EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 January 2015
EMA/707880/2020

Type II variation assessment report

Procedure No. EMEA/H/C/xxxx/WS/0676

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Hexacima	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/C/002702/WS0676/0015
Hexyon	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/C/002796/WS0676/0017

Medicinal Products authorised through Art.58 procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Hexaxim	diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	EMEA/H/W/002495/WS0676/0024

Note

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

Assessment Timetable/Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	23 November 2014	23 November 2014
CXMP Rapporteur Assessment Report	26 December 2014	19 December 2014
CXMP comments	12 January 2015	12 January 2015
Rapporteur Revised Assessment Report	16 January 2015	19 January 2015
Opinion	22 January 2015	22 January 2015

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur MSD SNC submitted to the European Medicines Agency on 4 November 2014 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

Pursuant to section 10 of the CHMP "Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community" (EMEA/CHMP/5579/04), Sanofi Pasteur MSD SNC submitted to the EMA on 4 November 2014 an application for a variation[1] to the CHMP Scientific Opinion.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 and 5.1 of the SmPC with regards to 2+1 vaccination schedule combining a 2 dose priming series with a booster vaccination, further to the results of Phase III Study A3L38 (EU) conducted in healthy infants and toddlers (MEA 005). The package leaflet is updated accordingly. Additionally, the results of the primary vaccination using the 2+1 scheme in South America are described in study A3L24.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

1.2. Rationale for the proposed change

The objective of this variation is to update the DTaP-IPV-Hep B-Hib vaccine's product information with the immunogenicity and safety results from the recently completed Phase III Study ***A3L38*** (NCT-01177722, Eudra CT 2012-001054-26). This study was conducted in healthy infants and toddlers in Sweden and Finland and to investigate a 2+1 vaccination schedule (vaccinations at 3, 5, 11 to 12 MoA) in the development program. The schedules combining a 2 dose priming series with a booster vaccination are either implemented at 2, 4, and 11 to 12 MoA (e.g. Italy, Austria and, more recently, France), or at 3, 5, and 11 to 12 MoA (e.g. in Finland and Sweden).

The supplement also includes immunogenicity data collected during a post-hoc exploratory analysis of immunogenicity in Study ***A3L24*** *(initially discussed during MAA –D150)*, a primary series investigation of Hexacima versus Infanrix hexa, with concomitant administration of Prevenar at 2, 4, and 6 MoA and Rotarix at 2 and 4 MoA, conducted in healthy infants in Colombia and Costa Rica (U1111-1111-5801). The data from the A3L24 Addendum Report are included to further characterize the immune response of hexavalent combined vaccines following administration of the second dose of primary immunization, as well as an indirect descriptive comparison of the immune response to the pertussis (PT), filamentous

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/2008

haemagglutinin (FHA) and PRP antigens in South American (Study A3L24, at 2 and 4 MoA) and Scandinavian infants (A3L38, at 3 and 5 MoA) one month after the administration of the second dose.

2. Overall conclusion and impact on the benefit/risk balance

The data presented with this worksharing are sufficient to implement the changes to the SmPC as suggested by the MAH

- provided that satisfactory answers are given to the 'other concerns' as detailed in section 5.

The benefit-risk balance of Hexaxim, Hexacima and Hexyon, remains positive.

No new safety concerns emerged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 and 5.1 of the SmPC with regards to 2+1 vaccination schedule combining a 2 dose priming series with a booster vaccination, further to the results of Phase III Study A3L38 conducted in healthy infants and toddlers (MEA 005). The package leaflet is updated accordingly.

☒ is recommended for approval.

The requested worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet.

4. Scientific discussion

4.1. Introduction

The initial authorization of Hexacima/Hexyon was based on data from studies conducted exclusively outside the EU and for the most parts not including Caucasians. Although the general applicability of data was accepted the company proposed several studies – including A3L38 – in Caucasians to show data similarity.

Exploratory analysis of anti-PT, anti-FHA and anti-PRP in study A3L24

The assessment of the immune response in the Phase III A3L24 was mainly based on the blood samples taken 1 month post-dose 3, and there were no objectives for describing the immunogenicity after the second dose of DTaP-IPV-Hep B-PRP-T. However, a blood sample had been taken 1 month post-dose 2 at 5 MoA to assess the immune response against rotavirus antigen on a subset of subjects (68 planned subjects in each batch group, i.e., 204 subjects in DTaP-IPV-Hep B-PRP-T pooled batches group; and 68

subjects in control vaccine group). In order to further describe the immunogenicity of the hexavalent paediatric combination vaccines administered in A3L24, complementary testing on remaining post-dose 2 sera were suggested by Sanofi Pasteur. The exploratory analyses described in the sections below were not planned in the A3L24 protocol.

4.2. Clinical Pharmacology aspects

Not applicable

4.3. Clinical Efficacy aspects

4.3.1. Methods – analysis of data submitted

Study A3L38

The study was part of the pediatric investigational plan as agreed by the EMA.

Design: Phase III, randomized, observer-blinded, multicentre study carried out in Finland and Sweden in healthy infants 3 months old at enrollment between 01 November 2012 (FVFS) and 10 January 2014 (LVLS).

A total of 554 Subjects were 1 : 1 randomized to one of the following groups (277 subjects per group):

- Group 1, Hexacima/Hexyon (DTaP-IPV-HB-Hib) + Prevenar 13
- Group 2, Infanrix Hexa (DTaP-IPV-HB-Hib reference vaccine) + Prevenar 13

All subjects received 3 doses of either DTaP-IPV-HB-Hib vaccine each co-administered with Prevenar 13 at 3, 5, and 11 to 12 months of age (2 + 1 schedule).

Overall, there were 50.2% of male and 49.8% of female subjects. The mean age of the subjects at vaccine Dose 1 was 89.3 days (range 85-95 days); the mean weight of subjects was 6.1 kg (range 4-9 kg). 95% of subjects were White, 4% of mixed origin, 1% others.

Blood sampling was performed at 4 time points: prior to dose 1, at 1 month post-dose 2, prior to and at 1 month post-dose 3.

Infants may have received a rotavirus vaccination as an additional vaccine, but not as part of the study protocol.

Inclusion criteria:

A potential subject had to meet **all** of the following criteria to be considered for trial enrollment:

- Aged 85 to 95 days on the day of the first study visit
- Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 2.5 kg
- Healthy subjects as established by medical history and clinical examination before entering into the study
- Informed consent form has been signed and dated by the parent(s) or other legally acceptable representative
- Subject and parent/legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures

- Covered by health insurance

Exclusion Criteria

A potential subject meeting **any** of the following criteria was ineligible for trial enrollment:

- Participation at the time of study enrollment (or in the 4 weeks preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
- Receipt of any vaccine in the 4 weeks preceding each trial vaccination or planned receipt of any vaccine in the 4 weeks following each trial vaccination (except rotavirus vaccination)
- Previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilus influenzae type b or pneumococcal infections with another vaccine(s)
- Receipt of immune globulins, blood or blood-derived products since birth
- Known or suspected congenital, hereditary or acquired immunodeficiency or other immunosuppressive or immunodeficient condition
- Receipt of immunosuppressive therapy or other immune-modifying drugs, such as anti-cancer chemotherapy or radiation therapy, since birth; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks since birth).
- Known personal or maternal history of hepatitis B (HBsAg) or hepatitis C seropositivity
- History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilus influenza type b, or pneumococcal infection(s), confirmed either clinically, serologically, or microbiologically
- Known systemic hypersensitivity to any of the vaccine components, or history of a lifethreatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances
- History of seizures or encephalopathy
- Known thrombocytopenia, as reported by the parent/legally acceptable representative
- Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination
- Subjects in an emergency setting, or hospitalized involuntarily
- Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
- Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature $\geq$ 38.0° C). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
- Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

Primary objective

- Non-inferiority of Hexacima as compared to Infanrix Hexa, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates, respectively, to all antigens 1 month after the 3rd dose (2+1 schedule).

Secondary objectives

Immunogenicity: antibody (Ab) concentrations

- against PT and FHA before the 1st dose
- against all antigens of hexavalent combined vaccines (D, T, poliovirus type 1, 2, and 3, Hep B, PRP, PT, and FHA) before and 1 month after the 3rd dose
- against pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F at 1 month post-Dose 3 (in a subset of 366 subjects, i.e. 183 subjects/group).

Safety: description of safety profile after each dose in both groups

Observational objectives:

- Non-inferiority of Hexacima as compared to Infanrix Hexa, both co-administered with Prevenar 13, in terms of seroprotection or vaccine response rates, respectively, to all antigens 1 month after the 2nd dose.
- Description of immune response against all antigens of hexavalent combined vaccines at 1 month post-dose 2.

