EMA/181341/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMEA/H/C/xxxx/WS1965/G

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Hexacima	diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inact.) and haemophilus type B conjugate vaccine (adsorbed)	EMEA/H/C/002702/WS1965/0110/G
Hexyon	diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inact.) and haemophilus type B conjugate vaccine (adsorbed)	EMEA/H/C/002796/WS1965/0114/G

Note

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

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur Europe submitted to the European Medicines Agency on 30 October 2020 an application for a group of variations 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 submitted to the EMA on 30 October 2020 an application for a variation[1] to the CHMP Scientific Opinion.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I and IIIB
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
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

C.I.4 (type II): Update of section 5.1 of the SmPC in order to describe the persistence of anti-HBs antibodies in subjects 6 years of age having received a hexavalent vaccine based on the final results from study A3L00052; this is a phase IV, open-label, multi-centre study in children previously vaccinated in Study A3L38a with 3 doses of either Hexacima/Hexyon/Hexaxim (Group 1) or Infanrix Hexa (Group 2).

C.I.4 (type II): Update of sections 4.4 and 5.1 of the SmPC in order to reword safety and immunogenicity information regarding individuals with immunodeficiency based on the final results from study A3L44; this is a Phase III, single centre, open-label, two-arm study including HIV-exposed infected and uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and a booster dose (at 15 to 18 months of age) with Hexacima/Hexyon/Hexaxim in Republic of South Africa. The updates to the SmPC were requested following assessment of these data by Article 46, EMEA/H/C/002702/P46/036 (Hexacima), EMEA/H/C/002796/P46/034 (Hexyon) and EMEA/H/W/002495/P46/036 (Hexaxim).

C.I.z (type IB): Update of section 4.4 of the SmPC in order to include syncope within the precautions for use. The package leaflet is updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet.

The RMP version 13.0 has also been submitted.

The requested grouped worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/200

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

Persistence of Anti-Hepatitis B Antibodies at 6 Years of Age and Hepatitis B Immune Memo

Trial A3L00052 evaluated the persistence of the immune responses against the hepatitis B component of Hexyon/Hexacima/Hexaxim in infants aged 6 years of age (yoa). For a 2-dose primary infant series at 3 and 5 months of age without hepatitis B at birth, followed by a toddler booster at 11-12 months of age, 53.8% of children were seroprotected (anti-HBsAg ≥ 10 mIU/mL) at 6 years of age, and 96.7% presented an anamnestic response after a challenge dose with a standalone Hepatitis B vaccine. These data support persisting immune memory induced in infants primed with Hexyon/Hexacima/Hexaxim. The results of the study lead to the changes in Section 5.1 of the SmPC, which are acceptable.

Immunogenicity and safety of Hexyon/Hexacima/Hexaxim in HIV-exposed infants

Study A3L44; is a Phase III, single centre, open-label, two-arm study including HIV-exposed infected and uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and a booster dose (at 15 to 18 months of age) with Hexyon/Hexacima/Hexaxim in Republic of South Africa.

Immunogenicity data in HIV-exposed infants (infected and uninfected) showed that Hexyon/Hexacima/Hexaxim is immunogenic in the potentially immunodeficient population of HIV-exposed infants whatever their HIV status at birth. No specific safety concern was observed in this population. The results of the study lead to changes in Section 4.4 and Section 5.1 of the SmPC, which are acceptable.

Syncope

The MAH took the opportunity to update the product information in order to include syncope within the precautions for use.

On 30 November 2020, Sanofi Pasteur informed the European Medicine Agency (EMA) of its decision to stop the maintenance of the scientific opinion under Article 58 for Hexaxim. Therefore, the application for EMEA/H/W/002495/WS1965/0115/G is not included in the below recommendation.

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

3. Recommendations

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

Variations requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I and IIIB
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
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C.I.4 (type II): Update of section 5.1 of the SmPC in order to describe the persistence of anti-HBs antibodies in subjects 6 years of age having received a hexavalent vaccine based on the final results from study A3L00052; this is a phase IV, open-label, multi-centre study in children previously

vaccinated in Study A3L38a with 3 doses of either Hexacima/Hexyon (Group 1) or Infanrix Hexa (Group 2).

C.I.4 (type II): Update of sections 4.4 and 5.1 of the SmPC in order to reword safety and immunogenicity information regarding individuals with immunodeficiency based on the final results from study A3L44; this is a Phase III, single centre, open-label, two-arm study including HIV-exposed infected and uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and a booster dose (at 15 to 18 months of age) with Hexacima/Hexyon in Republic of South Africa. The updates to the SmPC were requested following assessment of these data by Article 46, EMEA/H/C/002702/P46/036 (Hexacima) and EMEA/H/C/002796/P46/034 (Hexyon).

C.I.z (type IB): Updated of section 4.4 of the SmPC in order to include syncope within the precautions for use. The package leaflet is updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet.

In addition, the WSA took the opportunity to update the product information according to QRD-template 10.1.

The RMP version 13.0 has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the grouped worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

The persistence of the immune responses against the hepatitis B component of Hexyon/Hexacima was evaluated in infants. For a 2-dose primary infant series at 3 and 5 months of age without hepatitis B at birth, followed by a toddler booster at 11-12 months of age, 53.8% of children were seroprotected (anti-HBsAg ≥ 10 mIU/mL) at 6 years of age, and 96.7% presented an anamnestic response after a challenge dose with a standalone Hepatitis B vaccine. These data support persisting immune memory induced in infants primed with Hexyon/Hexacima

Immunogenicity data in HIV-exposed infants (infected and uninfected) showed that Hexyon//Hexacima is immunogenic in the potentially immunodeficient population of HIV-exposed infants whatever their HIV status at birth. No specific safety concern was observed in this population.

Inclusion of syncope within the precautions for use. Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The purpose of this document is to support a regulatory submission proposing two modifications of the Product Information. These two modifications are the following:

• Addition of one supplementary statement related to the persistence of anti-hepatitis B surface antibodies (anti-HBs) and hepatitis B (HB) immune memory in children aged 6 years of age (yoa) who were primed with Hexaxim following a 2+1 schedule, and who received a challenge dose of one standalone HB vaccine at 6 yoa to evaluate the quality of their immune memory against HB virus (trial A3L00052)

• Introduction of statements regarding the immunogenicity and safety of Hexaxim when used in human immunodeficiency virus (HIV)-exposed infants (both infected or uninfected) (trial A3L44).

