



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000973/P46/057

Note

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



1. Introduction

On June 29, 2015, the MAH submitted a completed paediatric study, as well as an extension study, for *Synflorix* in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study has not been conducted in accordance with the agreed *Synflorix* investigation plan.

The MAH stated that the submitted paediatric study does not influence the benefit risk for *Synflorix* and therefore no amendments to the product information have been identified.

A short critical expert overview of each study has been provided.

2. Scientific discussion

2.1. Information on the development program

Study DTPa-HBV-IPV=Hib-MenC-TT-002; "A phase II, open-label, randomised, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine in healthy infants when administered as a three-dose primary vaccination course at 2, 3 and 4 months of age".

Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002; "A phase II, open-label, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine as a booster dose in children aged 12 to 18 months, previously primed with the same vaccine in the primary vaccination study DTPa-HBV-IPV=Hib-MenC-TT-002 (112157)". Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002 is the extension of study DTPa-HBV-IPV=Hib-MenC-TT-002, to assess booster vaccination in children aged 12 to 18 months.

2.2. Information on the pharmaceutical formulation used in the study

The study vaccine was a combined DTPa-HBV-IPV/Hib-MenC-TT vaccine. This new combination vaccine is prepared by extemporaneous mixing of the DTPa-HBV-IPV vaccine (*Infanrix penta*) with the Hib-MenC-TT vaccine (*Menitorix*). The combined DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) and meningococcal serogroup C vaccine (*Menjugate*) were used as active controls. 10-valent pneumococcal conjugate vaccine (*Synflorix*) and human rotavirus (HRV) vaccine (*Rotarix*) were used as co-administered vaccines.

In both studies, *Synflorix* was administered using the currently approved formulation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has initiated the development of a combination vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib and group C meningococcal diseases. This clinical trial was the first to assess the immunogenicity and safety of this investigational DTPa-HBV-IPV/Hib-MenC-TT vaccine compared to the licensed DTPa- HBV-IPV/Hib (*Infanrix hexa*) and meningococcal serogroup C vaccine (*Menjugate*) when administered to infants at 2, 3 and 4 months of age.

The MAH submitted final reports for:

- Study DTPa-HBV-IPV=Hib-MenC-TT-002; “A phase II, open-label, randomised, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine in healthy infants when administered as a three-dose primary vaccination course at 2, 3 and 4 months of age.
- Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002; “A phase II, open-label, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine as a booster dose in children aged 12 to 18 months, previously primed with the same vaccine in the primary vaccination study DTPa-HBV-IPV=Hib-MenC-TT-002 (112157)”.

2.3.2. Clinical studies

Study DTPa-HBV-IPV=Hib-MenC-TT-002

“A phase II, open-label, randomised, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine in healthy infants when administered as a three-dose primary vaccination course at 2, 3 and 4 months of age”.

Description

Methods

Objectives

Primary

- To demonstrate that GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine, is non-inferior to GSK Biologicals’ DTPa-HBV-IPV/Hib vaccine co-administered with Novartis’ meningococcal serogroup C vaccine, in terms of seroprotection to MenC one month after the third dose of primary vaccination.

Non-inferiority for MenC will be demonstrated if the upper limit of the 95% CI on the group difference [HexaMnC minus Hepta] in the percentage of seroprotected subjects is $\leq 10\%$.

- To demonstrate that GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine, is non-inferior to GSK Biologicals’ DTPa-HBV-IPV/Hib vaccine co-administered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine, in terms of seroprotection to Hib one month after the third dose of primary vaccination.

Non-inferiority for Hib will be demonstrated if the upper limit of the 95% CI on the group difference [HexaPn minus Hepta] in percentage of seroprotected subjects is $\leq 10\%$.

Secondary

- To demonstrate that GSK Biologicals’ DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with GSK Biologicals’ 10-valent pneumococcal conjugate vaccine, is non-inferior to GSK

Biologicals' DTPa-HBV-IPV/Hib vaccine co-administered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine, in terms of seroprotection to diphtheria, tetanus, hepatitis B and poliovirus types 1, 2 and 3, and in terms of concentration of antibodies to pertussis one month after the third dose of primary vaccination.