Primary endpoints:

Seroprotection for D, T, poliovirus type 1, 2, and 3, Hep B, and PRP at 1 month post-dose 3 was defined as:

- Anti-D and anti-T antibody (Ab) concentrations ≥ 0.1 international units (IU)/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL
- Anti-PRP Ab concentrations ≥ 1 µg/mL

Vaccine response for PT and FHA at 1 month post-Dose 3 was defined as:

- Post-dose 3 Ab concentrations ≥ 4 × Lower Level Of Quantitation (LLOQ), if pre-dose 1 Ab concentrations (=baseline) < 4 × LLOQ
- Post-dose 3 Ab concentrations ≥ baseline, if baseline ≥ 4 × LLOQ

➔ remark: for PT and FHA, LLOQ was equal to 2 EU/mL

Secondary endpoints:

Immunogenicity, pre-Dose 1:

- Ab concentrations against PT and FHA
- Ab concentrations against PT and FHA ≥ LLOQ

Immunogenicity, pre-Dose 3:

- Ab concentrations/titers for each antigen (except pneumococcal serotypes)
- Ab concentrations/titers above a cut-off:
    - Anti-D and anti-T Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
    - Anti-PT and anti-FHA Ab concentrations ≥ LLOQ and ≥ 2 × LLOQ (4 EU/mL)

- Anti-poliovirus 1, 2, and 3 titers ≥ 8 (1/dil)
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PRP Ab concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

Immunogenicity, post-Dose 3:

- Ab concentrations/titers for each valence
- Ab concentrations/titers above a cut-off:
  - Anti-D and anti-T Ab concentrations ≥ 0.01 IU/mL and ≥ 1 IU/mL
  - Anti-PT and anti-FHA Ab concentrations ≥ 2 × LLOQ (4 EU/mL)
  - Anti-Hep B Ab concentrations ≥ 100 mIU/mL
  - Anti-PRP Ab concentrations ≥ 0.15 μg/mL
  - Anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F concentrations ≥ 0.35 μg/mL (in a subset of subjects)
- Individual Ab concentration ratios for PT and FHA (post-dose 3/baseline and post-dose 3/pre-dose 3)
- Individual Ab concentration/titer ratios for D, T, poliovirus 1, 2, and 3, Hep B, PRP (post-dose 3/pre-dose 3)
- Seroconversion for anti-PT and anti-FHA, defined as anti-PT and anti-FHA ≥ 4-fold Ab concentrations increase from baseline to post-dose 3
- Booster response for anti-PT and anti-FHA defined as follows:
  - Post-Dose 3 Ab concentrations ≥ 4-fold rise if pre-dose 3 Ab concentrations < 4x LLOQ
  - Post-Dose 3 Ab concentrations ≥ 2-fold rise if pre-dose 3 Ab concentrations ≥ 4x LLOQ

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

Safety:

- unsolicited AEs reported within 30 minutes after each dose
- solicited injection site and systemic reactions occurring up to 7 days after each dose
- unsolicited (spontaneously reported) AEs up to 30 days after each dose
- SAEs throughout the trial period (inclusion until 1 month post-Dose 3)

Observational endpoints (post-Dose 2):

- Seroprotection rates for D, T, Polio 1, 2, and 3, Hep B, and PRP defined as
    - Anti-D and anti-T Ab concentrations ≥ 0.01 IU/mL
    - Anti-Polio 1, 2, and 3 Ab titers ≥ 8 (1/dil)
    - Anti-Hep B Ab concentrations ≥ 10 mIU/mL
    - Anti-PRP Ab concentrations ≥ 0.15 µg/mL
- Vaccine response rates for PT and FHA defined as
    - Post-Dose 2 Ab concentrations ≥ 4× LLOQ, if pre-Dose 1 Ab concentrations < 4× LLOQ
    - Post-Dose 2 Ab concentrations ≥ pre-Dose 1, if pre-Dose 1 Ab concentrations ≥ 4× LLOQ
- Descriptive analyses:
    - Ab concentrations/titers for each valence (except pneumococcal serotypes)
    - For PT and FHA: Ab titers ≥ 2 × LLOQ (4 EU/mL)

    ➔ Management of extreme values (< LLOQ and ≥ ULOQ):

    - If a value was < LLOQ, then the computed value LLOQ/2 was used
    - If a value was ≥ ULOQ, then the computed value ULOQ was used

Immunogenicity assays used in the study:

- Diphtheria: Micrometabolic Inhibition Test using Vero cells and a pH indicator for development (MIT-pH)
- Tetanus: ELISA
- Pertussis toxin (PT) and FHA: ELISAs
- Poliovirus: Micrometabolic Inhibition Test (MIT) using wild type poliovirus strains 1, 2, and 3 and Vero cells (African green monkey kidney cells); were expressed as titers (1/dilution).
- Hepatitis B: antigen sandwich ELISA with chemiluminescence detection (VITROS ECi/ECiQ Immunodiagnostic System)
- Haemophilus influenzae type b: Polyribosylribitol phosphate (PRP) RIA

- Streptococcus pneumoniae capsular polysaccharide (PS) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F): ELISA

Remark: In (most of the) previous studies, diphtheria MIT assay using cell survival assessed by crystal violet staining of Vero cells (MIT-CV) was used. The MIT-pH used in the current study (introduced as Amendment No. 2 of clinical study protocol) was shown to be concordant to the MIT-CV assay; the respective validation report was provided by the sponsor within this variation/ worksharing.

Table 1 Correlates or surrogates of protection applied in study A3L38

Antigen	**Antibody titer as level of seroprotection/ seroconversion/ vaccine and booster response**	**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 type 1, 2, and 3	≥8 (1/dil)	Established correlate
PRP (HiB)	≥0.15 µg/mL (short-term) ≥1µg/mL (long-term)	Established correlate
Hep B	≥10 IU/mL (minimum) ≥100 IU/mL (optimum)	Established correlate
PT, FHA	Vaccine response: ≥4× LLOQ (=8 EU/mL) (at least baseline if baseline ≥4 x LLOQ)	Accepted surrogate
PT, FHA	Seroconversion: At least 4-fold increase from baseline to 1 month post-3rd dose	Accepted surrogate
PT, FHA	Booster response: At least 4-fold increase if pre-booster level < 4× LLOQ, or 2-fold increase if pre-booster level ≥4× LLOQ	Accepted surrogate
Pneumococcal serotypes	≥0.35 µg/mL	Established correlate

Statistical analysis (primary endpoint):

The difference [Hexacima – Infanrix Hexa] in seroprotection/vaccine response rates was calculated. The relevant limit for non-inferiority was −10% for D, T, Hep B, PRP, PT, and FHA antigens and –5% for poliovirus antigens, based on the lower bound of the 2-sided 95% CI of the difference of the seroprotection/vaccine response rates.

The hypothesis of non-inferiority was tested on the PP analysis set (subjects vaccinated according to protocol) at 1 month post-dose 3 (PP1, primary endpoint). It was repeated in the PP analysis set at 1 month post-dose 2 (PP2, secondary) and in the Full analysis set (FAS, subjects who received at least one vaccine dose).

Sample Size and Power Calculation

The sample size calculation was based on the test for the primary objective. A total of 554 subjects were to be included in the study, 277 per group. Using an alpha level of 2.5% (onesided hypotheses), and

under the assumption that approximately 80% (N=222 per group) of subjects were evaluable, the overall power was > 90% for non-inferiority of Hexacima versus Infanrix Hexa in terms of immunogenicity at 1 month post-Dose 3 (Table 2).

Table 2 Power for non-inferiority post-Dose 3

Endpoints	Expected reference seroprotection/ vaccine response rate	Clinically acceptable margin for non-inferiority (δ)	Power achieved with N=222
Anti-Hep B ≥ 10 mIU/mL	97%	10%	99.96%
Anti-D ≥ 0.1 IU/mL	95%	10%	99.27%
Anti-T ≥ 0.1 IU/mL	97%	10%	99.96%
Anti-PRP ≥1 µg/mL	96%	10%	99.76%
Anti-Polio 1 ≥ 8 (1/dil)	99%	5%	97.44%
Anti-Polio 2 ≥ 8 (1/dil)	99%	5%	97.44%
Anti-Polio 3 ≥ 8 (1/dil)	99%	5%	97.44%
Anti-PT vaccine response	95%	10%	99.27%
Anti-FHA vaccine response	95%	10%	99.27%
Overall power			> 90%

(Source: Table 3.7, A3L38 clinical study report [CSR])

Study A3L24

Post-hoc analysis of blood draws 1 month post 2nd dose in a subset of children. For details of study conduct please see the EPAR.

Use of established assays for anti-PT, anti-FHA (ELISA) and anti-PRP (RIA). Descriptive analysis of immunogenicity, comparability at baseline and comparison with post-dose 1 and 3 data to assure representativeness of the subset, calculation of 95% CIs, RCDCs plotted.

Exploratory endpoints:

- PT, FHA
    - Ab titer
    - Ab titer ratio
    - Ab titer ≥ LLOQ
    - Ab titer ≥ 4 EU/mL
    - Seroconversion: ≥ 4-fold titer increase from baseline to post-dose 3
    - Vaccine response: Response to pertussis antigens (PT, FHA) defined as anti-PT or anti-FHA≥ Lower Limit of Quantitation (LLOQ) in initially seronegative subjects, or at least persistence (post-titer ≥ pre-titer) of the antibody titer in initially seropositive subjects (titer ≥ LLOQ)
- PRP
    - Ab titer
    - Ab titer ≥ 0.15 µg/mL
    - Ab titer ≥ 1 µg/mL

4.3.2. Results

Study A3L38

Trial population:

A total of 554 subjects were presented at 1st visit of which 551 (99.5%) were eligible, 3 subjects were excluded because of acute illness/infection (2 subjects) and a hernia (1 subject).

A total of 546 subjects vaccinated at visit 1 (Hexacima: 271 subjects; Infanrix hexa: 275 subjects) were included in the FAS; 5 eligible subjects did not receive any study vaccine because of a missing blood sample at visit 1. A total of 533 subjects (97.6%) completed the study. Reasons for discontinuation were mainly voluntary withdrawal (10 subjects) or SAEs (3 subjects; refer to safety section for details).

A total of 49 subjects (22 in Hexacima group; 27 in Infanrix hexa group) were excluded from the PP1 because of protocol violation, e.g. vaccination outside specified time interval, missing vaccine injection or blood sampling etc. Thus, the PP1 comprised 497 subjects (249 in Hexacima; 248 in Infanrix hexa group), the PP2 (at post-Dose 2) comprised 495 subjects (249 in Hexacima, 246 in Infanrix hexa group).

Immunogenicity (primary endpoints):

For the primary objective, non-inferiority of Hexacima as compared to Infanrix Hexa was assessed in terms of seroprotection rates (for D, T, Hep B, PRP and Polio 1, 2 and 3) or vaccine response rates (for PT and FHA). Antibody thresholds applied were either established correlates (for D, T, Hep B, PRP and Polio 1, 2 and 3) or accepted surrogates (for PT and FHA) of protection (see Table 1). The primary analysis was based on the **PP1** subjects at **post-dose 3**.