The data related to the persistence of anti-HBs antibodies at 6 yoa are submitted for the first time within this submission, and the data generated in HIV-exposed infants were already reviewed by the European Medicines Agency (EMA) through an Article 46 Critical Expert Overview on 15 June 2020 (Hexaxim: EMEA/H/W/002495 / P46 036 ; Hexacima: EMEA/H/C/002702 / P46 036 ; Hexyon: EMEA/H/C/002796 / P46 034).

At that time, the Manufacture Authorization Holder (MAH) already considered adding the immunogenicity and safety data in HIV-exposed infants vaccinated with Hexaxim from A3L44 study to complement several sections of the Product Information, through a labelling variation. However, as there were other labelling variations under review at that time, the MAH decided to wait to implement this revision, and also to group it with another variation based one the persistence of anti-HBs antibodies and the persistence of immune memory.

6. Clinical Immunogenicity aspects

6.1. Persistence of Anti-Hepatitis B Antibodies at 6 Years of Age and Hepatitis B Immune Memo

A3L00052

"Persistence of Anti-HBs Antibodies at 6 to 7 Years of Age in Subjects Having Received a DTaP-IPVHB-PRP~T Hexavalent Vaccine at 3, 5, and 11 to 12 Months of Age, and Evaluation of Their Immune Memory through a Challenge Vaccination with a Standalone Hepatitis B Vaccine)."

Methods – analysis of data submitted

Study A3L00052 was a Phase IV, open-label, multi-centre study in children previously vaccinated in Study A3L38a with 3 doses of either Hexaxim (Group 1) or Infanrix hexa (Group 2). Vaccines were administered at 3, 5, and 11 to 12 moa, concomitantly with a pneumococcal conjugate vaccine (PCV13; Prevenar™ 13). Infants did not receive HB vaccination at birth.

The primary objectives were:

• To describe the persistence of anti-HBs antibodies at 6 yoa in subjects having received a hexavalent vaccine at 3, 5 and 11 to 12 moa according to the vaccine received during Study A3L38 (Hexaxim [Group 1] or Infanrix hexa [Group 2])

• To evaluate their immune responses against hepatitis B surface (HBs) antigen one month after a vaccination with a standalone monovalent HB vaccine (challenge dose to probe the quality and persistence of their immune memory)

The secondary objective was:

• To describe the occurrence of serious adverse events (SAEs) throughout the study Among the 487 subjects who received 3 injections of Hexaxim (241 subjects) or Infanrix hexa vaccines (246 subjects) at 3, 5, and 11 to 12 moa during Study A3L38, 225 subjects (ie, 111 primed with Hexaxim and 114 primed with Infanrix hexa) were present at V01 in Study A3L00052.

All enrolled subjects were 6 yoa and were initial responders, ie, had developed anti-HBs antibodies seroprotective levels (≥ 10 mIU/mL) after full primary vaccination schedule given in Study A3L38.

Results

Results for antibody persistence 5-6 years after the last dose in study A3L38 was obtain in nearly all subjects. In group 1 (Hexyon primed) 3 subjects did not receive a dose in this study and in group 2 (Infanrix hexa primed) only one subject did not receive a dose in this study. Details can be found in *Table 1*.

Table 1: Immunogenicity and safety analysis sets

	Group 1 (N=111) n (%)	Group 2 (N=114) n (%)	All (N=225) n (%)
Subjects with data in CRF	111 (100)	114 (100)	225 (100)
Subjects with data in CRF but did not receive any vaccination	3 (2.7)	1 (0.9)	4 (1.8)
Full Analysis Set	108 (97.3)	113 (99.1)	221 (98.2)
Per-Protocol Analysis Set	91 (82.0)	98 (86.0)	189 (84.0)

n: number of subjects fulfilling the item listed
Note: a subject may be associated with more than one deviation
Group 1: Hexaxim®, Group 2: Infanrix® hexa as received in study A3L38. Both administered at 3, 5, and 11 to 12 moa concomitantly with the pneumococcal conjugate vaccine.; All: Group 1 + Group 2

Prior to the dose given in this study 50% in the previously Hexyon vaccinated and 70% in the previously Infanrix hexa vaccinated group still had titres of ≥10 mIU/mL representing long-term protection. After the dose HB vaccine nearly all subjects showed this long-term protection titre. In the Hexyon primed group 87% showed a titre of ≥100 mIU/mL; this titre was seen in 96% in the Infanrix hexa group. Overall, the GM was significantly lower in the Hexyon primed (1.816 mIU/mL) compared to the Infanrix hexa primed (7.036 mIU/mL). Details can be found in Table 2.

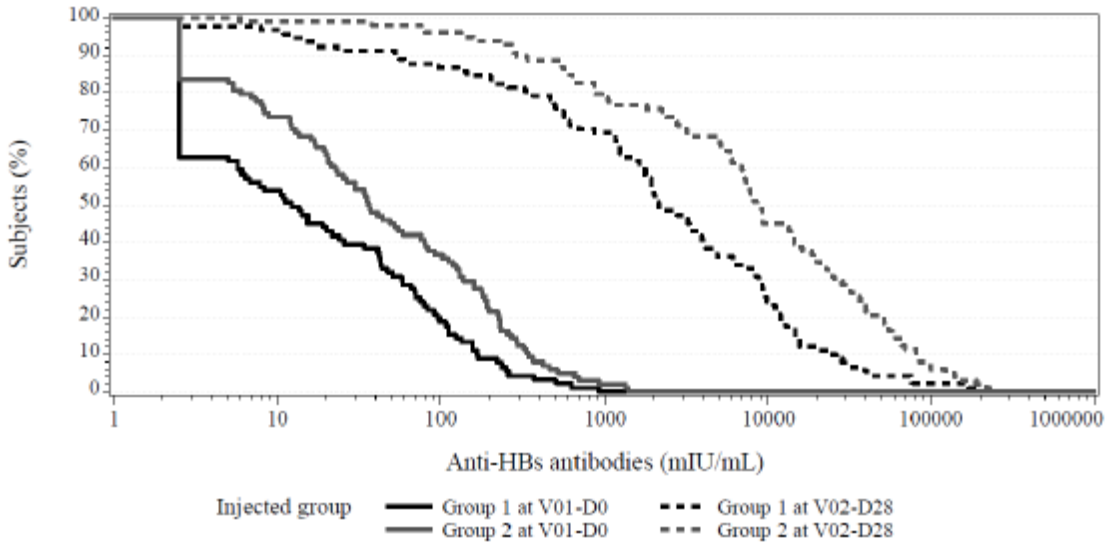
The reverse cumulation curve also shows a faster decline for Hexyon primed subjects in Figure 1.