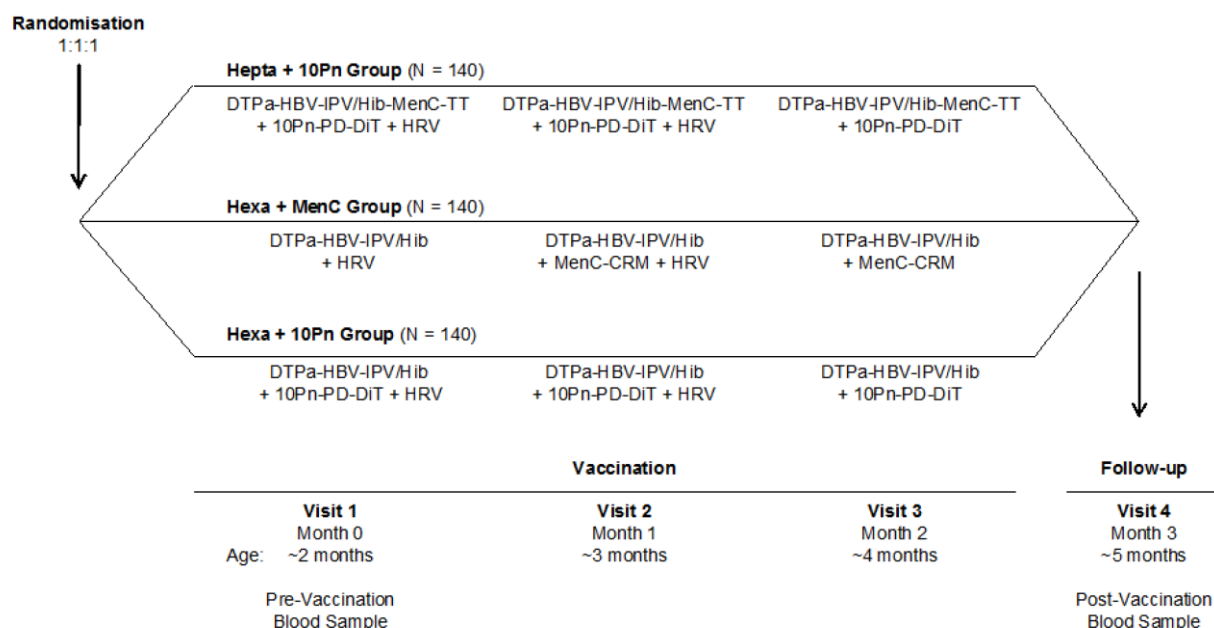
Non-inferiority with regard to diphtheria, tetanus, hepatitis B and poliovirus will be demonstrated if the upper limit of the 95% CI on the group difference [HexaPn minus Hepta] in percentage of seroprotected subjects is $\leq 10\%$. Non-inferiority with regard to pertussis antigens will be demonstrated if the upper limit of the 95% CI on the GMC ratio [HexaPn divided by Hepta] is < 1.5 .

- To assess the immunological response to the study vaccines in terms of seroprotection/seropositivity, geometric mean concentrations/titres to all antigens and in terms of vaccine response to pertussis antigens.
- To assess the pre-vaccination immunological status to MenC and Hib.
- To assess the safety and reactogenicity of the DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine, in terms of solicited, unsolicited, local and general symptoms and serious adverse events.

Study design

This was a phase 2, open-label, randomised, multicenter study in healthy infants receiving a three-dose primary vaccination course at 2, 3 and 4 months of age conducted in Poland. There were three parallel groups:

- **Hepta group:** three doses of DTPa-HBV-IPV/Hib-MenC-TT and three doses of 10Pn-PD-DiT (*Synflorix*) at 2, 3 and 4 months of age.
- **HexaMnC group:** three doses of DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 2, 3 and 4 months of age, and two doses of Novartis' meningococcal serogroup C conjugate vaccine (*Menjugate*) at 3 and 4 months of age.
- **HexaPn group:** three doses of DTPa-HBV-IPV/Hib (*Infanrix hexa*) and three doses of 10Pn-PD-DiT (*Synflorix*) at 2, 3 and 4 months of age.
- Subjects in all groups also received Rotavirus Vaccine (*Rotarix*) at 2 and 3 months of age.



N = Number of subjects that were planned to be enrolled

Hepta + 10Pn group= referred to as the Hepta group in this report

Hexa + MenC group= referred to as the HexaMnC group in this report

Hexa + 10Pn group= referred to as the HexaPn group in this report

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Figure Study design.

Study population

Number of subjects:	Hepta	HexaMnC	HexaPn	Total
<i>Planned</i>	140	140	140	420
<i>Enrolled & vaccinated (=Total vaccinated cohort)</i>	141	139	141	421
<i>According-to-protocol (ATP) cohort for safety:</i>	141	138	141	420
<i>ATP cohort for immunogenicity:</i>	127	132	132	391

Diagnosis and criteria for inclusion

Healthy male or female infant aged between 8 and 12 weeks at the time of first vaccination, born after a gestation period between 36 and 42 weeks who had received one dose of hepatitis B (HBV) vaccine at birth according to the local recommendations. The subject should not have had diphtheria, tetanus, pertussis, hepatitis B, polio, Hib, pneumococcal and/or MenC vaccination or disease(s). Written informed consent was obtained from the parents/legally acceptable representative (LAR) of the subject before entry into the study.

Treatments

The target sample size was 420 enrolled subjects (140 per group) in order to reach 378 evaluable subjects (126 per group) at the time of the analysis.