Minimum 93% of subjects in both vaccine groups showed seroprotection or vaccine response (with CIs between 90 and 100%), respectively, except for PRP in the Infanrix Hexa group for which a seroprotection rate of 85.2% (CI, 80.2; 89.4) was found. For Hexacima, a higher PRP seroprotection rate of 93.5% was observed at 1 month post-dose 3 (CI, 89.6; 96.2).

Compared to Infanrix Hexa, Hexacima showed somewhat lower response or seroprotection rates for PT (98% vs. 99.6%) and Hep B (96.4% vs. 99.6%), each with overlapping CI.

Hexacima was non-inferior to Infanrix Hexa for every antigen since the lower bounds of the 95% CI of the difference in seroprotection/ vaccine response percentages between Hexacima and Infanrix Hexa for each valence was greater than −δ (i.e., −10 for D, T, PT, FHA, B, and PRP, and −5 for Polio) Table 3).

Very similar results were obtained for non-inferiority testing on full analysis set at 1 month-post dose 3 (for further details please refer to A3L38 CSR, Table 9.23).

Immunogenicity against DTaPHepBHiB antigens (secondary and observational endpoints; Table 3 to Table 7**):**

Non-inferiority of Hexacima compared to Infanrix Hexa was also given at 1 month post-Dose 2 except for poliovirus type 1 and 2 for which the lower bounds of the 95% CI of the difference in seroprotection rates between both vaccines was lower than −5. Please note that for D, T, and PRP short-term protection levels of 0.01 IU/mL (D, T) and 0.15 µg/mL (PRP) were used for non-inferiority testing at 1 month post-Dose 2.

Diphtheria: 100 and 99% of subjects in the Hexacima and Infanrix Hexa group, respectively, showed (long-term) seroprotection levels ≥ 0.1 IU/mL at 1 month post-Dose 3. At this time point, higher GMCs of 1.7 IU/mL were achieved in the Hexacima group compared to 1.2 IU/mL in the Infanrix Hexa group (non-overlapping CI). At 1 month post-Dose 2, 99.6% of subjects in both groups showed short-term

seroprotection levels of ≥ 0.01 IU/mL. These levels were still seen in 98% of subjects in both groups 6 months later at pre-booster time point.

Tetanus: 100% of subjects in both groups showed (long-term) seroprotection at ≥ 0.1 IU/mL at 1 month post-dose 3. At this time point, similar GMCs of 2.2 and 2.4 IU/mL were achieved in the Hexacima and Infanrix hexa group, respectively. All subjects in both groups showed short-term seroprotection at ≥ 0.01 IU/mL at 1 month post-dose 2. These levels were still detected in all subjects of both groups at pre-dose 3.

PT, FHA: Between 98 and 100% of subjects in both groups showed vaccine response as defined by antibody levels ≥ 4x LLOQ (i.e., ≥ 8 EU/mL) at 1 month post-3rd dose. At this time point, subjects of Hexacima and Infanrix hexa groups showed GMC of 91 and 129 EU/mL for PT and 148 and 167 EU/mL for FHA, respectively. The corresponding antibody levels at 1 month post-dose 2 were in the same range or somewhat lower, i.e, at 105 and 106 EU/mL for PT and 95 and 98 EU/mL for FHA, respectively. Until pre-dose-3, these levels decreased to 21 and 24 EU/mL for PT and 31 and 29 EU/mL for FHA in the Hexacima and Infanrix hexa group, respectively.

In the Hexacima and Infanrix Hexa groups, 48 respective 45% and 80 respective 82% of subjects had detectable PT and FHA levels ≥ LLOQ (i.e., ≥ 2EU/mL) already at baseline (=pre-Dose 1). The GMC for PT lay at 2.5 and 2.2 EU/mL in the Hexacima and Infanrix hexa group, respectively. For FHA, GMC of 3.7 and 3.9 EU/mL, respectively, were found. In both groups, subjects showed antibody increases of at least 37-fold from baseline to 1 month post-dose 3 indicating a significant seroconversion for both antigens. Additionally, both groups showed a considerable booster response as mean PT and FHA antibody GMC increased at least 4.4-fold from pre-dose 3 to 1 month post-dose 3.

Polio type 1, 2, and 3: 99 to 100% of subjects in both groups showed protective antibody levels ≥ 8 (1/dil.) against polio type 1, 2, and 3 at 1 month post-dose 3. After 2 vaccine doses, seroprotection was achieved by at least 90% of subjects in both groups. High anti-polio 1, 2, and 3 titres of >1200 (1/dil.) were achieved following 3 vaccine doses in both groups. Respective titres lay in the range of 60 - 142 (1/dil.) at 1 month post-dose 2 and decreased to 14 – 27 (1/dil.) until pre-3rd dose. Generally, geometric mean anti-polio titres of the Hexacima group were lower than those of the Infanrix hexa group (mostly non-overlapping CI).

Hep B: 96.4 vs. 99.6 % of subjects in the Hexacima and Infanrix hexa group, respectively, showed seroprotective anti-Hep B levels ≥ 10mIU/mL at 1 month post-dose 3 (with overlapping CI). Corresponding seroprotection rates lay at 97 and 98% at 1 month post-2nd dose and at 88 and 98%, respectively, at pre-dose 3 (the latter with non-overlapping CI). At post-3rd dose, 45% of subjects in the Hexacima group compared to 81% in the Infanrix hexa group reached optimal anti-Hep B levels ≥ 100mIU/mL.

Compared to Infanrix hexa, much lower GMC (1370 vs. 5015 mIU/mL) were achieved in the Hexacima group at 1 month post-dose 3. Similarly, at 1 month post-dose 2 and prior to dose 3, GMC were lower in the Hexacima group (401 vs. 699 and 77 vs. 260 mIU/mL, respectively; with non-overlapping CI at each time point).

PRP: Following 3 doses of Hexacima or Infanrix hexa, 94 vs. 85% of subjects showed seroprotection against PRP at ≥ 1 µg/mL. At post-dose 2, 72 and 58% of subjects in the Hexacima and Infanrix hexa group, respectively, showed short-term protection at antibody levels ≥ 0.15 µg/mL. These rates decreased to 51 and 41% in the Hexacima and Infanrix hexa group, respectively, until pre-dose 3. Generally, GMC were about twice as high in the Hexacima group compared to the Infanrix hexa group: 0.51 vs. 0.23 µg/mL at post-dose 2 and 9.7 vs. 5.6 µg/mL at post-dose 3 (with non-overlapping CI).

Immunogenicity against Prevenar 13 (secondary endpoints; Table 8 and Table 9**):**

Immunogenicity against Prevenar 13 antigens was assessed in a subset of vaccinees (164 and 162 subjects in the Hexacima and Infanrix hexa PP1 group, respectively) at 1 month post-dose 3 only. Please note that no functional antibody assay (OPA) was performed on sera obtained in study A3L38.

Seroprotective antibody levels of $\geq$ 0.35 µg/mL against every serotype were obtained in 98 to 100% of subjects in both groups except for serotype 3, for which seroprotection rates of 86 and 88% were achieved in the Hexacima and Infanrix hexa group, respectively. The GMCs ranged from 0.7 to 6.8 µg/mL in the Hexacima group and from 0.8 to 7.8 µg/mL in the Infanrix hexa group. However, for many serotypes, somewhat lower GMC were found in the Hexacima group compared to the Infanrix Hexa group (with non-overlapping CI).

Assessor's comment:

The immunogenicity of Hexacima in terms of seroprotection/ vaccine response rate was non-inferior to that of Infanrix hexa for every antigen at 1 month after the 3rd dose. Both hexavalent vaccines elicited similar antibody responses against each valence following the 2+1 vaccination scheme with co-administration of Prevenar 13. The protective antibody titers chosen by the sponsor to calculate seroprotection/vaccine response rates were accepted surrogates (for PT and FHA) or established correlates (other antigens) of protection.

Compared to Infanrix Hexa, generally lower GMC were achieved for Hep B and polio type 1, 2, and 3 but higher GMC for D and PRP following vaccination with Hexacima. Additionally, in the Hexacima group, lower antibody levels were seen for several PCV13 serotypes. Despite these differences in GM titers, overall both hexavalent vaccines induced very similar seroprotection/vaccine response rates following the primary (2 doses) and booster vaccination indicating that Hexacima and Infanrix hexa provide equal protection against diseases to infants following the 2+1 vaccination schedule at 3, 5, and 11 to 12 MoA.

Following co-administration of PCV13, Hexacima and Infanrix hexa equally induced antibody titers $\geq$ 0.35 µg/ml against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in >95% of subjects. The respective seroresponse against serotype 3 was lower, i.e. 86% in the Hexacima group and 88% in the Infanrix hexa group. The results confirm that Hexacima can be equally well administered concomitantly with Prevenar 13 in the 2+1 as in the 3+1 vaccination schedule.