Table 2: Persistence of immunity at 6 years of age and immune response post-challenge dose with a standalone HB vaccine - PPAS

Time Point		Group 1 (N=91) n (%)	Group 2 (N=98) n (%)
Pre-Dose HB vaccine (V01 – D0)	Available data (M)	91	98
	Sample characteristics		
	<5 mIU/mL (LLOQ) n (%)	34 (37.4)	16 (16.3)
	(95% CI)	(27.4; 48.1)	(9.6; 25.2)
	Cut-offs (including seroprotection level)		
	<10 mIU/mL n (%)	42 (46.2)	26 (26.5)
	(95% CI)	(35.6; 56.9)	(18.1; 36.4)
	>=10 mIU/mL n (%)	49 (53.8)	72 (73.5)
	(95% CI)	(43.1; 64.4)	(63.6; 81.9)
	>=100 mIU/mL n (%)	17 (18.7)	36 (36.7)
	(95% CI)	(11.3; 28.2)	(27.2; 47.1)
	Concentrations (mIU/mL)		
	Geometric Mean	15.8	38.5
	(95% CI)	(10.9; 22.8)	(26.8; 55.2)
Post-Dose HB vaccine (V02 – D28)	Available data (M)	91	98
	Sample characteristics		
	<5 mIU/mL (LLOQ) n (%)	2 (2.2)	0 (0.0)
	(95% CI)	(0.3; 7.7)	(0; 3.7)
	Cut-offs		
	>=10 mIU/mL n (%)	88 (96.7)	97 (99.0)
	(95% CI)	(90.7; 99.3)	(94.4; 100)
	>=100 mIU/mL n (%)	79 (86.8)	94 (95.9)
	(95% CI)	(78.1; 93.0)	(89.9; 98.9)
	Concentrations (mIU/mL)		
	Geometric Mean	1816	7036
	(95% CI)	(1100; 2998)	(4591; 10783)
Post-/pre-challenge HB vaccine dose (V02/V01)	Available data (M)	91	98
	Anamnestic response*		
	n (%)	88 (96.7)	97 (99.0)
	(95% CI)	(90.7; 99.3)	(94.4; 100)
	Concentrations ratio		
	Geometric Mean	90.1	163
	(95% CI)	(63.8; 127)	(126; 211)

M: number of subjects with available data for the relevant endpoint
n: number of subjects experiencing the endpoint listed in the first column
*Anamnestic response is defined as anti-Hep B Ab concentrations >=4-fold increase from pre-challenge dose (V01) to post-challenge dose (V02) in subjects seroprotected (>=10 mIU/mL) prior to challenge dose OR anti-Hep B Ab concentrations >=10 mIU/mL post-challenge dose in subjects not seroprotected prior to challenge dose (< 10 mIU/mL).
Group 1: Hexaxim, Group 2: Infanrix hexa as received in study A3L38. Both administered at 3, 5, and 11 to 12 moa concomitantly with the pneumococcal conjugate vaccine.

Figure 1 Figure 2.1: RCDC of anti-HBs antibodies - PPAS



Discussion

Although subjects that were primed with Hexyon show lower GMs, a faster decline of titre and a lower rate of the long-term protection titre ≥10 mIU/mL 5-6years after the last dose these findings are not considered clinically relevant. The rate of long-term protected is still 50%. The immune response to a further dose of HB-vaccine is sufficient and the long-term protection titre is reached in nearly 90% of subjects. GMs are still significantly lower than for Infanrix hexa primed subjects.

These results are reflected in section 5.1 of the SmPC (addendum to the data with 3-dose + booster) as text only. Although a tabular presentation would be nice it is hard to make a real comparison to the other schedules (with/without birth dose) due to different follow-up times (4,5 ys, 5-6 ys, 9ys all in different studies).

6.2. *Immunogenicity and safety of Hexaxim in HIV-exposed infants*

A3L44

"Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-HB-PRP~T Combined Vaccine Given as a Primary Series and a Second Year of Life Booster in HIV-Exposed Infected and in HIV-Exposed Uninfected Infants in Republic of South Africa"

The data regarding this study were discussed in Article 46 Critical Expert Overview on 15 June 2020 (Hexaxim: EMEA/H/W/002495 / P46 036 ; Hexacima: EMEA/H/C/002702 / P46 036 ; Hexyon: EMEA/H/C/002796 / P46 034)

The results are now reflected in sections 4.4 and 5.1 of the SmPC.

7. Clinical Safety aspects

No new information.

8. Risk management plan

The WSA submitted an updated RMP version (Version 13.0 with DLP 14 April 2020) with this application. The (main) proposed RMP changes were the following:

1) The RMP was updated with the clinical data of the A3L52 clinical study: "Persistence of Anti-HBs Antibodies at 6 to 7 Years of age in subjects having received a DTaP-IPV-HB-PRP-T Hexavalent Vaccine at 3, 5, and 11 to 12 Months of Age and evaluation of their immune memory through a challenge vaccination with a standalone Hepatitis B vaccine".

   Update on the "on-going" status of the study A3L52 in part II Module SIII Clinical trial exposure

2) The RMP was updated with the clinical data of the A3L44 clinical study: "Immunogenicity and safety of DTaP-IPV-HB-PRP-T combined vaccine given as a primary series and a second year of life booster in HIV-exposed infected and in HIV-exposed uninfected infants in Republic of South Africa".

   Update on the "on-going" status of the study A3L44 in part II Module SIII Clinical trial exposure

   Update on the "on-going" status of the study A3L44 in part II Module SVII Identified and potential risks in section "Immunocompromised individuals (from disease or treatment)".

In RMP Version 13.0 there have been no changes to the list of safety concerns; there have been no changes to the pharmacovigilance plan as well as to the identified and potential risks.

Rationale for the revisited RMP:

Clinical study A3L52

A Phase IV, open-label, multi-center study, in children aged 6 to 7 years and vaccinated with two infant primary series doses at 3 and 5 months of age and a toddler booster at 11-12 months of age with a DTaP-IPV-HB-PRP-T hexavalent combined vaccine (Hexyon vaccine [Group 1]) or a DTaP-IPV-HB/PRP-T combined vaccine (Infanrix hexa vaccine [Group 2]) in Study A3L38 in Finland, without hepatitis B vaccination at birth. The aim of this study was to describe the long-term persistence of anti-HBs antibodies in these children and to evaluate their anamnestic humoral response to the HBs antigen upon challenge vaccination with a standalone monovalent HB vaccine.