The randomisation was performed at GSK Biologicals, Rixensart, using MATEX, a programme developed by GSK Biologicals for use in SAS® (Cary, NC, USA).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, an over-randomisation of supplies was prepared.

The vaccine doses were distributed to the study centre while respecting the randomisation block size.

Outcomes/endpoints

Primary endpoints

Immunogenicity one month after the third dose of primary vaccination:

- Anti-PRP seroprotection status
- rSBA-MenC seroprotection status

Secondary endpoints

Immunogenicity one month after the third dose of primary vaccination:

- Anti-PRP, rSBA-MenC, anti-PSC, anti-tetanus, anti-diphtheria, anti-PT, anti-FHA, anti-PRN, anti-HBs, anti- poliovirus type 1, anti-poliovirus type 2, anti- poliovirus type 3 and anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F and protein D antibody concentrations or titres, and seroprotection or seropositivity status.
- Vaccine response to PT, FHA and PRN.

Immunogenicity before the first dose of primary vaccination:

- Anti-PRP, rSBA-MenC, anti-PSC, PT, FHA and PRN antibody concentrations or titres.

Statistical Methods

The primary analysis was based on the According to protocol (ATP) cohort for analysis of immunogenicity. If, for any group, the percentage of enrolled subjects with serological results excluded from this ATP cohort was 5% or more, a second analysis based on the total vaccinated cohort was to be performed to complement the ATP analysis. The analysis of safety was based on the Total vaccinated cohort. Since less than 5% of the vaccinated subjects in each group were eliminated, the analysis on the ATP safety cohort was not done.

Derived and transformed data

- A seronegative subject was a subject whose antibody concentration/titre was below the defined assay cut-off.
- A seropositive subject was a subject whose antibody concentration/titre was greater than or equal to the defined assay cut-off. The following seropositivity thresholds were applicable:
 - anti-PT, anti-FHA or anti-PRN antibody concentrations ≥ 5 EL.U/mL
 - anti-HBs antibody concentrations ≥ 3.3 mIU/mL
 - anti-PSC antibody concentrations ≥ 0.3 µg/mL
 - anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥ 0.05 µg/mL
 - anti-PD antibody concentrations ≥ 100 EL.U/mL
- A seroprotected subject was a subject whose antibody concentration/titre was greater than or equal to the level defining clinical protection. The following seroprotection thresholds were applicable:

- anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$
- rSBA-MenC antibody titres ≥ 8
- anti-diphtheria or anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$
- anti-HBs antibody concentrations $\geq 10 \text{ mIU/mL}$
- anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8
- The following other cut-offs were also used:
 - anti-PRP antibody concentrations $\geq 1 \mu\text{g/mL}$
 - anti-PSC antibody concentrations $\geq 2 \mu\text{g/mL}$
 - anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.2 \mu\text{g/mL}$
- Vaccine response to PT, FHA and PRN, was defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations $<$ cut-off value) or at least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e. with concentrations $\geq$ cut-off value), taking into consideration the decreasing maternal antibodies.
- Vaccine response to MenC, was defined as antibody titres $\geq 1:32$ for initially seronegative subjects or a ≥ 4 -fold increase in post-primary vaccination antibody titres, for initially seropositive subjects.
- The GMT/ GMC calculations were performed by taking the anti-log of the mean of the log₁₀ titre/ concentration transformations. Antibody titres/concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.

Recruitment/ Number analysed

A total of 421 subjects were enrolled in the study after having been checked for the inclusion and exclusion criteria; for details refer to table 1.

Of the 421 subjects vaccinated in this study, 413 subjects completed the study and eight subjects were withdrawn from the study.

The reasons for withdrawal of the subjects were as follows:

- One subject in the Hepta group was withdrawn from the study as a result of a SAE.
- The parents/LARs of seven subjects (two in the Hepta group, three in the HexaMnC group and two in the HexaPn group) withdrew consent. None of these consent withdrawals was due to an adverse event.

Table 1. Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (total vaccinated cohort)

	Hepta	HexaMnC	HexaPn	Total
Number of subjects vaccinated	141	139	141	421
Number of subjects completed	138	136	139	413
Number of subjects withdrawn	3	3	2	8
Reasons for withdrawal:				
Serious Adverse Event	1	0	0	1
Non-serious adverse event	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	2	3	2	7
Migrated/moved from study area	0	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0
Sponsor study termination	0	0	0	0
Others	0	0	0	0

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age. HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age. HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age. Vaccinated = number of subjects who were vaccinated in the study Completed = number of subjects who completed last study visit Withdrawn = number of subjects who did not come for the last visit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 11.

Baseline data

In the ATP cohort for immunogenicity, the mean age of subjects at the first vaccination dose was 8.7 weeks, the percentage of females was 54.7% and all subjects were of White- Caucasian/European heritage. The demographic profile was comparable between the three groups, with respect to mean age, gender and racial distribution (Table 2).