Table 3: Non-inferiority of seroprotection / vaccine response rates of Hexacima vs. Infanrix hexa at one month post-Dose 3 - PP1 (primary objective)

		Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=248)			Hexacima minus Infanrix hexa (i.e. Test - Reference)			
Component	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**% observed**	**2-sided (95% CI) †**	**Clinical delta (δ%)**	**Conclusion ‡**
Anti-D (MIT - IU/mL)	**≥ 0.1 IU/mL**	248/248	100.0	(98.5; 100.0)	244/246	99.2	(97.1; 99.9)	0.8	(-0.82; 2.92)	10	Reject H0
Anti-T (ELISA - IU/mL)	**≥ 0.1 IU/mL**	248/248	100.0	(98.5; 100.0)	246/246	100.0	(98.5; 100.0)	0.0	(-1.53; 1.54)	10	Reject H0
Anti-PT (ELISA -EU/mL)	**Vaccine response***	240/245	98.0	(95.3; 99.3)	242/243	99.6	(97.7; 100.0)	-1.6	(-4.30; 0.58)	10	Reject H0
Anti-FHA (ELISA -EU/mL)	**Vaccine response***	247/247	100.0	(98.5; 100.0)	241/242	99.6	(97.7; 100.0)	0.4	(-1.16; 2.30)	10	Reject H0
Anti-Polio 1 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	248/248	100.0	(98.5; 100.0)	246/246	100.0	(98.5; 100.0)	0.0	(-1.53; 1.54)	5	Reject H0
Anti-Polio 2 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	246/246	100.0	(98.5; 100.0)	246/246	100.0	(98.5; 100.0)	0.0	(-1.54; 1.54)	5	Reject H0
Anti-Polio 3 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	247/248	99.6	(97.8; 100.0)	245/246	99.6	(97.8; 100.0)	0.0	(-1.87; 1.89)	5	Reject H0
Anti-Hep B (VITROS ECi - mIU/mL)	**≥ 10 mIU/mL**	240/249	96.4	(93.2; 98.3)	246/247	99.6	(97.8; 100.0)	-3.2	(-6.34; -0.69)	10	Reject H0
Anti-PRP (RIA - µg/mL)	**≥ 1 µg/mL**	229/245	93.5	(89.6; 96.2)	208/244	85.2	(80.2; 89.4)	8.2	(2.77; 13.80)	10	Reject H0

N: Number of subjects analyzed according to the PP1; n: number of subjects; M: number of subjects available for the endpoint
%: percentages were calculated according to the subjects available for the endpoint; 2-sided 95% CI on the point estimate of seroconversion, derived by the normal approximation to the binomial.
* Vaccine response for PT and FHA defined as follows: post-Dose 3 Ab concentrations ≥ 4 × LLOQ, if pre-Dose 1 Ab concentrations < 4 × LLOQ; Post-Dose 3 Ab concentrations ≥ pre-Dose 1 Ab concentrations, if pre-Dose 1 Ab concentrations ≥ 4 × 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

(Source: Table 5.1, A3L38 CSR)

Table 4 : Seroprotection/seroconversion/booster response rates of Hexacima vs. Infanrix hexa - PP1 (secondary objectives)

			Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=248)		
Component	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti-D (MIT- IU/mL)	**Pre-Dose 3**	**≥ 0.01 IU/mL**	237/241	98.3	(95.8; 99.5)	235/241	97.5	(94.7; 99.1)
		≥ 0.1 IU/mL	96/241	39.8	(33.6; 46.3)	54/241	22.4	(17.3; 28.2)
	Post-Dose 3	**≥ 0.01 IU/mL**	248/248	100.0	(98.5; 100.0)	245/246	99.6	(97.8; 100.0)
		≥ 1.0 IU/mL	204/248	82.3	(76.9; 86.8)	172/246	69.9	(63.8; 75.6)
Anti-T (ELISA - IU/mL)	**Pre-Dose 3**	**≥ 0.01 IU/mL**	235/235	100.0	(98.4; 100.0)	239/239	100.0	(98.5; 100.0)
		≥ 0.1 IU/mL	138/235	58.7	(52.1; 65.1)	166/239	69.5	(63.2; 75.2)
	Post-Dose 3	**≥ 0.01 IU/mL**	248/248	100.0	(98.5; 100.0)	246/246	100.0	(98.5; 100.0)
		≥ 1.0 IU/mL	212/248	85.5	(80.5; 89.6)	215/246	87.4	(82.6; 91.3)
Anti- PT (ELISA - EU/mL)	**Pre-Dose 1**	**≥ 2 EU/mL**	118/245	48.2	(41.8; 54.6)	111/245	45.3	(39.0; 51.8)
	Pre-Dose 3	**≥ 2 EU/mL**	232/233	99.6	(97.6; 100.0)	237/237	100.0	(98.5; 100.0)
		≥ 4 EU/mL	232/233	99.6	(97.6; 100.0)	235/237	99.2	(97.0; 99.9)
	Post-Dose 3	**≥ 4 EU/mL**	249/249	100.0	(98.5; 100.0)	246/246	100.0	(98.5; 100.0)
	Post-Dose 3/ Pre-Dose 1	**Seroconversion***	231/245	94.3	(90.6; 96.8)	232/243	95.5	(92.0; 97.7)
	Post-Dose 3/ Pre-Dose 3	**Booster response†**	219/233	94.0	(90.1; 96.7)	234/236	99.2	(97.0; 99.9)

(Table 4, continued)

			Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=248)		
Component	**Timepoint**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Anti- FHA (ELISA - EU/mL)	**Pre-Dose 1**	**≥ 2 EU/mL**	197/247	79.8	(74.2; 84.6)	198/243	81.5	(76.0; 86.2)
	Pre-Dose 3	**≥ 2 EU/mL**	237/237	100.0	(98.5; 100.0)	237/237	100.0	(98.5; 100.0)
		≥ 4 EU/mL	237/237	100.0	(98.5; 100.0)	237/237	100.0	(98.5; 100.0)
	Post-Dose 3	**≥ 4 EU/mL**	249/249	100.0	(98.5; 100.0)	247/247	100.0	(98.5; 100.0)
	Post-Dose 3/ Pre-Dose 1	**Seroconversion***	241/247	97.6	(94.8; 99.1)	228/242	94.2	(90.5; 96.8)
	Post-Dose 3/ Pre-Dose 3	**Booster response†**	229/237	96.6	(93.5; 98.5)	226/236	95.8	(92.3; 97.9)
Anti-Polio 1 (MIT-WT - 1/dil)	**Pre-Dose 3**	**≥ 8 (1/dil)**	151/240	62.9	(56.5; 69.0)	184/240	76.7	(70.8; 81.9)
Anti-Polio 2 (MIT-WT - 1/dil)	**Pre-Dose 3**	**≥ 8 (1/dil)**	145/239	60.7	(54.2; 66.9)	173/238	72.7	(66.6; 78.2)
Anti-Polio 3 (MIT-WT - 1/dil)	**Pre-Dose 3**	**≥ 8 (1/dil)**	158/239	66.1	(59.7; 72.1)	182/239	76.2	(70.2; 81.4)
Anti-Hep B (VITROS ECi - mIU/mL)	**Pre-Dose 3**	**≥ 10 mIU/mL**	211/241	87.6	(82.7; 91.4)	235/241	97.5	(94.7; 99.1)
		≥ 100 mIU/mL	109/241	45.2	(38.8; 51.7)	194/241	80.5	(74.9; 85.3)
	Post-Dose 3	**≥ 100 mIU/mL**	227/249	91.2	(86.9; 94.4)	242/247	98.0	(95.3; 99.3)
Anti-PRP RIA (µg/mL)	**Pre-Dose 3**	**≥ 0.15 µg/mL**	121/239	50.6	(44.1; 57.1)	98/240	40.8	(34.6; 47.3)
		≥ 1.0 µg/mL	35/239	14.6	(10.4; 19.8)	19/240	7.9	(4.8; 12.1)
	Post-Dose 3	**≥ 0.15 µg/mL**	244/245	99.6	(97.7; 100.0)	241/244	98.8	(96.4; 99.7)

N: number of subjects calculated according to the PPP1; n: number of subjects; M: number of subjects available for the endpoint

%: percentages and 95% CIs were calculated according to the subjects available for the endpoint

* Seroconversion for PT and FHA defined as: ≥ 4-fold Ab concentrations increase from pre-Dose 1 to post-Dose 3

† Booster response for PT and FHA defined as: Post-Dose 3 Ab concentrations ≥ 4-fold rise if pre-Dose 3 Ab concentrations < 4x LLOQ; Post-Dose 3 Ab concentrations ≥ 2-fold rise if pre-Dose 3 Ab concentrations ≥ 4x LLOQ.

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

(Source: Table 5.2, A3L38 CSR)

Table 5 Non-inferiority of seroprotection/vaccine response rates of Hexacima vs. Infanrix hexa at one month post-Dose 2 - PP2 (observational objective)

		Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=246)			Hexacima minus Infanrix hexa (i.e. Test - Reference)			
Component	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**% observed**	**2-sided (95% CI) †**	**Clinical delta (δ%)**	**Conclusion ‡**
Anti-D (MIT - IU/mL)	**≥ 0.01 IU/mL**	239/240	99.6	(97.7; 100.0)	240/241	99.6	(97.7; 100.0)	-0.0	(-1.94; 1.93)	10	Reject H0
Anti-T (ELISA - IU/mL)	**≥ 0.01 IU/mL**	237/237	100.0	(98.5; 100.0)	235/235	100.0	(98.4; 100.0)	0.0	(-1.60; 1.61)	10	Reject H0
Anti-PT (ELISA -EU/mL)	**Vaccine response***	239/243	98.4	(95.8; 99.5)	237/239	99.2	(97.0; 99.9)	-0.8	(-3.39; 1.57)	10	Reject H0
Anti-FHA (ELISA -EU/mL)	**Vaccine response***	240/241	99.6	(97.7; 100.0)	231/235	98.3	(95.7; 99.5)	1.3	(-0.88; 3.90)	10	Reject H0
Anti-Polio 1 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	216/238	90.8	(86.3; 94.1)	227/238	95.4	(91.9; 97.7)	-4.6	(-9.42; 0.00)	5	Non Reject H0
Anti-Polio 2 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	226/238	95.0	(91.4; 97.4)	230/238	96.6	(93.5; 98.5)	-1.7	(-5.61; 2.11)	5	Non Reject H0
Anti-Polio 3 (MIT-WT - 1/dil)	**≥ 8 (1/dil)**	231/239	96.7	(93.5; 98.5)	234/238	98.3	(95.8; 99.5)	-1.7	(-4.95; 1.37)	5	Reject H0
Anti-Hep B (VITROS ECi - mIU/mL)	**≥ 10 mIU/mL**	239/246	97.2	(94.2; 98.8)	241/245	98.4	(95.9; 99.6)	-1.2	(-4.29; 1.67)	10	Reject H0
Anti-PRP (RIA - µg/mL)	**≥ 0.15 µg/mL**	171/239	71.5	(65.4; 77.2)	139/240	57.9	(51.4; 64.2)	13.6	(5.08; 21.91)	10	Reject H0

N: Number of subjects analyzed according to the PP2; n: number of subjects; M: number of subjects available for the endpoint

%: percentages were calculated according to the subjects available for the endpoint.