Prior to vaccination with a challenge dose of a standalone HB vaccine, the persistence of antiHBs antibodies was observed in subjects aged 6 years and previously vaccinated with two infant primary series doses at 3 and 5 months of age and a toddler booster at 11-12 months of age with either Hexyon or Infanrix hexa. More than half of the subjects previously vaccinated with a primary and booster infant/toddler vaccination with Hexyon and more than 70% of the subjects previously vaccinated with Infanrix hexa showed seroprotective levels of anti-HBs antibodies before the challenge dose

After the challenge dose, GMC of anti-HBs antibody was higher in Group 2 (Infanrix hexa; 7036 mIU/mL) than in Group 1 (Hexyon; 1816 mIU/mL). The clinical relevance of this finding is unknown as vast majority of vaccinees in both groups demonstrated anamnestic responses. An anamnestic response was observed 28 days after the administration of the challenge standalone HB vaccine in most subjects (96.7% of subjects in the Hexyon Group and 99.0% of subjects in the Infanrix hexa

Group). In addition, 96.7% of subjects in Hexyon Group and 99.0% of subjects in Infanrix hexa Group achieved seroprotective levels of anti-HBs antibodies (≥ 10 mIU/ mL) following challenge vaccination-

No SAEs were reported following the administration of the challenge standalone HB vaccine.

The MAH proposes an Addition of persistence of Anti-HBs Antibodies information in SmPC section 5.1, and an update on the "on-going" status of the study A3L52 in part II Module SIII Clinical trial exposure.

Clinical study A3L44

A phase III, single center, open-label, two-arm study planned in 50 HIV-exposed infected and 50 HIVexposed uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10 and 14 weeks of age) and a second year of life booster dose (at 15 to 18 months of age) with the DTaP-IPV-HB-PRP-T combined vaccine in the Republic of South Africa.

Due to low number of HIV-exposed infected subjects enrolled in the study, it is difficult to draw definitive conclusions. Nevertheless, DTaP-IPV-HB-PRP-T combined vaccine appears to be highly immunogenic with adequate seroprotection achieved in more than 95% of subjects for all antibodies after infant primary series and in all subjects after the toddler booster dose. Before booster dose, persistence of anti-PRP and anti-Hep B antibodies was observed in less subjects (ranging from 71.4% to 85.4%) than for the other antibodies (ranging from 85.7% to 100%).

The safety profile of DTaP-IPV-HB-PRP-T combined vaccine following the primary series schedule and a booster vaccination in HIV-exposed infants was good in both groups. DTaP-IPV-HB-PRP-T combined vaccine is a safe and immunogenic solution to be used in the potentially immunodeficient population of HIV-exposed infants whatever their HIV status at birth.

The MAH proposes an Addition and rewording of the information regarding individuals with immunodeficiency in SmPC section 4.4 and 5.1 and an update on the "on-going" status of the study A3L44 in part IISIII Clinical Trial exposure as well as in part IISVII Identified and potential risks in section "Immunocompromised individuals (from disease or treatment)"

DTaP-IPV-HB-PRP-T vaccine is marketed since 2013 and has accumulated significant subject exposure (7249 subjects have received at least 1 dose of DTaP-IPV-HB-PRP-T in clinical trials and more than 87 million doses have been distributed in post-marketing settings as of 30 September 2019).

Assessors comment:

The MAH provided an updated version (Version 13.0 with DLP 14 April 2020) of the RMP.

DTaP-IPV-HB-PRP-T vaccine is marketed since 2013 and has accumulated significant subject exposure (7249 subjects have received at least 1 dose of DTaP-IPV-HB-PRP-T in clinical trials and more than 87 million doses have been distributed in post-marketing settings as of 30 September 2019).

There have been no changes to the list of the safety concerns as well as to the identified and potential risks.

There have been no changes to the pharmacovigilance plan.

Since the last version of the RMP sponsored trials A3L44 and A3L00052 have been completed.

Part II Module SIII Clinical trial exposure has been updated with the data of the clinical study A3L44 as well as of the clinical study A3L00052.

Part II Module SVII Identified and potential risks has been updated with the data of the clinical study A3L44 in regard of missing information for "Immunocompromised individuals (from disease or treatment)".

Despite the data from study A3L44, safety data in this population remains limited and the MAH proposes to keep this missing information in the EU-RMP version 13.0.

The proposed RMP updates by the MAH based on completed studies A3L00052 (Persistence of Anti-HBs Ab) and A3L44 (immunodeficiency) are accepted. Further, the MAH made several minor editorial changes that are accepted as well.

8.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this group of variations, sections 4.4 and 5.1 of the SmPC were updated.

The WSA took the opportunity to update the list of local representatives in the Package Leaflet

In addition, the product information was updated according to QRD-template 10.1.

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

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

PI should be updated according to QRD-template 10.1.

Inclusion with AR update send on 08.01.2021 – comment by CMS regarding section 5.1:

With regard to the added text to section 5.1 of the SmPC concerning pertussis. As the text is not clear and the word seroprotection is not used for pertussis, the following changes are recommended (deletions ~~strike-trough~~):

Regarding pertussis, one month after primary vaccination, 100% of subjects developed antibodies ≥ 8 ~~were seroprotected against~~ EU/mL against both PT and FHA antigens. One month after the booster dose, 100% of subjects developed antibodies ≥ 8 EU/mL against both PT and FHA antigens. Seroconversion rates defined as minimum 4-fold increase compared to pre-vaccination level (pre-dose 1) were 100% in the HIV-exposed and infected group for anti-PT and anti-FHA, and 96.6% for anti-PT and 89.7% for anti-FHA in the HIV-exposed and uninfected group.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1
PI should be updated according to QRD-template 10.1.

Question 2
With regard to the added text to section 5.1 of the SmPC concerning pertussis. As the text is not clear and the word seroprotection is not used for pertussis, the following changes are recommended (deletions ~~strike trough~~):

Regarding pertussis, one month after primary vaccination, 100% of subjects developed antibodies ≥ 8 ~~were seroprotected against~~ EU/mL against both PT and FHA antigens. One month after the booster dose, 100% of subjects developed antibodies ≥ 8 EU/mL against both PT and FHA antigens. Seroconversion rates defined as minimum 4-fold increase compared to pre-vaccination level (pre-dose 1) were 100% in the HIV-exposed and infected group for anti-PT and anti-FHA, and 96.6% for anti-PT and 89.7% for anti-FHA in the HIV-exposed and uninfected group.