Table 2. Summary of demographic characteristics at visit 1 (ATP cohort for immunogenicity)

		Hepta N = 127		HexaMnC N = 132		HexaPn N = 132		Total N = 391	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (weeks)	Mean	8.6	-	8.8	-	8.7	-	8.7	-
	SD	0.94	-	1.02	-	1.12	-	1.03	-
	Median	8.0	-	8.0	-	8.0	-	8.0	-
	Minimum	8	-	8	-	8	-	8	-
	Maximum	12	-	12	-	12	-	12	-
Gender	Female	68	53.5	83	62.9	63	47.7	214	54.7
	Male	59	46.5	49	37.1	69	52.3	177	45.3
Geographic Ancestry	White - Caucasian/European Heritage	127	100	132	100	132	100	391	100

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.
HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.
HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

N = total number of subjects

n (%) = number (percentage) of subjects in a given category

Value = value of the considered parameter

SD = standard deviation

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 13.

Immunogenicity results

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Since at least 5% of the subjects with available immunogenicity data in a given group were excluded from the ATP cohort for immunogenicity, the analysis on total vaccinated cohort was also performed to complement the ATP analysis. Immunogenicity analysis of the total vaccinated cohort yielded similar results as the ATP cohort analysis and are not further presented in this report.

Immune response to the Heptavalent vaccine

Primary Objectives (Non-inferiority in terms of anti-PRP and anti-rSBA-MenC response)

Anti-PRP response

The seroprotection rates, the percentage of subjects with anti-PRP antibody concentrations ≥ 1.0 $\mu\text{g/mL}$, and anti-PRP GMCs at the pre- and post-primary vaccination time points are presented in Table 3.

One month post-primary vaccination:

- The immune response of the heptavalent DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with *Synflorix* was demonstrated to be non-inferior to that of *Infanrix hexa* co-administered with *Synflorix* in terms of seroprotection rate against *Haemophilus influenzae* type b, as the upper limit of the standardised asymptotic 95% CI on the group difference (HexaPn group minus Hepta group) for the percentage of seroprotected subjects was below 10%, the pre-defined clinical limit for non-inferiority.
- Seroprotection rates to PRP were 100% in the Hepta group, 93.2% in the HexaMnC group and 99.2% in the HexaPn group.
- The percentage of subjects with anti-PRP antibody concentrations ≥ 1 $\mu\text{g/mL}$ was 90.5% in the Hepta group, 52.3% in the HexaMnC group and 64.1% in the HexaPn group.
- Anti-PRP GMCs were 4.255 $\mu\text{g/mL}$ in the Hepta group, 1.123 $\mu\text{g/mL}$ in the HexaMnC group and 1.721 $\mu\text{g/mL}$ in the HexaPn group.

Table 3. Percentage of subjects with anti-PRP concentrations equal to or above the cut-off values of 0.15 and 1.0 $\mu\text{g/mL}$ and geometric mean concentration before the first vaccination dose and one month after primary vaccination

				≥ 0.15 $\mu\text{g/mL}$				≥ 1.0 $\mu\text{g/mL}$				GMC		
				95% CI				95% CI				95% CI		
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PRP	Hepta	Pre	124	64	51.6	42.5	60.7	15	12.1	6.9	19.2	0.197	0.162	0.240
		Post	126	126	100	97.1	100	114	90.5	84.0	95.0	4.255	3.591	5.043
	HexaMnC	Pre	127	45	35.4	27.2	44.4	10	7.9	3.8	14.0	0.152	0.125	0.184
		Post	132	123	93.2	87.5	96.8	69	52.3	43.4	61.0	1.123	0.890	1.416
	HexaPn	Pre	127	55	43.3	34.5	52.4	13	10.2	5.6	16.9	0.176	0.143	0.217
		Post	131	130	99.2	95.8	100	84	64.1	55.3	72.3	1.721	1.383	2.143

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

GMC = geometric mean antibody concentration calculated on all subjects

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pre = Pre-primary blood sample timepoint.

Post = Post-primary blood sample timepoint

Note: bold indicates exploratory significant statistical difference was found versus the Hepta group.

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 20.

Assessor's comment

Seroprotection rates to PRP were higher in the Hepta and HexaPn groups, respectively, compared to the HexaMnC group. This difference might potentially be explained by the fact that *Synflorix* was co-administered in the Hepta and HexaPn groups but not in the HexaMnC group, as *Synflorix* is previously known to have the ability to increase the anti-PRP response (refer to EPAR: EMEA/H/C/000973/P46/040 for details). The positive effect by *Synflorix* on the anti-PRP response might potentially also be reflected in the generally higher levels of anti-PRP antibody concentrations and anti-PRP GMCs in the Hepta group than the other two groups.