* Vaccine response for PT and FHA defined as: post-Dose 2 Ab concentrations ≥ 4 × LLOQ, if pre-Dose 1 Ab concentrations < 4 × LLOQ; Post-Dose 2 Ab concentrations ≥ pre-Dose 1, if pre-Dose 1 Ab concentrations ≥ 4 × 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 (same statistical method as the one used for the primary objective was applied).

(Source: Table 5.6, A3L38 CSR)

Table 6 Geometric mean concentrations/titers for Hexacima and Infanrix hexa antigens – PP1 (secondary objective)

		Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=248)		
Component	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Anti-D (MIT- IU/mL)	**Pre-Dose 3**	241	0.080	(0.069; 0.092)	241	0.053	(0.046; 0.060)
	Post-Dose 3	248	1.70	(1.54; 1.87)	246	1.20	(1.07; 1.34)
Anti-T (ELISA - IU/mL)	**Pre-Dose 3**	235	0.129	(0.114; 0.146)	239	0.167	(0.149; 0.188)
	Post-Dose 3	248	2.23	(2.01; 2.47)	246	2.37	(2.16; 2.60)
Anti-PT (ELISA -EU/mL)	**Pre-Dose 1**	245	2.48	(2.15; 2.86)	245	2.23	(1.95; 2.54)
	Pre-Dose 3	233	20.5	(18.8; 22.5)	237	23.7	(21.5; 26.0)
	Post-Dose 3	249	90.9	(84.9; 97.4)	246	129	(119; 139)
Anti-FHA (ELISA -EU/mL)	**Pre-Dose 1**	247	3.71	3.27; 4.21)	243	3.89	(3.42; 4.42)
	Pre-Dose 3	237	30.6	(28.3; 33.1)	237	28.7	(26.3; 31.4)
	Post-Dose 3	249	148	(138; 158)	247	167	(155; 179)
Anti-Polio 1 (MIT-WT - 1/dil)	**Pre-Dose 3**	240	15.8	(12.8; 19.4)	240	27.3	(22.4; 33.3)
	Post-Dose 3	248	1749	(1494; 2047)	246	3279	(2869; 3746)
Anti-Polio 2 (MIT-WT - 1/dil)	**Pre-Dose 3**	239	14.1	(11.5; 17.2)	238	22.4	(18.0; 27.8)
	Post-Dose 3	246	1729	(1454; 2058)	246	2954	(2520; 3462)
Anti-Polio 3 (MIT-WT - 1/dil)	**Pre-Dose 3**	239	15.7	(12.8; 19.1)	239	20.9	(17.4; 25.0)
	Post-Dose 3	248	1213	(1005; 1463)	246	1906	(1594; 2279)
Anti-Hep B (VITROS ECi - mIU/mL)	**Pre-Dose 3**	241	76.5	(62.0; 94.4)	241	260	(218; 311)
	Post-Dose 3	249	1370	(1069; 1757)	247	5015	(4178; 6020)
Anti-PRP (RIA - µg/mL)	**Pre-Dose 3**	239	0.168	(0.137; 0.205)	240	0.115	(0.096; 0.137)
	Post-Dose 3	245	9.73	(8.12; 11.7)	244	5.64	(4.66; 6.81)

N: Number of subjects analyzed according to the PP1
M: number of subjects available for the endpoint
GM: geometric mean

(Source: Table 5.3, A3L38 CSR)

Table 7 Geometric mean concentrations/titers at one month post-Dose 2 – PP2 (observational objective

		Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=246)		
Component	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Anti-D (MIT- IU/mL)	**Post-Dose 2**	240	0.130	(0.112; 0.152)	241	0.118	(0.103; 0.134)
Anti-T (ELISA - IU/mL)	**Post-Dose 2**	237	0.491	(0.439; 0.549)	235	0.594	(0.540; 0.652)
Anti-PT (ELISA -EU/mL)	**Post-Dose 2**	245	105	(97.8; 113)	242	106	(97.7; 115)
Anti-FHA (ELISA -EU/mL)	**Post-Dose 2**	242	94.9	(88.5; 102)	241	97.7	(90.5; 105)
Anti-Polio 1 (MIT-WT - 1/dil)	**Post-Dose 2**	238	60.0	(47.6; 75.5)	238	105	(84.5; 129)
Anti-Polio 2 (MIT-WT - 1/dil)	**Post-Dose 2**	238	62.1	(49.1; 78.5)	238	89.5	(70.9; 113)
Anti-Polio 3 (MIT-WT - 1/dil)	**Post-Dose 2**	239	122	(97.7; 152)	238	142	(115; 175)
Anti-Hep B (VITROS ECi - mIU/mL)	**Post-Dose 2**	246	401	(330; 488)	245	699	(577; 847)
Anti-PRP (RIA - µg/mL)	**Post-Dose 2**	239	0.507	(0.398; 0.647)	240	0.226	(0.184; 0.277)

N: Number of subjects analysed according to the PP2
M: number of subjects available for the endpoint
GM: geometric mean

(Source: Table 5.7, A3L38 CSR)

Table 8 Seroconversion rates for Prevenar 13 – PP1 (secondary objective)

		Hexacima + Prevenar 13 (N=249)			Infanrix hexa + Prevenar 13 (N=248)		
Component	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Serotype 1 (ELISA - µg/mL)	**≥ 0.35 µg/mL**	163/164	99.4	(96.6; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 3 (ELISA - µg/mL)	**≥ 0.35 µg/mL**	139/161	86.3	(80.0; 91.2)	139/158	88.0	(81.9; 92.6)
Serotype 4 (ELISA - µg/mL)	**≥ 0.35 µg/mL**	163/164	99.4	(96.6; 100.0)	160/162	98.8	(95.6; 99.9)
Serotype 5 (ELISA - µg/mL)	**≥ 0.35 µg/mL**	156/164	95.1	(90.6; 97.9)	159/162	98.1	(94.7; 99.6)
Serotype 6A (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	159/161	98.8	(95.6; 99.8)
Serotype 6B (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 7F (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 9V (ELISA - µg/mL)	**≥ 0.35 µg/mL**	163/164	99.4	(96.6; 100.0)	161/162	99.4	(96.6; 100.0)
Serotype 14 (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 18C (ELISA - µg/mL)	**≥ 0.35 µg/mL**	161/164	98.2	(94.7; 99.6)	162/162	100.0	(97.7; 100.0)
Serotype 19A (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 19F (ELISA - µg/mL)	**≥ 0.35 µg/mL**	164/164	100.0	(97.8; 100.0)	162/162	100.0	(97.7; 100.0)
Serotype 23F (ELISA - µg/mL)	**≥ 0.35 µg/mL**	163/163	100.0	(97.8; 100.0)	159/160	99.4	(96.6; 100.0)

Table 9 Geometric Mean Concentrations for Prevenar 13 - PP1 (secondary objective)

		Hexacima + Prevenar 13			Infanrix hexa + Prevenar 13		
		Group 1 (N=249)			Group 2 (N=248)		
Component	**Timepoint**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
Serotype 1 (ELISA - µg/mL)	**Post-Dose 3**	164	2.15	(1.95; 2.36)	162	2.47	(2.21; 2.75)
Serotype 3 (ELISA - µg/mL)	**Post-Dose 3**	161	0.669	(0.605; 0.740)	158	0.824	(0.735; 0.924)
Serotype 4 (ELISA - µg/mL)	**Post-Dose 3**	164	1.50	(1.36; 1.66)	162	1.95	(1.74; 2.18)
Serotype 5 (ELISA - µg/mL)	**Post-Dose 3**	164	1.07	(0.973; 1.19)	162	1.32	(1.20; 1.45)
Serotype 6A (ELISA - µg/mL)	**Post-Dose 3**	164	4.01	(3.63; 4.44)	161	4.92	(4.34; 5.58)
Serotype 6B (ELISA - µg/mL)	**Post-Dose 3**	164	2.82	(2.51; 3.17)	162	4.29	(3.80; 4.84)
Serotype 7F (ELISA - µg/mL)	**Post-Dose 3**	164	3.04	(2.79; 3.31)	162	3.97	(3.60; 4.38)
Serotype 9V (ELISA - µg/mL)	**Post-Dose 3**	164	1.36	(1.24; 1.50)	162	1.70	(1.53; 1.88)
Serotype 14 (ELISA - µg/mL)	**Post-Dose 3**	164	6.79	(6.00; 7.69)	162	7.77	(6.98; 8.65)
Serotype 18C (ELISA - µg/mL)	**Post-Dose 3**	164	1.27	(1.14; 1.41)	162	1.79	(1.61; 1.99)
Serotype 19A (ELISA - µg/mL)	**Post-Dose 3**	164	4.43	(3.88; 5.06)	162	5.78	(5.10; 6.55)
Serotype 19F (ELISA - µg/mL)	**Post-Dose 3**	164	4.75	(4.27; 5.30)	162	6.00	(5.31; 6.78)
Serotype 23F (ELISA - µg/mL)	**Post-Dose 3**	163	2.89	(2.60; 3.22)	160	4.24	(3.74; 4.80)

N: number of subjects calculated according to the PP1; n: number of subjects

M: number of subjects available for the endpoint; GM: geometric mean

%: percentages and 95% CI were calculated according to the subjects available for the endpoint

(Source: Table 5.4 and Table 5.5, A3L38 CSR)

Study A3L24

Demographic parameters of the children in the two subgroups were similar between the subgroups and to the 'all subjects' groups.