Summary of the WSA's response

- QRD template 10.1. is used
- Correction of text regarding Pertussis results in section 5.1

Assessment of the WSA's response

Both changes are made as requested.

Issues resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

12. Appendix 1

CHMP Assessment Report for EMEA/H/C/002702/P46/036 (Hexacima) and EMEA/H/C/002796/P46/034 (Hexyon) dated 25 June 2022

25 June 2020
EMA/181341/2024
Human Medicines Division

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

Hexacima

diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/002702/P46/036

Hexyon

diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/002796/P46/034

Note

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

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13. Introduction

On 26th March 2020, the MAH submitted a completed paediatric study A3L44 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.

14. Scientific discussion

14.1. Information on the development program

The MAH stated that A3L44 Study, a Phase III, open-label, multicenter, two-arm study in HIV-exposed infected and HIV-exposed uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10 and 14 weeks of age) and a second year of life booster dose (at 15 to 18 months of age) with the DTaP-IPV-HB-PRPT (diphtheria, tetanus, acellular pertussis- inactivated poliovirus vaccine-hepatitis B-Haemophilus influenzae (Hib) capsular polyribosyl ribitol phosphate conjugated to tetanus protein) combined vaccine in the Republic of South Africa is a standalone study.

14.2. Information on the pharmaceutical formulation used in the study

Licensed product. The DTaP-IPV-HB-PRP-T combined vaccine manufactured by Sanofi Pasteur, France is supplied as a suspension in pre-filled syringe.

14.3. Clinical aspects

14.3.1. 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:

A3L44: *"A single center, open-label, two-arm study planned in 50 HIV-exposed infected and 50 HIVexposed uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10 and 14 weeks of age) and a second year of life booster dose (at 15 to 18 months of age) with the DTaP-IPV-HB-PRP~T combined vaccine in the Republic of South Africa."*

This study was not conducted as part of the EU-approved Paediatric Investigational Plan for this product.

14.3.2. Clinical study

A3L44: "A single center, open-label, two-arm study planned in 50 HIV-exposed infected and 50 HIVexposed uninfected infants vaccinated with a 3-dose infant primary series (at 6, 10 and 14 weeks of age) and a second

year of life booster dose (at 15 to 18 months of age) with the DTaP-IPV-HB-PRP~T combined vaccine in the Republic of South Africa."

Description

Study A3L44 was conducted to describe the immunogenicity and safety of DTaP-IPV-HBPRP~TSP vaccine in human immunodeficiency virus (HIV)-exposed infected and uninfected infants given as a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and as a booster dose (at 15 to 18 months of age) in the Republic of South Africa (RSA).

Methods

Objectives

Primary Objectives

- To evaluate the immunogenicity of the study vaccine 1 month after the 3-dose primary series in HIV-exposed infected and in HIV-exposed uninfected infants
- To describe the persistence of all antibodies before receipt of the booster vaccination in HIV-exposed infected and in HIV-exposed uninfected infants
- To evaluate the immunogenicity of the study vaccine 1 month after the booster dose in HIV-exposed infected and in HIV-exposed uninfected infants

Secondary Objectives

- To describe the safety profile after each and all doses of the study vaccine administered as a 3-dose infant primary series in HIV-exposed infected and in HIV-exposed uninfected infants
- To describe the safety profile of the study vaccine administered as a booster in HIV-exposed infected and in HIV-exposed uninfected infants.

Study design

Phase III, open-label, randomized, parallel-group, single study.

Study population /Sample size

All subjects were to be enrolled into one of 2 groups and were to receive primary vaccinations as follows:

- Group A (50 planned HIV-exposed infected subjects): Infants identified as HIV-exposed during pregnancy and PCR positive (infected) for HIV were to receive a 3-dose infant primary vaccination with Sanofi Pasteur's DTaP-IPV-HB-PRP~T combined vaccine at 6, 10 and 14 weeks of age.
- Group B (50 planned HIV-exposed uninfected subjects): Infants identified as HIV-exposed during pregnancy but PCR negative (uninfected) for HIV were to receive a 3-dose infant primary vaccination with Sanofi Pasteur's DTaP-IPV-HB-PRP~T combined vaccine at 6, 10 and 14 weeks of age.

According to the RSA national recommendations on immunization, oral polio vaccine (OPV) could have been given at birth and at 6 weeks of age. Also, Hexaxim vaccine now forms part of the standard-of-care vaccine provided to all children through the public immunization program in South Africa, irrespective of the infant's HIV exposure or infection status. Additional RSA-recommended vaccinations were to be given as per the expanded program on immunization schedule, outside the scope of the protocol: 13- valent pneumococcal conjugate vaccine at 6 and 14 weeks, oral rotavirus vaccine at 6 and 10 weeks, and measles vaccine at 9 and 15-18 months.

Booster

At approximately 15 to 18 months of age, infants in both groups were to receive a booster dose with Sanofi Pasteur's DTaP-IPV-HB-PRP~T combined vaccine.

Collection of immunogenicity data

A blood sample (BS) was to be taken at Visit 1 (pre-vaccination), at Visit 4 (1 month after the third infant dose), at Visit 5 (before administration of the toddler booster dose) and at Visit 6 (1 month after administration of the toddler booster dose).

An additional blood sample (up to 2 mL) was to be taken from Group B subjects at Visit 6 for HIV detection by PCR in order to make sure that these subjects were still HIV negative at the end of the study. This test could have been done at any moment during the study if the infant presented with HIV symptoms.

Collection of safety data

Only Serious Adverse Events (SAEs) related to trial procedures (blood sampling) and SAEs occurring during travel from the Investigator site were to be collected between the Screening Visit and the inclusion visit.

Safety data were to be collected for D0–D7 after each vaccine dose for solicited reactions and for D0–D30 after each vaccine dose for unsolicited non-serious adverse events (AEs). SAEs were to be collected throughout the trial (but only related SAEs, unrelated deaths, and life-threatening SAEs were to be collected between Visits 4 and 5).

The total study duration for each enrolled subject was to be 14.5 to 17.5 months.

Laboratory assays were the same as for the previous studies; analysis was done at the sponsor's laboratory in Swiftwater, USA.