No further regulatory action is required based on these results regarding *Synflorix*.

rSBA-MenC response

The seroprotection rates, percentage of subjects with titres $\geq 1:128$, and GMTs for rSBAMenC antibodies at the pre- and post-primary vaccination time points are presented in Table 4. Subjects in the HexaPn group did not receive a MenC vaccine and therefore only the results of the Hepta and HexaMnC groups are discussed.

One month post-primary vaccination:

- The immune response of the heptavalent DTPa-HBV-IPV/Hib-MenC-TT vaccine was demonstrated to be non-inferior to *Menjugate* co-administered with *Infanrix hexa* in terms of seroprotection rate for rSBA MenC, as the upper limit of the standardised asymptotic 95% CI on the group difference (HexaMnC group minus Hepta group) for the percentage of seroprotected subjects was below 10%, the predefined clinical limit for non-inferiority.
- Seroprotective rSBA-MenC antibody titres $\geq 1:8$ were observed in 98.4% of subjects in the Hepta group and 97.7% of subjects in the HexaMnC group.
- High percentages (94.4% in the Hepta group and 97.7% in the HexaMnC group) of subjects exhibited anti-rSBA-MenC titres $\geq 1:128$. rSBA-MenC GMTs were 786.9 $\mu\text{g/mL}$ in the Hepta group and 2674 $\mu\text{g/mL}$ in the HexaMnC group.

Table 4. Percentage of subjects with rSBA-MenC titres equal to or above the cut-off values of 1:8 and 1:128 and geometric mean titre before the first vaccination dose and one month after primary vaccination

Antibody	Group	Timing	N	$\geq 1:8$				$\geq 1:128$				GMT		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
rSBA-MenC	Hepta	Pre	118	4	3.4	0.9	8.5	0	0.0	0.0	3.1	4.3	4.0	4.7
		Post	126	124	98.4	94.4	99.8	119	94.4	88.9	97.7	786.9	637.2	971.9
	HexaMnC	Pre	119	8	6.7	2.9	12.8	3	2.5	0.5	7.2	4.8	4.2	5.5
		Post	130	127	97.7	93.4	99.5	127	97.7	93.4	99.5	2674.0	2125.1	3364.7
	HexaPn	Pre	120	3	2.5	0.5	7.1	0	0.0	0.0	3.0	4.2	4.0	4.5
		Post	128	10	7.8	3.8	13.9	9	7.0	3.3	12.9	6.1	4.7	8.0

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

GMT = geometric mean antibody titre calculated on all subjects.

N = number of subjects with available results.

n (%) = number (percentage) of subjects with titre within the specified range.

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit.

Pre = Pre-primary blood sample timepoint.

Post = Post-primary blood sample timepoint.

Note: bold indicates exploratory significant statistical difference was found versus the Hepta group.

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 21.

Anti-PSC response

The percentage of subjects with anti-PSC concentrations $\geq 0.3 \mu\text{g/mL}$ and $\geq 2.0 \mu\text{g/mL}$ and GMCs at the pre- and post-primary vaccination time points are shown in Table 5. Subjects in the HexaPn group did not receive a MenC vaccine and therefore only the results of the Hepta and Hexa MenC groups are discussed.

One month post-primary vaccination:

- All but one subjects (99.2%) had anti-PSC concentrations $\geq 2.0 \mu\text{g/mL}$ in the Hepta and HexaMnC groups.

Table 5. Percentage of subjects with anti-PSC concentrations equal to or above the cut-off values of 0.3 and 2.0 $\mu\text{g/mL}$ and geometric mean concentration before the first vaccination dose and one month after primary vaccination

Antibody	Group	Timing	N	$\geq 0.3 \mu\text{g/mL}$				$\geq 2.0 \mu\text{g/mL}$				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
Anti-PSC	Hepta	Pre	122	9	7.4	3.4	13.5	2	1.6	0.2	5.8	0.17	0.16	0.19
		Post	125	124	99.2	95.6	100	124	99.2	95.6	100	19.15	16.88	21.74
	HexaMnC	Pre	121	10	8.3	4.0	14.7	2	1.7	0.2	5.8	0.17	0.16	0.19
		Post	126	125	99.2	95.7	100	125	99.2	95.7	100	18.10	15.91	20.59
	HexaPn	Pre	126	14	11.1	6.2	17.9	1	0.8	0.0	4.3	0.18	0.16	0.20
		Post	132	8	6.1	2.7	11.6	6	4.5	1.7	9.6	0.19	0.16	0.22

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

GMC = geometric mean antibody concentration calculated on all subjects.

N = number of subjects with available results.

n (%) = number (percentage) of subjects with concentration within the specified range.

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit.

Pre = Pre-primary blood sample timepoint.

Post = Post-primary blood sample timepoint.

Note: bold indicates exploratory significant statistical difference was found versus the Hepta group.

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 22.

