Post-Injection 3 | 105/264 | 39.8 | (33.8; 46.0) | 89/261 | 34.1 | (28.4; 40.2) | 95/263 | 36.1 | (30.3; 42.2) |
| Anorexia | 148/265 | 55.8 | (49.6; 61.9) | 127/261 | 48.7 | (42.4; 54.9) | 171/265 | 64.5 | (58.4; 70.3) |
| Post-Injection 1 | 105/265 | 39.6 | (33.7; 45.8) | 84/261 | 32.2 | (26.6; 38.2) | 130/265 | 49.1 | (42.9; 55.2) |
| Post-Injection 2 | 89/265 | 33.6 | (27.9; 39.6) | 66/261 | 25.3 | (20.1; 31.0) | 94/264 | 35.6 | (29.8; 41.7) |
| Post-Injection 3 | 63/264 | 23.9 | (18.9; 29.5) | 48/261 | 18.4 | (13.9; 23.6) | 97/263 | 36.9 | (31.0; 43.0) |
| Irritability | 209/265 | 78.9 | (73.5; 83.6) | 198/261 | 75.9 | (70.2; 80.9) | 222/265 | 83.8 | (78.8; 88.0) |
| Post-Injection 1 | 172/265 | 64.9 | (58.8; 70.6) | 145/261 | 55.6 | (49.3; 61.7) | 187/265 | 70.6 | (64.7; 76.0) |
| Post-Injection 2 | 158/265 | 59.6 | (53.4; 65.6) | 134/261 | 51.3 | (45.1; 57.6) | 166/264 | 62.9 | (56.7; 68.7) |
| Post-Injection 3 | 122/264 | 46.2 | (40.1; 52.4) | 117/261 | 44.8 | (38.7; 51.1) | 156/263 | 59.3 | (53.1; 65.3) |

n: number of subjects experiencing the respective endpoint

N: number of subjects analyzed in the SafAS

M: number of subjects with available data for the relevant endpoint

Source: Table 6.3 A3L39 CSR

Table 18: Summary of unsolicited AEs within 30 days after any vaccine injection - SafAS

| | Group 1 (N=265) | | | Group 2 (N=261) | | | Group 3 (N=265) | | |
|--|--------------------|------|-------|--------------------|------|-------|--------------------|------|-------|
| | n/M | % | n AEs | n/M | % | n AEs | n/M | % | n AEs |
| Subjects experiencing at least one: | | | | | | | | | |
| Immediate unsolicited AE | 5/265 | 1.9 | 7 | 2/261 | 0.8 | 2 | 0/265 | 0.0 | 0 |
| Grade 3 Immediate unsolicited non-serious AE | 0/265 | 0.0 | 0 | 1/261 | 0.4 | 1 | 0/265 | 0.0 | 0 |
| Immediate unsolicited AR | 3/265 | 1.1 | 3 | 2/261 | 0.8 | 2 | 0/265 | 0.0 | 0 |
| Grade 3 Immediate unsolicited non-serious AR | 0/265 | 0.0 | 0 | 1/261 | 0.4 | 1 | 0/265 | 0.0 | 0 |
| Unsolicited AE | | | | | | | | | |
| | 109/265 | 41.1 | 227 | 103/261 | 39.5 | 218 | 186/265 | 70.2 | 365 |
| Unsolicited AR | | | | | | | | | |
| | 15/265 | 5.7 | 23 | 8/261 | 3.1 | 12 | 5/265 | 1.9 | 6 |
| Unsolicited non-serious AE | | | | | | | | | |
| | 103/265 | 38.9 | 218 | 99/261 | 37.9 | 210 | 184/265 | 69.4 | 356 |
| Grade 3 unsolicited non-serious AE | | | | | | | | | |
| | 8/265 | 3.0 | 12 | 6/261 | 2.3 | 8 | 11/265 | 4.2 | 13 |
| Unsolicited non-serious AR | | | | | | | | | |
| | 14/265 | 5.3 | 22 | 8/261 | 3.1 | 12 | 5/265 | 1.9 | 6 |
| Grade 3 unsolicited non-serious AR | | | | | | | | | |
| | 2/265 | 0.8 | 3 | 1/261 | 0.4 | 1 | 0/265 | 0.0 | 0 |
| Unsolicited non-serious injection site AR | | | | | | | | | |
| | 5/265 | 1.9 | 6 | 2/261 | 0.8 | 4 | 0/265 | 0.0 | 0 |
| Grade 3 unsolicited non-serious injection site AR | | | | | | | | | |
| | 2/265 | 0.8 | 3 | 0/261 | 0.0 | 0 | 0/265 | 0.0 | 0 |
| Unsolicited non-serious systemic AE | | | | | | | | | |
| | 100/265 | 37.7 | 212 | 99/261 | 37.9 | 206 | 184/265 | 69.4 | 356 |
| Grade 3 unsolicited non-serious systemic AE | | | | | | | | | |
| | 6/265 | 2.3 | 9 | 6/261 | 2.3 | 8 | 11/265 | 4.2 | 13 |
| Unsolicited non-serious systemic AR | | | | | | | | | |
| | 10/265 | 3.8 | 16 | 6/261 | 2.3 | 8 | 5/265 | 1.9 | 6 |
| Grade 3 unsolicited non-serious systemic AR | | | | | | | | | |
| | 0/265 | 0.0 | 0 | 1/261 | 0.4 | 1 | 0/265 | 0.0 | 0 |
| SAE | | | | | | | | | |
| | 9/265 | 3.4 | 9 | 8/261 | 3.1 | 8 | 7/265 | 2.6 | 9 |