Table 3 Assays and Units for Immunogenicity of Hexyon (source: study report)

Antigen	Assays and reference standards	Units
Diphtheria	ECL multiplex	IU/ml
Tetanus	ECL multiplex	IU/ml
Pertussis (PT, FHA)	ECL multiplex	EU/ml
Hib (PRP)	Farr-type radioimmunoassay (CBER standard)	µg/mL
HepB	VITROS ECi/ECiQ (WHO standard)	mIU/mL
Polio (IPV1, 2, 3)	Vero cell neutralization test	1/dilution

Treatments

Licensed product. The DTaP-IPV-HB-PRP-T combined vaccine manufactured by Sanofi Pasteur, France is supplied as a suspension in pre-filled syringe.

Outcomes/endpoints

<u>Primary Endpoint:</u>

At baseline, before the first dose of study vaccine (D0, Visit 1, at 6 weeks of age):

- Anti-D Ab concentrations ≥ 0.01 international units (IU)/milliliter (mL), ≥ 0.1 IU/ mL, and 1.0 IU/mL, and individual Ab concentrations
- Anti-T Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL, and individual Ab concentrations
- Anti-pertussis toxoid (PT) and anti-filamentous hemagglutinin (FHA) antibody (Ab) concentrations ≥ lower limit of quantification (LLOQ) and ≥ 4 x LLOQ
- Anti-PT and anti-FHA individual Ab concentrations

One month after the third dose of study vaccine (D90, Visit 4, at 18 weeks of age):

- Anti-D Ab concentrations ≥ 0.01 international units (IU)/milliliter (mL), ≥ 0.1 IU/ mL, and 1.0 IU/mL
- Anti-T Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL
- Anti-polyribosylribitol phosphate (PRP) Ab concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dilution [dil])
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PT and anti-FHA:
- Seroconversion: ≥ 4-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from pre-vaccination (pre-Dose 1) to one-month
- post-Dose 3
- Vaccine response: Post-Dose 3 anti-PT and anti-FHA Ab concentrations ≥ 4x LLOQ if pre-Dose 1 Ab concentrations < 4x LLOQ; or post-Dose 3 anti-
- PT and anti-FHA Ab concentrations ≥ pre-Dose 1 Ab concentrations if pre-Dose 1 Ab concentrations ≥ 4x LLOQ
- Individual Ab concentrations/titers: all Abs

Before the booster dose of study vaccine (Visit 5, at 15 to 18 months of age):

- Individual Ab concentrations/titers: all Abs
- Anti-PT and anti-FHA Ab concentrations ≥ LLOQ and ≥ 4 x LLOQ
- Anti-D Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL

- Anti-T Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL
- Anti-PRP Ab concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

One month after the booster dose of study vaccine (Visit 6, at 16 to 19 months of age):

- Anti-D Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL
- Anti-T Ab concentrations ≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, and 1.0 IU/mL
- Anti-PRP Ab concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PT and anti-FHA:
- Seroconversion: ≥ 4-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from pre-vaccination (pre-Dose 1) to one-month
- post-Booster (post-Dose 4)
- Vaccine response: Post-Booster (Dose 4) anti-PT and anti-FHA Ab concentrations ≥ 4x LLOQ if pre-Dose 1 Ab concentrations < 4xLLOQ; or
- post-Booster (Dose 4) anti-PT and anti-FHA Ab concentrations ≥ pre-Dose 1 Ab concentrations if pre-Dose 1 Ab concentrations ≥ 4x LLOQ
- Booster response: ≥ 4-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from pre-Booster to one-month post-Booster if pre-
- Booster Ab concentrations <4x LLOQ; or ≥ 2-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from pre-Booster to one-month post-
- Booster if pre- Booster Ab concentrations ≥ 4x LLOQ
- Individual Ab concentrations/titers: all Abs
- Individual Ab concentration/titer ratios for all antigens (Ag) (1-month post-Dose 4/pre-Dose 4)

<u>Secondary endpoints:</u>

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and all infant dose(s) and after the booster dose.
- Occurrence of any solicited (pre-listed in the subject's diary card [DC] and CRF) injection site and systemic reactions occurring through 7 days (D0-D7) following each and all infant dose(s) and after the booster dose.
- Occurrence of any unsolicited AEs through 30 days following each and all infant dose(s) and after the booster dose.
- Occurrence of any SAEs throughout the primary series trial period (from Visit 1 to Visit 4) and throughout the booster trial period (from Visit 5 to Visit 6). In addition, all related SAEs, unrelated deaths, and life-threatening SAEs were to be collected between Visit 4 and Visit 5.

- Other endpoints recorded or derived as described in the statistical analysis plan(SAP). Depending on the item, these could have included: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration, clinical severity (Grade), relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, and outcome.

Statistical Methods

All analyses were descriptive. No hypotheses were tested. All immunogenicity analyses were performed on the Full Analysis Set (FAS). All safety analyses were performed on the Safety Analysis Set (SafAS).

Immunogenicity

Descriptive statistics were provided for the antibody (Ab) titers for the antigens contained in the licensed vaccines. In general, categorical variables were summarized and presented by frequency counts, percentages, and confidence of intervals (CIs). The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs or geometric mean concentrations (GMCs), 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

Statistical Analysis for Primary Endpoints

Immunogenicity titers were described as follows by time points:

- At baseline: for PT, FHA, D, and T
- One month after the third dose: for all Antibodies
- Before the booster dose: for all Antibodies
- One month after the booster dose: for all Antibodies.

Immunogenicity endpoints were described for available BSs before the first dose, 1-month post-Dose 3, before the booster dose, and 1 month after the booster dose of study combined vaccine.

The following main parameters are presented in HIV-exposed infected and in HIV-exposed uninfected infants as well as overall:

- GM of Ab concentrations/titers at pre-Dose 1, at one-month post-Dose 3, before the booster dose, and one-month post-Booster dose
- GM of individual Ab concentrations/titers ratio:
- Post-Dose 3 / pre-Dose 1 (for PT, FHA)
- Post-Dose 4/pre-Dose 4 for all antigens
- Percentage of subjects with concentrations/titers above pre-defined thresholds
- Vaccine response for PT and FHA
- Booster response for PT and FHA
- Seroconversion rates for PT and FHA

RCDCs of individual concentrations/titers are presented for all antibodies per group at each available time point.