Secondary objectives (Non-inferiority in terms of anti-tetanus, anti-diphtheria, anti-pertussis, anti-HBs and anti-poliovirus types 1, 2 and 3 response)

The non-inferiority of the immune response of the heptavalent DTPa-HBV-IPV/Hib- MenC-TT vaccine co-administered with *Synflorix* (Hepta group) to that of *Infanrix hexa* co-administered with *Synflorix* (HexaPn group) concerning the secondary endpoints was assessed in a sequential manner according to the ranking: tetanus, diphtheria, pertussis, hepatitis B and the three poliovirus types. A conclusion on one objective was only possible if the primary objective and all objectives with a lower rank were demonstrated before.

One month post-primary vaccination:

- Non-inferiority in terms of seroprotection rates against tetanus and diphtheria was demonstrated since the upper limits of the standardised asymptotic 95% CI on the group

differences (HexaPn group minus Hepta group) for the percentage of seroprotected subjects were below 10%, the pre-defined clinical limit for noninferiority.

- The upper limit of the 95% CI on the GMC ratio (HexaPn group divided by Hepta group) was below 1.5, the pre-defined clinical limit for non-inferiority, in terms of immune response to PT and FHA. The upper limit of the 95% CI on the GMC ratio for anti-PRN was 1.57, and exceeded the pre-defined non-inferiority margin. Therefore non-inferiority in terms of pertussis immune response was not demonstrated.
- For hepatitis B, the upper limit of the standardised asymptotic 95% CI on the group difference (HexaPn group minus Hepta group) for the percentage of seroprotected subjects was below 10%, the pre-defined clinical limit for non-inferiority. However since non-inferiority for the higher ranking anti-pertussis antibodies was not demonstrated, non-inferiority for hepatitis B could not be concluded.
- *For hepatitis B, the upper limit of the standardised asymptotic 95% CI on the group difference (HexaPn group minus Hepta group) for the percentage of subjects with post-vaccination anti-HBs concentrations ≥ 100 mIU/mL as measured by ELISA was below 10%, the pre-defined clinical limit for non-inferiority. (Note that this is a post-hoc analysis, which is not part of the primary analysis.)* (Amended: 14 January 2014)
- For poliovirus types 1, 2 and 3, the upper limits of the standardised asymptotic 95% CI on the group difference (HexaPn group minus Hepta group) for the percentage of seroprotected subjects were all below 10%, the pre-defined clinical limit for noninferiority. However since non-inferiority for the higher ranking anti-pertussis antibodies was not demonstrated, non-inferiority for the three polioviruses could not be concluded

Assessor's comment

The primary objectives of the present study were met; i.e. the non-inferiority of the study vaccine, co-administered with *Synflorix*, to *Infanrix hexa* and *Menjugate* regarding immune response to PRP and MenC was shown. Concerning the secondary objectives, the non-inferiority of the study vaccine co-administered with *Synflorix* to *Infanrix hexa* co-administered with *Synflorix* was shown for seroprotection rates to tetanus and diphtheria. Regarding the pertussis antigens, hepatitis B and the three poliovirus types, non-inferiority could not be concluded.

No further regulatory action is required regarding *Synflorix* based on these results.

Immune response to the co-administered 10-valent pneumococcal conjugate vaccine

The geometric mean concentrations (GMCs) of antibodies against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and the percentage of subjects with pneumococcal antibody concentrations $\geq$ the assay cut-off of 0.05 $\mu\text{g/mL}$ and $\geq$ the threshold value of 0.20 $\mu\text{g/mL}$, one month post-primary vaccination are presented in Table 6.

Subjects in the HexaMnC group did not receive a pneumococcal vaccine and therefore only the results of the Hepta and HexaPn groups are discussed.

One month post-primary vaccination:

- The percentage of subjects with pneumococcal antibody concentrations $\geq$ the threshold value of 0.20 $\mu\text{g/mL}$ was at least 97.6% for all serotypes except 6B (74.8%) and 23F (81.4%).
- All subjects but one had measurable antibodies against protein D ($\geq 100 \text{ EL.U/mL}$).

Exploratory group comparisons indicated that the GMCs against serotype 18C in the Hepta group were significantly higher than those in HexaPn group. 18C is the serotype conjugated to TT.

Table 6. Percentage of subjects with anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F concentrations equal to or above the cut-off values of 0.05 and 0.2 $\mu\text{g/mL}$ and geometric mean concentration one month after primary vaccination