Lot-to-lot consistency had been demonstrated in the study, thus, the pooled data are discussed only. As the ITT and PP results were also very similar the ITT results are shown here.

Anti-PT

30 days after the second dose all subgroup subjects in all vaccination groups showed a 4-fold increase of the titres and the resulting GMTs were similar. There was no significant titre increase resulting from the 3rd dose.

Anti-FHA

30 days after the second dose all subgroup subjects in all vaccination groups showed a 4-fold increase of the titres and the resulting GMTs were similar. Titres doubled roughly from the second to the third dose. After three doses there was a statistically significant higher GMT in the Hexyon groups compared to the Infanrix hexa group.

Anti-PRP

30 days after the second dose >70% of the subgroup subjects in all vaccination groups had at least reached seroprotection levels (≥ 0.15 µg/ml) and ~30% long-term protection levels of ≥ 1µg/ml. After the third dose nearly all subjects had reached seroprotection and 70% the long-term protection levels. GMTs were again similar between the different vaccination groups although slightly lower in the Infanrix hexa group.

Table 10 Anti-PRP (RIA - µg/mL) Descriptive Antibody Level Results By Group – Post-dose 2 Subset of Subjects, ITT Analysis Set (source: Table 2.14, study report)

	DTaP-IPV-Hep-B-PRP-T pooled (N=158)	Infanrix hexa (N=56)
V04 (D84)		
Available data (M)	158	56
Sample characteristics: n(%)		
<0.06 µg/mL (LLOQ)	23 (14.6)	5 (8.9)
Cut-off (including seroprotection level)		
>=0.15 µg/mL		
n(%)	117 (74.1)	41 (73.2)
(95% CI)	(66.5; 80.7)	(59.7; 84.2)
>=1 µg/mL		
n(%)	54 (34.2)	13 (23.2)
(95% CI)	(26.8; 42.1)	(13.0; 36.4)

Table 11 Summary of Geometric Means of Titers for Study Vaccine – ITT Analysis Set (source: Table 2.8, study report)

		DTaP-IPV-Hep-B-PRP-T pooled						Infanrix hexa					
		All subjects (N=1030)			Subset (N=158)			All subjects (N=345)			Subset (N=56)		
		M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)
Anti-PT (ELISA - EU/mL)	**V01 (D0)**	1020	3.34	(3.09; 3.60)	157	3.26	(2.70; 3.94)	341	3.24	(2.82; 3.71)	56	2.36	(1.81; 3.08)
	V04 (D84)	-	-	-	157	122	(110; 135)	-	-	-	56	102	(83.2; 125)
	V04 (D84)/V01 (D0)	-	-	-	156	37.6	(29.7; 47.7)	-	-	-	56	43.2	(30.7; 60.8)
	V06 (D140)	992	102	(98.4; 106)	156	102	(93.0; 112)	335	98.3	(92.0; 105)	55	105	(90.4; 122)
	V06 (D140)/V01 (D0)	983	30.7	(27.9; 33.7)	155	31.5	(25.2; 39.3)	331	31.3	(26.6; 36.9)	55	46.0	(33.8; 62.5)
Anti-FHA (ELISA - EU/mL)	**V01 (D0)**	1013	5.57	(5.22; 5.95)	155	5.78	(4.86; 6.88)	339	5.11	(4.61; 5.66)	56	4.69	(3.73; 5.91)
	V04 (D84)	-	-	-	158	89.8	(82.1; 98.2)	-	-	-	56	74.2	(63.0; 87.4)
	V04 (D84)/V01 (D0)	-	-	-	155	15.7	(12.9; 19.0)	-	-	-	56	15.8	(11.4; 21.9)
	V06 (D140)	989	182	(176; 190)	156	182	(164; 201)	336	119	(111; 128)	55	130	(111; 152)
	V06 (D140)/V01 (D0)	973	32.8	(30.2; 35.5)	153	31.1	(25.4; 38.1)	330	23.4	(20.5; 26.8)	55	28.3	(21.2; 37.9)
Anti-PRP (RIA - µg/mL)	**V04 (D84)**	-	-	-	158	0.492	(0.370; 0.653)	-	-	-	56	0.357	(0.248; 0.513)
	V06 (D140)	993	3.55	(3.20; 3.95)	156	3.40	(2.61; 4.42)	337	2.25	(1.92; 2.64)	55	2.43	(1.73; 3.42)

N: Number of subjects analyzed according to ITT Analysis Set M: number of subjects available for the endpoint All subjects were co-administered with Prevenar at 2, 4 and 6 months and with Rotarix at 2 and 4 months

4.3.3. Discussion

Study A3L38

After a complete 2+1 vaccination schedule, non-inferiority of Hexacima to Infanrix hexa was demonstrated for each valence. High proportions of subjects (94 to 100% in the Hexacima group and 85 to 100% in the Infanrix hexa group) showed seroprotection or vaccine response rates above thresholds defined as established correlates or accepted surrogates of protection.

Compared to Infanrix Hexa, generally lower GMC were achieved for Hep B and polio type 1, 2, and 3 but higher GMC for D and PRP following vaccination with Hexacima. Additionally, in the Hexacima group, lower antibody levels were seen for several PCV13 serotypes. Despite these differences in GM titers, overall both hexavalent vaccines induced very similar seroprotection/vaccine response rates following the primary (2 doses) and booster vaccination indicating that Hexacima and Infanrix hexa provide equal protection against diseases to infants following the 2+1 vaccination schedule at 3, 5, and 11 to 12 MoA.

Study A3L24

The descriptive analysis of the post-dose 2 results in the subgroups tested for anti-PT, anti-FHA and anti-PRP shows that the final anti-PT GMTs are already reached after two doses of either Hexyon or Infanrix hexa. Anti-FHA and anti-PT are both significantly increased with a further dose. Seroprotection against Hib is only achieved in 70% of subjects after two doses and long-term protection levels in only 30% regardless of the vaccine used. After three doses for primary immunization nearly all subjects have seroprotection and >70% long-term protection thresholds reached. The GMT of anti-FHA is doubled with the third dose.

4.4. Clinical Safety aspects

4.4.1. Methods – analysis of data submitted

Study A3L38

Safety endpoints (secondary only):

- Occurrence of any unsolicited AEs reported in the 30 minutes after each and any dose
- Occurrence of solicited, i.e. pre-listed in the subject's diary and eCRF, injection site and systemic reactions (always considered related to vaccination) occurring up to 7 days after each and any dose
  Prelisted injection site reactions were: injection site tenderness, injection site erythema, injection site swellings, and, after administration of the third dose at 11 to 12 MoA, extensive swelling of the vaccinated limb (ELS).
  Solicited systemic reactions were: fever, vomiting, crying abnormal, drowsiness, appetite lost, and irritability.
- Occurrence of unsolicited (spontaneously reported) AEs up to 30 days after each and any dose including documentation of start and stop dates, intensity of event, action taken if any (e.g. medication), and whether AE led to study discontinuation.
  AEs likely to be related to the product that persisted at the end of the trial were followed up by the investigator until their complete disappearance or the stabilization of the subject's condition.

- Occurrence of SAEs throughout the trial period

Adverse Events of Special Interest (AESI)

Extensive limb swelling (ELS), hypotonic hyporesponsive episode (HHE) and convulsions (whether febrile or not), anaphylactic reactions, apnea, severe neurological conditions are considered as important identified or potential risks due to the age group, morbidity specifics of the vaccinated population and historical data on similar combined vaccines. Although no increased risk of sudden infant death syndrome (SIDS) or sudden unexpected death (SUD) has been associated with hexavalent pediatric vaccines, these events are considered as other AESI and were closely monitored. By definition, convulsions, HHE, anaphylactic reactions, severe neurological conditions and fatal outcomes were to be considered as SAEs. Medical judgment of the investigator was required to assess seriousness of extensive limb swelling and apnea.

The **Safety Analysis Set (SafAS)** included, for each dose, the subset of subjects having received this dose. Out of the 554 randomized subjects, 546 subjects received at least 1 vaccine dose and were included in the SafAS. Of these 546 subjects 271 subjects received at least 1 dose of Hexacima concomitantly with Prevenar 13 and 275 subjects received at least 1 dose of Infanrix hexa concomitantly with Prevenar 13. A total of 541 subjects (99.1%) were included in the SafAS at post-dose 2 and 535 subjects (98.0%) in the SafAS at post-dose 3.

Study A3L24

No (additional) safety data were collected.

4.4.2. Results

Study A3L38

An overview of the safety results is presented in Table 12 for the SafAS.

Immediate unsolicited AEs were not observed in any subject.

Most subjects in both groups experienced at least 1 solicited injection site reaction (94% in the Hexacima and 89% in the Infanrix hexa Group) and at least 1 solicited systemic reaction (100% in the Hexacima and 99% in the Infanrix hexa group).

Injection site reactions

Pain, erythema, and swelling were the most frequent solicited injection site reactions reported by up to 80% of subjects within 7d following vaccination at both administration sites (hexavalent vaccine and Prevenar 13). They were observed with similar frequencies for the Hexacima and Infanrix hexa administration site as well as for the Prevenar 13 administration site with a tendency of higher frequencies after the 3rd injection. However, overall injection site pain was more frequently observed after Hexacima injection than after Infanrix hexa injection (80 vs. 69% of subjects after any injection, Table 13). This mainly affected site pain of grade 2 (for more details refer to study A3L38 CSR, tables 9.92 ff.).

Most injection site reactions were of grade 1 to 2, were reported within the first 3 days after vaccination and lasted a maximum of 3 days.

Solicited systemic reactions

Overall, no differences were observed between groups regarding frequency of vomiting, crying, somnolence, anorexia (appetite loss), or irritability which were experienced by up to 97% of subjects within 7d after at least one vaccination (Table 14). However, pyrexia ($\geq$ 38.0°C) was recorded more

frequently in the Hexacima group compared to the Infanrix hexa group (82 vs. 69%, respectively).