Statistical Analysis for Secondary Endpoints

Safety was described in HIV-exposed infected and in HIV-exposed uninfected infants as well as for all subjects after each and all infant doses and after the booster dose.

For each safety criterion, the number and the percentage of subjects with the criterion (ie, with a given symptom) were computed with its 95% CI.

Confidence intervals (95% CI) were calculated using the exact binomial method (Clopper-Pearson method) for single proportions.

Results

Recruitment/Number analysed

Despite the screening of more than 5,000 HIV-exposed subjects (born from HIV-infected mothers) over a period of 18 months, the investigators failed to enrol the 50 HIV-exposed infected subjects that were planned to be enrolled. The Sponsor decided to put an end to the screening process, and continued to follow the subjects that were enrolled during that period. The enrolment target failure was due to an unexpected and unanticipated high compliance to anti-HIV treatment of HIV-infected women in the RSA, decreasing dramatically the antenatal and postnatal transmission of the virus to their new-borns.

A total of 64 infants were enrolled in the study: 14 HIV-exposed infected infants (Group A) and 50 HIV-exposed uninfected infants (Group B). Among them, 52 infants completed the study (12 infants in Group A and 40 infants in Group B).

Table 4 Disposition of subjects

	Group A HIV-exposed infected infants n (%)	Group B HIV-exposed uninfected infants n (%)	All n (%)
Planned subjects	50	50	100
Enrolled subjects	14 (100.0)	50 (100.0)	64 (100.0)
Completed	12 (85.7)	40 (80.0)	52 (81.3)
Early termination	2 (14.3)	10 (20.0)	12 (18.8)

n: number of subjects fulfilling the item listed

Baseline demographic characteristics of enrolled subjects were similar in both primary series and booster phases of the study even if a lower number of patients composed the booster PPAS compared to the primary series PPAS.

Moreover, no HIV-exposed uninfected subjects changed their HIV infection status during the study.

CHMP comment:

The resulting numbers are rather small for HIV-exposed subjects. All results should be read with caution.

Deviations from protocol were mainly due to a vaccination dose not given or serological samples not being collected in time; this occurred in both groups.

Immunogenicity results

Table 5 Summary of seroprotection/seroconversion/vaccine response rates before and after primary series – Per-Protocol Analysis Set

		HIV-Exposed Infected subjects (N=9)			HIV-Exposed Uninfected subjects (N=42)		
		M	GM	(95% CI)	M	GM	(95% CI)
Anti-D IU/mL	Pre-Dose 1 (V01)	9	0.003	(0.002; 0.007)	42	0.005	(0.004; 0.007)
	Post-Dose 3 (V04)	8	4.72	(3.42; 6.53)	42	2.78	(2.40; 3.22)
Anti-T IU/mL	Pre-Dose 1 (V01)	9	0.140	(0.034; 0.575)	42	0.480	(0.298; 0.774)
	Post-Dose 3 (V04)	8	4.81	(2.89; 8.01)	42	1.37	(1.04; 1.80)
Anti-PT EU/mL	Pre-Dose 1 (V01)	9	1.73	(0.905; 3.31)	42	2.83	(1.95; 4.11)
	Post-Dose 3 (V04)	8	287	(181; 457)	42	151	(128; 178)
	Post-Dose 3 (V04)/ Pre-dose 1 (V01)	8	186	(69.5; 496)	42	53.4	(33.2; 85.9)
Anti-FHA EU/mL	Pre-Dose 1 (V01)	9	4.56	(1.81; 11.5)	42	9.62	(6.38; 14.5)
	Post-Dose 3 (V04)	8	618	(303; 1261)	42	315	(261; 379)
	Post-Dose 3 (V04)/ Pre-dose 1 (V01)	8	162	(42.7; 614)	42	32.7	(19.5; 54.9)
Anti-Polio 1 (1/dil)	Post-Dose 3 (V04)	8	3298	(1476; 7369)	41	1523	(1139; 2038)
Anti-Polio 2 (1/dil)	Post-Dose 3 (V04)	8	3756	(1569; 8989)	41	1365	(1009; 1847)
Anti-Polio 3 (1/dil)	Post-Dose 3 (V04)	8	4096	(1918; 8747)	40	2253	(1647; 3082)
Anti-Hep B mIU/mL	Post-Dose 3 (V04)	9	705	(268; 1854)	42	244	(174; 342)
Anti-PRP µg/mL	Post-Dose 3 (V04)	9	3.94	(1.42; 10.9)	41	2.48	(1.61; 3.81)

Table 6 Summary of geometric means of titers/concentrations before and after booster – Booster Per-Protocol Analysis Set