Antibody	Group	Timing	N	$\geq 0.05 \mu\text{g/mL}$				$\geq 0.2 \mu\text{g/mL}$				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
Anti-Pneumo 1	Hepta	Post	125	125	100	97.1	100	125	100	97.1	100	1.53	1.36	1.72
	HexaMnC	Post	123	37	30.1	22.1	39.0	12	9.8	5.1	16.4	0.04	0.04	0.05
	HexaPn	Post	125	124	99.2	95.6	100	122	97.6	93.1	99.5	1.41	1.20	1.65
Anti-Pneumo 4	Hepta	Post	122	122	100	97.0	100	121	99.2	95.5	100	1.92	1.66	2.22
	HexaMnC	Post	119	21	17.6	11.3	25.7	7	5.9	2.4	11.7	0.04	0.03	0.04
	HexaPn	Post	128	127	99.2	95.7	100	126	98.4	94.5	99.8	1.99	1.69	2.33
Anti-Pneumo 5	Hepta	Post	126	126	100	97.1	100	126	100	97.1	100	2.23	1.99	2.50
	HexaMnC	Post	111	44	39.6	30.5	49.4	10	9.0	4.4	15.9	0.05	0.04	0.06
	HexaPn	Post	127	126	99.2	95.7	100	126	99.2	95.7	100	2.23	1.90	2.61
Anti-Pneumo 6B	Hepta	Post	119	114	95.8	90.5	98.6	89	74.8	66.0	82.3	0.40	0.32	0.49
	HexaMnC	Post	120	28	23.3	16.1	31.9	5	4.2	1.4	9.5	0.04	0.03	0.04
	HexaPn	Post	126	117	92.9	86.9	96.7	100	79.4	71.2	86.1	0.44	0.35	0.55
Anti-Pneumo 7F	Hepta	Post	125	125	100	97.1	100	125	100	97.1	100	2.26	2.02	2.53
	HexaMnC	Post	123	56	45.5	36.5	54.8	14	11.4	6.4	18.4	0.06	0.05	0.07
	HexaPn	Post	129	128	99.2	95.8	100	128	99.2	95.8	100	2.24	1.95	2.56
Anti-Pneumo 9V	Hepta	Post	126	126	100	97.1	100	126	100	97.1	100	2.16	1.90	2.46
	HexaMnC	Post	121	37	30.6	22.5	39.6	13	10.7	5.8	17.7	0.05	0.04	0.06
	HexaPn	Post	127	126	99.2	95.7	100	125	98.4	94.4	99.8	1.99	1.72	2.30
Anti-Pneumo 14	Hepta	Post	126	126	100	97.1	100	126	100	97.1	100	3.75	3.23	4.36
	HexaMnC	Post	119	106	89.1	82.0	94.1	65	54.6	45.2	63.8	0.22	0.17	0.28
	HexaPn	Post	128	128	100	97.2	100	127	99.2	95.7	100	3.75	3.26	4.32
Anti-Pneumo 18C	Hepta	Post	122	122	100	97.0	100	121	99.2	95.5	100	3.83	3.22	4.56
	HexaMnC	Post	111	52	46.8	37.3	56.6	10	9.0	4.4	15.9	0.05	0.04	0.07
	HexaPn	Post	126	126	100	97.1	100	125	99.2	95.7	100	2.51	2.11	2.99
Anti-Pneumo 19F	Hepta	Post	127	127	100	97.1	100	126	99.2	95.7	100	3.99	3.37	4.72
	HexaMnC	Post	121	88	72.7	63.9	80.4	28	23.1	16.0	31.7	0.10	0.08	0.13
	HexaPn	Post	128	127	99.2	95.7	100	127	99.2	95.7	100	3.86	3.19	4.66
Anti-Pneumo 23F	Hepta	Post	126	123	97.6	93.2	99.5	107	84.9	77.5	90.7	0.68	0.55	0.84
	HexaMnC	Post	127	34	26.8	19.3	35.4	8	6.3	2.8	12.0	0.04	0.03	0.05
	HexaPn	Post	129	124	96.1	91.2	98.7	105	81.4	73.6	87.7	0.63	0.50	0.79

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

GMC = geometric mean antibody concentration calculated on all subjects.

N = number of subjects with available results.

n (%) = number (percentage) of subjects with concentration within the specified range.

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit.

Post = Post-primary blood sample timepoint.

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 28.

Assessor's comment

97.6% of subjects in the Hepta group had antibody concentrations ≥ 0.2 $\mu\text{g/mL}$ for all pneumococcal serotypes included in *Synflorix*, except 6B and 23F. These results are in line with previous study results of *Synflorix*, demonstrating a lower immune response to serotypes 6B and 23F. Consequently, no further action based on these results are required.

Additional analysis (Amended 14 January 2014)

A risk was identified that subjects whose post-vaccination titres were initially measured between 10 and 100 mIU/mL might have been informed of an incorrect seroprotection status. Individual seroprotection of the study subjects was reviewed on a case-by-case basis, taking into account the seroprotection status at other available time-points. Retesting was performed as an urgent precaution using a commercial assay used for routine testing. The results of that retesting, were communicated to the investigators to allow individual counselling of the impacted study subjects or their parents/legally authorized representatives, including revaccination when appropriate. Since the testing was only performed on a limited number of subjects based on an individual need, and since the assay has not been validated by GSK Biologicals for the purpose of clinical research, the results of that testing were not taken into account for study analyses.