Unsolicited AEs and ARs

A similar proportion of subjects reported unsolicited AEs (73% in the Hexacima group and 80% in the Infanrix hexa group) and unsolicited ARs (18% in the Hexacima and 21% in the Infanrix hexa group).

For both vaccine groups, the most frequent unsolicited AEs reported both within 7 d as well as within 30 d after any vaccination were in the SOC of 'infections and infestations' and 'gastrointestinal disorders' (Table 15 and Table 16).

Neither of these unsolicited AEs/ARs were serious, except for 1 subject in the Infanrix hexa group who experienced urticaria in relation to the 3rd dose of Infanrix hexa (see below).

SAEs

A total of 30 subjects experienced 33 SAEs during the course of the study. In the Hexacima group, 15 subjects experienced 1 SAE each; and in the Infanrix hexa group, 12 subjects reported 1 SAE each and 3 subjects reported 2 SAEs each. Within 30 days after any vaccination, 8 subjects in the Hexacima group and 7 subjects in the Infanrix hexa group experienced an SAE. 5 SAEs were reported within 7 d post-vaccination, 3 in the Hexacima group and 2 in the Infanrix hexa group. These SAEs comprised 2 cases of bronchitis and one case of otitis media in the Hexacima group and one case each of apnea and urticaria in the Infanrix hexa group. Only the urticaria on the day of 3rd injection with Infanrix hexa was vaccine-related (see below).

Of the 30 subjects in both vaccine groups who experienced SAEs, 3 subjects discontinued. In the Hexacima group, 1 subject discontinued 17 days after the first dose due to petechiae; in the Infanrix hexa group, 1 subject discontinued due to cerebral palsy reported 36 days after the 2nd dose, and 1 subject discontinued due to epilepsy reported 5 months after the 2nd dose.

Apart from the urticaria case reported for one subject on the day of the 3rd Infanrix hexa injection (see below), none of the other 32 SAEs were related to treatment.

AESIs

3 AESIs were experienced during the study: 1 subject in the Hexacima group reported febrile convulsion; and 2 subjects in the Infanrix hexa group presented with apnea or convulsions. None of the AESIs were related to vaccination.

There were no deaths during the study.

Selected narratives, Hexacima group:

One male subject aged 3 months developed petechiae on face, chest, and extremities 17 days after the 1st vaccination with Hexacima and Prevenar 13. He also received one dose of RotaTeq on the same vaccination day. The subject had a family history of easy bruising (father) and bleeding in operations (grandmother). Laboratory test showed low vitamin K-dependent and hepatic blood clotting factors, low fibrinogen and thromboplastin time decreased at 64%. The subject received vitamin K i.m. He was reported to have bleeding disorder, with petechiae still ongoing. No etiology for low hepatic blood clotting factors was found. The SAE was reported as unrelated to vaccination; the subject discontinued .

One 4-month-old female experienced fever at 39°C and convulsions 41 days after the 1st vaccination with Hexacima and Prevenar 13. She also received RotaTeq on the same vaccination day. The convulsion was considered due to rapid fever rise in influenza. Nasal swab test for influenza A non-vH1N1 type was proven positive; EEG was normal. Following treatment with paracetamol and ibuprofen, the subject fully recovered and continued in the trial. The event of febrile convulsion was reported as unrelated to

vaccination.

Selected narratives, Infanrix hexa group:

A female subject developed cerebral palsy 36 days after 2nd vaccination with Infanrix hexa concomitantly with Prevenar 13. She had also received RotaTeq on the same day. The clinical examination revealed spastic hemiplegia of the left hand. Left-sided motor impairment was evident in both upper and lower limb, but was more severe in the arm. The subject's medical history reported delivery in poor health with vacuum extraction and low Apgar value probably because of umbilical cord slung twice around the neck. The subject recovered with sequelae. She discontinued due to the SAE. The SAE was reported as unrelated to study vaccination and trial procedures.

Another female experienced convulsions attack with tremble of hands 5 months after 2nd vaccination with Infanrix hexa concomitantly with Prevenar 13, again plus additional vaccination with RotaTeq. The girl was hospitalized with diagnosis of epilepsy. MRI revealed inborn developmental disorder in the left brain block (Dandy-Walker malformations in cerebellum). She discontinued due to the SAE. The investigator reported the event of epilepsy as unrelated to vaccination and unrelated to trial procedures.

Four days after the first Infanrix hexa plus Prevenar 13 dose a female subject experienced 2 episodes of apnea (gasping for breath) for few seconds within one day with the 1st episode following feeding. Clinical examination was normal, aspiration was excluded. The reason for apnea episodes was suspected diving reflex due to the subject mother's plentiful milk production. The subject recovered without any new episodes of apnea and continued in the trial. She experienced otitis media serosa at 6.5 months post-2nd vaccine dose and underwent tympanostomy. She recovered under chloramphenicol treatment. The (S)AEs for this subject were reported unrelated to vaccination and trial procedures.

A male subject experienced convulsions 10 days after 2nd dose of Infanrix hexa and Prevenar 13. He had also received a RotaTeq dose on the same day. Further episodes of head and neck stiffness and/ or right arm shaking were documented on several days afterwards with last convulsions episode at 40 days-post vaccination. EEG was normal. The probable diagnosis was infant benign epilepsy. The subject recovered without treatment and continued in the trial. The convulsions were reported as unrelated to vaccination and trial procedures.

A male subject experienced extensive urticaria 6 hours after the 3rd vaccination with Infanrix hexa concomitantly with Prevenar 13. The urticaria worsened after hospitalization. The subject had a medical history of atopic eczema, milk allergy and egg allergy plus a family history of allergies from food, animal, pollen, and penicillin (parents). He fully recovered under prolonged treatment with antihistamine and corticosteroids and continued in the trial. The event of urticarial was reported by the investigator as related to vaccination and unrelated to the trial procedure.

Assessor's comments:

Solicited (injection site and systemic) reactions, unsolicited AEs, and unsolicited ARs were reported with similar frequencies between the 2 vaccine groups. Few subjects in both groups reported AEs of grade 3.

From the narratives provided by the sponsor it can be inferred that none of the SAEs were related to vaccination. An exception was the urticaria case in a subject with a history of food allergy which was (causally and timely) related to the 3rd vaccination with Infanrix hexa and Prevenar 13.

Overall, no new safety signals emerged during the course of study A3L38.

Table 12 Safety overview after any injection - Safety Analysis Set

	Hexacima + Prevenar 13 (N=271)			Infanrix hexa + Prevenar 13 (N=275)		
Subject experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 days of any vaccine injections						
Immediate unsolicited AE	0/271	0.0	(0.0; 1.4)	0/275	0.0	(0.0; 1.3)
Immediate unsolicited AR	0/271	0.0	(0.0; 1.4)	0/275	0.0	(0.0; 1.3)
Solicited reaction	271/271	100.0	(98.6; 100.0)	270/274	98.5	(96.3; 99.6)
Solicited injection site reaction	255/271	94.1	(90.6; 96.6)	245/274	89.4	(85.2; 92.8)
Solicited systemic reaction	271/271	100.0	(98.6; 100.0)	270/274	98.5	(96.3; 99.6)
Unsolicited AE	198/271	73.1	(67.4; 78.3)	219/275	79.6	(74.4; 84.2)
Unsolicited AR	48/271	17.7	(13.4; 22.8)	57/275	20.7	(16.1; 26.0)
Unsolicited non-serious AE	196/271	72.3	(66.6; 77.6)	217/275	78.9	(73.6; 83.6)
Unsolicited non-serious AR	48/271	17.7	(13.4; 22.8)	56/275	20.4	(15.8; 25.6)
Unsolicited non-serious injection site AR	17/271	6.3	(3.7; 9.9)	25/275	9.1	(6.0; 13.1)
Unsolicited non-serious systemic AE	192/271	70.8	(65.0; 76.2)	212/275	77.1	(71.7; 81.9)
Unsolicited non-serious systemic AR	34/271	12.5	(8.8; 17.1)	35/275	12.7	(9.0; 17.3)
AE leading to study discontinuation*	1/271	0.4	(0.0; 2.0)	2/275	0.7	(0.1; 2.6)
SAE	8/271	3.0	(1.3; 5.7)	7/275	2.5	(1.0; 5.2)
Death	0/271	0.0	(0.0; 1.4)	0/275	0.0	(0.0; 1.3)
During the study						
SAE	15/271	5.5	(3.1; 9.0)	15/275	5.5	(3.1; 8.8)
Death	0/271	0.0	(0.0; 1.4)	0/275	0.0	(0.0; 1.3)

N: number of subjects analyzed according to SafAS n: number of subjects
M: number of subjects available for the endpoint
%: percentages and 95% CI were calculated according to the subjects available for the endpoint
Note: For each individual solicited reaction, 'n' was based on any reaction after any of the 3 vaccinations (study vaccine or Prevenar)

Source: A3L38 CSR, Table 9.84

Table 13 Solicited injection site reactions within 7 days after each injection with hexavalent vaccine or Prevenar 13 - Safety Analysis Set