n: number of subjects experiencing respective endpoint

N: number of subjects analyzed in the SafAS

M : number of subjects with available data for the relevant endpoint

n AEs: number of AEs

Source: Table 6.8 A3L39 CSR

2.3.3. Discussion on clinical aspects

Non-inferiority of Hexyon compared to Infanrix hexa in terms of seroprotection/vaccine response rates 1 month after the 3rd dose of the primary vaccination at 2, 3 and 4 months was demonstrated for PT, FHA, Hep B, and PRP antigens.

Hexyon and Infanrix hexa were highly immunogenic. Most of the subjects were seroprotected against D, T, poliovirus types 1, 2 and 3, PRP and Hep B at 1 month-post 3rd dose. Most of the subjects showed a vaccine response to PT and FHA antigens 1 month after the third dose of the primary series. These results were consistent with the results obtained in other trials with these hexavalent vaccines.

The immunogenicity data elicited by Prevenar 13 and RotaTeq were similar whether co-administered with Hexyon or Infanrix hexa.

GMCs / GMTs following the 2, 4, 6 months vaccination schedule were either in the same range or higher than after the condensed 2, 3, 4 month schedule. The successive administrations of Hexyon and Pentavac in the 'Hexa/Penta/Hexa' schedule elicited a high immune response against Hep B in subjects who had received a first Hep B vaccine dose at birth.

The safety profile of Hexyon administered at 2, 3, 4 MoA was good and similar to that of Infanrix hexa. Both vaccines were well tolerated. Similarly, the safety profile of Hexyon administered in the 'Hexa/Penta/Hexa' schedule at 2, 4, and 6 MoA was good, too.

No new safety concerns evolved. No death or AEs leading to study discontinuation were reported during the study. However, one SAE (convulsions) related to Hexyon vaccination (2nd dose) led to the subject's discontinuation for the 3rd dose.

3. CHMP overall conclusion and recommendation

Hexyon was non-inferior compared to Infanrix hexa in terms of seroprotection rates for Hep B and PRP and vaccine response rates for PT and FHA, determined at 1 month-post 3rd dose following the primary vaccination at 2, 3 and 4 months with co-administration of Prevenar 13 and RotaTeq.

Hexyon and Infanrix hexa were highly immunogenic. At least 90% of the subjects in both groups were seroprotected against D, T, poliovirus types 1, 2 and 3, PRP and Hep B at 1 month-post 3rd dose at the pre-defined short-term protection thresholds except for PRP in the Infanrix hexa subjects (86% seroprotection). At least 95% of the subjects showed a vaccine response to PT and FHA antigens 1 month after the third primary dose. In the Hexyon group, GMCs for PRP were somewhat higher and those for Hep B were somewhat lower than following vaccination with Infanrix hexa. This has already been observed in previous comparative studies using these hexavalent vaccines.

Regarding PRP, in the present study the seroprotection rate at $\geq 0.15 \mu\text{g/mL}$ in the Hexyon group (91%; 95% CI: 87; 95%) was somewhat lower than, however still in the range of, that documented in the SmPC (96%).

The seroprotection rates elicited by Prevenar 13 and RotaTeq (co-administered) were similar in the Hexyon and Infanrix hexa groups.