		HIV-Exposed Infected subjects (N=7)			HIV-Exposed Uninfected subjects (N=29)		
		M	GM	(95% CI)	M	GM	(95% CI)
Anti-D IU/mL	Pre-Booster (V05)	7	0.257	(0.090; 0.740)	29	0.407	(0.281; 0.589)
	Post-Booster (V06)	7	9.72	(4.59; 20.6)	29	6.20	(4.86; 7.92)
	Post-Booster (V06)/ Pre-Dose 1 (V01)	7	2679	(633; 11341)	29	1282	(852; 1930)
	Post-Booster (V06)/ Pre-Booster (V05)	7	37.8	(12.0; 119)	29	15.2	(11.3; 20.6)
Anti-T IU/mL	Pre-Booster (V05)	7	0.389	(0.198; 0.765)	29	0.174	(0.123; 0.245)
	Post-Booster (V06)	7	13.0	(7.11; 23.9)	29	5.90	(4.30; 8.10)
	Post-Booster (V06)/ Pre-Dose 1 (V01)	7	102	(13.3; 787)	29	13.9	(6.77; 28.5)
	Post-Booster (V06)/ Pre-Booster (V05)	7	33.5	(15.6; 71.8)	29	34.0	(27.7; 41.8)
Anti-PT EU/mL	Pre-Booster (V05)	7	18.5	(4.57; 74.8)	29	10.7	(7.43; 15.4)
	Post-Booster (V06)	7	310	(165; 582)	29	194	(149; 252)
	Post-Booster (V06)/ Pre-Dose 1 (V01)	7	188	(57.8; 610)	29	70.1	(42.8; 115)
	Post-Booster (V06)/ Pre-Booster (V05)	7	16.8	(4.84; 57.9)	29	18.1	(13.3; 24.5)
Anti-FHA EU/mL	Pre-Booster (V05)	7	49.1	(12.7; 189)	29	39.3	(25.4; 60.9)
	Post-Booster (V06)	7	369	(187; 726)	29	229	(162; 324)
	Post-Booster (V06)/ Pre-Dose 1 (V01)	7	93.1	(24.0; 362)	29	28.5	(16.3; 49.7)
	Post-Booster (V06)/ Pre-Booster (V05)	7	7.51	(2.51; 22.5)	29	5.83	(4.30; 7.89)
Anti-Polio 1 (1/dil)	Pre-Booster (V05)	7	345	(46.4; 2560)	29	329	(178; 608)
	Post-Booster (V06)	7	3710	(944; 14583)	29	3999	(2848; 5617)
	Post-Booster (V06)/ Pre-Booster (V05)	7	10.8	(1.85; 62.6)	29	12.2	(7.02; 21.1)
Anti-Polio 2 (1/dil)	Pre-Booster (V05)	7	362	(52.0; 2522)	29	175	(108; 283)
	Post-Booster (V06)	7	7420	(2153; 25574)	29	7445	(5361; 10340)
	Post-Booster (V06)/ Pre-Booster (V05)	7	20.5	(3.85; 109)	29	42.6	(25.3; 71.7)
Anti-Polio 3 (1/dil)	Pre-Booster (V05)	7	190	(27.0; 1340)	29	278	(164; 473)
	Post-Booster (V06)	7	5247	(1543; 17834)	29	6450	(4207; 9889)
	Post-Booster (V06)/ Pre-Booster (V05)	7	27.6	(2.91; 261)	29	23.2	(12.5; 43.0)
Anti-Hep B mIU/mL	Pre-Booster (V05)	7	61.4	(13.8; 273)	29	32.1	(19.0; 54.3)
	Post-Booster (V06)	7	2371	(394; 14286)	29	2014	(945; 4292)
	Post-Booster (V06)/ Pre-Booster (V05)	7	38.6	(17.4; 85.7)	29	62.7	(40.2; 97.7)
Anti-PRP µg/mL	Pre-Booster (V05)	7	0.598	(0.117; 3.04)	28	0.401	(0.224; 0.718)
	Post-Booster (V06)	7	40.1	(8.71; 184)	29	39.8	(20.8; 76.3)
	Post-Booster (V06)/ Pre-Booster (V05)	7	67.1	(26.0; 173)	28	110	(65.8; 183)

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

CHMP comment:
Due to the small sample size of the HIV-exposed group all results should be read with caution.

Serological protection thresholds are reached in all cases and for all antigens of Hexyon.

GMTs are seemingly higher in the HIV-exposed group but all CIs overlap and due to the small numbers there is no statistical significance.

Overall, the results show that at least for HIV-exposed infants Hexyon is as immunogenic as for healthy children. If this is transferable to the immunogenicity in other/more severely immune compromised is open for debate. Nevertheless, the information generated here is intended to be implemented into the SmPC in a later Type II variation.

Safety results

Primary vaccination:
Injections site tenderness was the most frequently reported injection site reaction (4 subjects [28.6%] in Group A and 27 subjects [56.3%] in Group B).

Abnormal crying was the most frequently reported systemic reaction (7 subjects [50.0%] in Group A and 30 subjects [62.5%] in Group B).

Overall, in Group A, solicited systemic reactions were reported in more subjects after the second (e.g. crying abnormal, appetite lost or irritability) or the third (e.g. appetite loss) injection compared to the first injection. In Group B, solicited systemic reactions were reported in more subjects after the first injection (e.g. vomiting, drowsiness, and irritability) compared to the other injections (except for fever and appetite loss).

Booster vaccination:

Injections site tenderness was the most frequently reported injection site reaction (4 subjects [33.3%] in Group A and 14 subjects [34.1%] in Group B). Injection site erythema was reported in 1 subject (2.4%) in Group B. Injection site swelling was reported in 1 subject (8.3%) in Group A.

There was no extensive limb swelling.

There were no Grade 3 injection site reactions after the booster dose of vaccine and Grade 2 injection site tenderness were reported in only 4 subjects (1 subject [8.3%] in Group A; 3 subjects [7.5%] in Group B).

Abnormal crying was the most frequently reported systemic reaction (5 subjects [41.7%] in Group A and 12 subjects [30.0%] in Group B) followed by appetite lost (4 subjects [33.3%] in Group A and 11 subjects [27.5%] in Group B), and irritability (3 subjects [25.0%] in Group A and 10 subjects [25.0%] in Group B). Drowsiness was reported only in Group B (12 subjects [30.0%]). Fever and vomiting were reported in a few subjects (3 subjects [25.0%] in Group A and 1 subject [2.5%] in Group B for fever; 2 subjects [16.7%] in Group A and 1 subject [2.5%] in Group B for vomiting).

CHMP comment:

Due to the small sample size of the HIV-exposed group all results should be read with caution.
Solicited AEs were less frequent in the HIV-exposed group.
No deaths occurred in this study.
No SAEs related to the vaccines were reported. No (S)AEs led to discontinuation of the study.
Otherwise similar event rates were seen for solicited local and systemic events as already known from other trials with this vaccine.
No safety issues are identified.
The safety profile remains unchanged.

14.3.3. Discussion on clinical aspects

Overall, the results show that at least for HIV-exposed infants Hexyon is as immunogenic as for healthy children. If this is transferable to the immunogenicity in other/more severely immune compromised is open for debate. Nevertheless, the information generated here is intended to be implemented into the SmPC in a later Type II variation.

The B/R profile remains unchanged.

15. CHMP overall conclusion and recommendation

Study A3L44 was conducted to describe the immunogenicity and safety of DTaP-IPV-HBPRP~TSP vaccine in human immunodeficiency virus (HIV)-exposed infected and uninfected infants given as a 3-dose infant primary series (at 6, 10, and 14 weeks of age) and as a booster dose (at 15 to 18 months of age) in the Republic of South Africa (RSA).

The resulting numbers are rather small for HIV-exposed subjects (i.e. 14 HIV-exposed infected infants of the initially intended 50). Immunogenicity and safety results should be read with caution.

Overall, the results show that at least for HIV-exposed infants Hexacima/Hexaxim/Hexyon is as immunogenic as for healthy children. If this is transferable to the immunogenicity in other/more severely immune compromised is open for debate. Nevertheless, the information generated here is intended to be implemented into the SmPC in a later Type II variation.

☒ **Fulfilled:**No regulatory action required.

In view of the available data regarding study A3L44, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided by 31st October 2020.