	Hexacima (N=271)						Infanrix hexa (N=275)					
	Hexacima administration site (N=271)			Prevenar administration site (N=271)			Infanrix hexa administration site (N=275)			Prevenar administration site (N=275)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Injection site pain	217/271	80.1	(74.8; 84.7)	210/271	77.5	(72.0; 82.3)	190/274	69.3	(63.5; 74.7)	195/274	71.2	(65.4; 76.5)
Post-injection 1	119/271	43.9	(37.9; 50.0)	99/271	36.5	(30.8; 42.6)	88/274	32.1	(26.6; 38.0)	83/274	30.3	(24.9; 36.1)
Post-injection 2	108/269	40.1	(34.2; 46.3)	98/269	36.4	(30.7; 42.5)	81/271	29.9	(24.5; 35.7)	97/271	35.8	(30.1; 41.8)
Post-injection 3	173/266	65.0	(59.0; 70.8)	170/266	63.9	(57.8; 69.7)	151/266	56.8	(50.6; 62.8)	153/265	57.7	(51.5; 63.8)
Injection site erythema	194/271	71.6	(65.8; 76.9)	162/271	59.8	(53.7; 65.7)	174/274	63.5	(57.5; 69.2)	167/274	60.9	(54.9; 66.8)
Post-injection 1	89/271	32.8	(27.3; 38.8)	65/271	24.0	(19.0; 29.5)	73/274	26.6	(21.5; 32.3)	84/274	30.7	(25.3; 36.5)
Post-injection 2	125/269	46.5	(40.4; 52.6)	97/269	36.1	(30.3; 42.1)	110/271	40.6	(34.7; 46.7)	101/271	37.3	(31.5; 43.3)
Post-injection 3	142/266	53.4	(47.2; 59.5)	110/266	41.4	(35.4; 47.5)	138/266	51.9	(45.7; 58.0)	121/265	45.7	(39.6; 51.9)
Injection site swelling	138/271	50.9	(44.8; 57.0)	114/271	42.1	(36.1; 48.2)	139/274	50.7	(44.6; 56.8)	114/274	41.6	(35.7; 47.7)
Post-injection 1	67/271	24.7	(19.7; 30.3)	37/271	13.7	(9.8; 18.3)	50/274	18.2	(13.9; 23.3)	40/274	14.6	(10.6; 19.3)
Post-injection 2	74/269	27.5	(22.3; 33.3)	56/269	20.8	(16.1; 26.2)	80/271	29.5	(24.2; 35.3)	64/271	23.6	(18.7; 29.1)
Post-injection 3	75/266	28.2	(22.9; 34.0)	70/266	26.3	(21.1; 32.0)	103/266	38.7	(32.8; 44.9)	76/265	28.7	(23.3; 34.5)

N: number of subjects analyzed according to the SafAS n: number of subjects

M: number of subjects available for the endpoint

%: percentages and 95% CI were calculated according to the subjects available for the endpoint

Note: For each individual solicited reaction, 'n' was based on any reaction after any of the 3 vaccinations (study vaccine or Prevenar) No extensive swelling of vaccinated limb was reported in this study

Source: A3L38 CSR, Table 9.88

Table 14 Solicited systemic reactions within 7 days of each vaccine injection – Safety Analysis Set

	DTaP-IPV-HB-Hib + Prevenar 13 (N=271)			Infanrix hexa + Prevenar 13 (N=275)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Pyrexia	223/271	82.3	(77.2; 86.6)	189/274	69.0	(63.1; 74.4)
Post-injection 1	125/270	46.3	(40.2; 52.4)	72/274	26.3	(21.2; 31.9)
Post-injection 2	166/269	61.7	(55.6; 67.5)	135/271	49.8	(43.7; 55.9)
Post-injection 3	138/265	52.1	(45.9; 58.2)	127/264	48.1	(41.9; 54.3)
Vomiting	102/271	37.6	(31.8; 43.7)	106/274	38.7	(32.9; 44.7)
Post-injection 1	42/271	15.5	(11.4; 20.4)	60/274	21.9	(17.1; 27.3)
Post-injection 2	55/269	20.4	(15.8; 25.8)	61/271	22.5	(17.7; 28.0)
Post-injection 3	35/266	13.2	(9.3; 17.8)	31/266	11.7	(8.1; 16.1)
Crying	241/271	88.9	(84.6; 92.4)	242/274	88.3	(83.9; 91.9)
Post-injection 1	195/271	72.0	(66.2; 77.2)	179/274	65.3	(59.4; 71.0)
Post-injection 2	169/269	62.8	(56.7; 68.6)	174/271	64.2	(58.2; 69.9)
Post-injection 3	170/266	63.9	(57.8; 69.7)	171/265	64.5	(58.4; 70.3)
Somnolence	225/271	83.0	(78.0; 87.3)	217/274	79.2	(73.9; 83.8)
Post-injection 1	164/271	60.5	(54.4; 66.4)	161/274	58.8	(52.7; 64.6)
Post-injection 2	134/269	49.8	(43.7; 55.9)	134/271	49.4	(43.3; 55.6)
Post-injection 3	141/266	53.0	(46.8; 59.1)	138/265	52.1	(45.9; 58.2)
Anorexia	182/271	67.2	(61.2; 72.7)	183/274	66.8	(60.9; 72.3)
Post-injection 1	96/271	35.4	(29.7; 41.4)	78/274	28.5	(23.2; 34.2)
Post-injection 2	86/269	32.0	(26.4; 37.9)	76/271	28.0	(22.8; 33.8)
Post-injection 3	118/266	44.4	(38.3; 50.6)	130/266	48.9	(42.7; 55.1)
Irritability	262/271	96.7	(93.8; 98.5)	255/274	93.1	(89.4; 95.8)
Post-injection 1	222/271	81.9	(76.8; 86.3)	210/274	76.6	(71.2; 81.5)
Post-injection 2	206/269	76.6	(71.1; 81.5)	201/271	74.2	(68.5; 79.3)
Post-injection 3	201/266	75.6	(69.9; 80.6)	198/265	74.7	(69.0; 79.8)

N: number of subjects analyzed according to SafAS; n: number of subjects
M: number of subjects available for the endpoint
%: percentages and 95% CI were calculated according to the subjects available for the endpoint
Note: For each individual solicited reaction, 'n' was based on any reaction after any of the 3 vaccinations (study vaccine or Prevenar 13)

Source: A3L38 CSR, Table 9.104

Table 15 Most frequent unsolicited AEs within 7 Days of any vaccination – SafAS

	Hexacima + Prevenar 13 (N=271)				Infanrix hexa + Prevenar 13 (N=275)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**
Unsolicited AEs	127	46.9	(40.8;53.0)	194	131	47.6	(41.6;53.7)	213
Infections and infestations	60	22.1	(17.3;27.6)	78	67	24.4	(19.4;29.9)	82
Upper respiratory tract infection	22	8.1	(5.2;12.0)	24	30	10.9	(7.5;15.2)	36
Rhinitis	22	8.1	(5.2;12.0)	23	21	7.6	(4.8;11.4)	21
Gastrointestinal disorders	34	12.5	(8.8;17.1)	37	32	11.6	(8.1;16.0)	44
Diarrhoea	19	7.0	(4.3;10.7)	19	19	6.9	(4.2;10.6)	23
Respiratory, thoracic and mediastinal disorders	24	8.9	(5.8;12.9)	27	19	6.9	(4.2;10.6)	19
Cough	20	7.4	(4.6;11.2)	22	14	5.1	(2.8;8.4)	14
General disorders and administration site conditions	16	5.9	(3.4;9.4)	23	24	8.7	(5.7;12.7)	43
Injection site induration	12	4.4	(2.3;7.6)	16	17	6.2	(3.6;9.7)	32

Table 16 Most frequent unsolicited AEs within 30 Days of any vaccination– SafAS

	Hexacima + Prevenar 13 (N=271)				Infanrix hexa + Prevenar 13 (N=275)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**
Unsolicited AEs	198	73.1	(67.4;78.3)	464	219	79.6	(74.4;84.2)	520
Infections and infestations	139	51.3	(45.2;57.4)	240	163	59.3	(53.2;65.1)	258
Upper respiratory tract infection	62	22.9	(18.0;28.3)	77	71	25.8	(20.7;31.4)	96
Rhinitis	45	16.6	(12.4;21.6)	52	45	16.4	(12.2;21.3)	53
Otitis media	27	10.0	(6.7;14.2)	32	26	9.5	(6.3;13.5)	31
Nasopharyngitis	24	8.9	(5.8;12.9)	35	29	10.5	(7.2;14.8)	33
Gastrointestinal disorders	49	18.1	(13.7;23.2)	62	52	18.9	(14.5;24.0)	73
Diarrhoea	23	8.5	(5.5;12.5)	23	22	8.0	(5.1;11.9)	27
Teething	13	4.8	(2.6;8.1)	18	23	8.4	(5.4;12.3)	31
General disorders and administration site conditions	48	17.7	(13.4;22.8)	61	71	25.8	(20.7;31.4)	99
Pyrexia	25	9.2	(6.1;13.3)	28	42	15.3	(11.2;20.1)	46
Respiratory, thoracic and mediastinal disorders	35	12.9	(9.2;17.5)	42	33	12.0	(8.4;16.4)	37
Cough	31	11.4	(7.9;15.8)	35	26	9.5	(6.3;13.5)	28

N: number of subjects analyzed according to the Safety Analysis Set
n: number of subjects experiencing the endpoint listed in the first column n AEs: number of AEs
%: percentages and 95% CI were calculated according to the subjects available for the endpoint
Source: A3L38 CSR, Tables 9.122 and 9.129

4.4.3. Discussion

The safety profile of Hexacima was generally similar to Infanrix hexa although a higher rate of subjects in the Hexacima group reported pain and fever.

Overall, there is no safety concern with Hexacima administered in a 2+1 schedule.

There is no interaction with Prevenar 13 in terms of immune responses or safety profile, when it is administered concomitantly with Hexacima.

4.5. Changes to the Product Information

As a result of this variation, sections 4.2 and 5.1 of the SmPC are being updated.

The Package Leaflet (PL) is updated accordingly.

Clinical aspects -Changes to the packet leaflet:
To avoid misuse in the 2+1 vaccination schedule with only 1 month in between the 1st and 2nd dose the assessor suggests the following change:

First course of vaccination (primary vaccination)

'Your child will receive **two or three injections** given at **an interval of one to two months** (at least four weeks apart). This vaccine should be used according to the local vaccination programme.'

Should be adjusted to:

'Your child will receive **either two injections given at an interval of two months or three injections given at an interval of one to two months** (at least four weeks apart). This vaccine should be used according to the local vaccination programme. '

This was accepted.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5. Attachments

1. Product Information (changes highlighted) as adopted on 22 January 2015