Seroprotection /vaccine response rates and GMCs / GMTs for D, T, poliovirus types 1, 2, and 3, PT, FHA, PRP following the 2, 4, 6 months vaccination schedule were either in the same range or higher than after the condensed 2, 3, 4 month schedule. This is known from previous studies using this vaccination schedule.

Hexyon and Pentavac administered alternately in the 'Hexa/Penta/Hexa' schedule elicited a very high immune response and long-term seroprotective Ab levels against Hep B in subjects who received a first Hep B vaccine dose at birth.

The safety profile of Hexyon was good in both vaccination schedules. No death or AEs leading to study discontinuation were reported although one SAE of convulsions related to Hexyon led to the subject's discontinuation for the subsequent dose.

In summary, no new safety concerns evolved.

Fulfilled:

(Following response to RSI:) No regulatory action required.

Not fulfilled:

Based on the data submitted, the MAH should provide a description of the additional clarifications requested as part of this procedure. (see section 'Additional clarification requested')

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- It is not clear why 2 subjects were excluded from the FAS due to improper unblinding. The MAH is asked to comment on this.

The timetable is a 30 day response timetable with clock stop.

MAH response to Request for supplementary information

Sanofi Pasteur, Sponsor of the Phase III A3L39 study was notified during the course of the study that RP Düsseldorf, Local Regulatory, was planning an inspection in the region of their responsibility. Local Regulatory decision was to inspect the Investigational site #312, Dr. Donner (Dr. Matthias Donner & Dr. Martin Lühtrath, Specialist for Pediatrics and Adolescent Medicine, Neuropediatrics – Neonatology, Nordstraße 75, 41236 Mönchengladbach, Germany); the inspection was performed on December 17, 2014 and February 04, 2015.

It was noted during the inspection that a critical defect was determined regarding the blinding of 2 patients. Therefore, the Inspectors' request was that the data of the patients concerned cannot be used.

Summary of the observation:

'The randomization (visit 1) along with the further allocation of vaccines for visits 2 and 3 is made via the company Clinphone's IWR (Interactive Web Response) system. The randomization as well as the operations for visits 2 and 3 were carried out exclusively by the unblinded study staff. An unblinding IWRS confirmation email is sent to the unblinded study team. Within this email the unblinded co-workers receive the instructions as to which medication is to be prepared for each respective patient (indication of medication numbers and vaccine names on the email). This email is filed in the unblinded study file.

A corresponding blinded confirmation email (only the indication of the medication number) is sent to the blinded co-workers (blinded IWRS confirmation).

On examining the blinded patient files the following was established: Patient [confidential information] and [confidential information] - In the blinded patient file, the unblinded IWRS confirmation emails for visits 2 or 3 were found. It was indicated on these emails which vaccine the patient received. Both email confirmations were dated and signed by Mr. Donner (blinded investigator). Both patients were thus unblinded by the study site.'

In answer to the Local Regulatory's request to not use the data of Patients [confidential information] and [confidential information], which were unblinded by the study site, Sanofi Pasteur (Sponsor of the study), acknowledged the Inspectors' recommendation and these 2 subjects were not included in the immunogenicity and safety analyses.

Immunogenicity analyses

The 2 subjects were not in the Per Protocol Analysis set as the information on the group allocation is a violation to the defined procedures for a randomized blind-observer study. For the same reason, the 2 subjects were not part of the Full Analysis set (randomized subjects who received at least one dose of the study vaccine).

Nevertheless, testing of samples drawn at the successive time points was completed, and immunogenicity data were presented as listing for individual subjects only; information on the deviation to the study procedure for these 2 subjects was briefly presented in the Clinical Study Report (CSR).

Safety analyses

The 2 subjects were not included in the Safety Analysis Set (subjects who have received the study or control vaccine) as the information on the group allocation might have created a bias in the reporting of adverse events (AE) and reactions (AR). Moreover, considering that ruling out a subject from the safety analysis might be considered as removing AE or AR impacting the global safety profile, safety data for these 2 subjects were presented as individual listings.

In Summary, due to the unblinding of the 2 patients, the decision was to not use the data of the patients in the study analyses as recommended by the Inspectors.

CHMP comment:

The exclusion of immunogenicity and safety data of 2 subjects not only from the PP set but also the FAS as well as the safety analysis set, respectively, was requested by GCP inspectors due to improper unblinding of the 2 subjects. Although in the opinion of the CHMP this is disproportionate, it is accepted. From the individual immunogenicity results of the subjects it can be inferred that both subjects reached seroprotective antibody levels at post-dose 3 against Hexyon and Rotavirus antigens.

Issue has been solved.