One month post-dose 3, three subjects had anti- HBs antibody concentrations which were initially measured between 10 and 100 mIU/mL.

For one subject, the results of anti-HBs retesting were above 10 mIU/mL showing that this subject was seroprotected. Since no change in seroprotection status was found, no other actions were taken.

For two other subjects, the results of anti-HBs retesting could not be determined since an insufficient quantity of the sample was available, suggesting that the subjects might not be seroprotected. This was communicated to the investigator on 22 November 2012 to allow individual counselling.

As per follow-up information from the investigator, one subject had an additional blood collection on 8 May 2013, with a result of anti-HBs antibody concentrations of 0.08 mIU/mL. The subject returned to the site for revaccination on 10 May 2013.

One subject had an additional blood collection on 24 June 2013, with a result of anti-HBs antibody concentrations of 572 mIU/mL. Since no change in seroprotection status was found, no other actions were taken.

Safety results

A summary of local and systemic solicited and unsolicited AEs during the 8-day period after each vaccination and any vaccination is provided below in tables 7-12.

Table 7. Incidence and nature of symptoms (solicited and unsolicited) reported during the 8-day (Days 0-7) post-vaccination period overall by dose

		Any symptom						General symptoms						Local symptoms					
					95% CI						95% CI						95% CI		
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%
Overall/dose	Hepta	419	332	79.2	75.0	83.0	419	302	72.1	67.5	76.3	419	224	53.5	48.6	58.3			
	HexaMnC	411	332	80.8	76.6	84.5	411	269	65.5	60.6	70.0	411	232	56.4	51.5	61.3			
	HexaPn	421	353	83.8	80.0	87.2	421	322	76.5	72.1	80.5	421	259	61.5	56.7	66.2			

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.
HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.
HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.
N= number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 31.

Table 8. Incidence and nature of local symptoms (solicited and unsolicited) reported for each vaccine during the 8-day (Days 0-7) post-vaccination period overall by dose

		Infanrix hexa					Menjugate					DTPa-HBV-IPV/Hib-MenC-TT					Synflorix				
					95% CI					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall /dose	Hepta	-	-	-	-	-	-	-	-	-	-	419	194	46.3	41.4	51.2	419	194	46.3	41.4	51.2
	HexaMnC	411	221	53.8	48.8	58.7	272	124	45.6	39.6	51.7	-	-	-	-	-	-	-	-	-	-
	HexaPn	421	240	57.0	52.1	61.8	-	-	-	-	-	-	-	-	-	-	421	228	54.2	49.3	59.0

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.
HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.
HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.
N= number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 32.

Table 9. Incidence of solicited local symptoms reported during the 8-day (Days 0-7) post-vaccination period overall by dose

			Hepta					HexaMnC					HexaPn				
						95 % CI					95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	417	118	28.3	24.0	32.9	410	118	28.8	24.4	33.4	420	167	39.8	35.0	44.6
		Grade 3	417	6	1.4	0.5	3.1	410	11	2.7	1.3	4.7	420	11	2.6	1.3	4.6
	DTPa-HBV-IPV/Hib-MenC-TT	All	417	102	24.5	20.4	28.9	-	-	-	-	-	-	-	-	-	-
		Grade 3	417	5	1.2	0.4	2.8	-	-	-	-	-	-	-	-	-	-
	Infanrix hexa	All	-	-	-	-	-	410	109	26.6	22.4	31.1	420	147	35.0	30.4	39.8
		Grade 3	-	-	-	-	-	410	11	2.7	1.3	4.7	420	10	2.4	1.1	4.3
	Menjugate	All	-	-	-	-	-	272	68	25.0	20.0	30.6	-	-	-	-	-
		Grade 3	-	-	-	-	-	272	3	1.1	0.2	3.2	-	-	-	-	-
	Synflorix	All	417	104	24.9	20.9	29.4	-	-	-	-	-	420	154	36.7	32.0	41.5
		Grade 3	417	5	1.2	0.4	2.8	-	-	-	-	-	420	10	2.4	1.1	4.3
Redness (mm)	Total	All	417	150	36.0	31.4	40.8	410	168	41.0	36.2	45.9	420	176	41.9	37.1	46.8
		>20	417	6	1.4	0.5	3.1	410	12	2.9	1.5	5.1	420	13	3.1	1.7	5.2
	DTPa-HBV-IPV/Hib-MenC-TT	All	417	120	28.8	24.5	33.4	-	-	-	-	-	-	-	-	-	-
		>20	417	2	0.5	0.1	1.7	-	-	-	-	-	-	-	-	-	-
	Infanrix hexa	All	-	-	-	-	-	410	158	38.5	33.8	43.4	420	156	37.1	32.5	42.0
		>20	-	-	-	-	-	410	10	2.4	1.2	4.4	420	10	2.4	1.1	4.3
	Menjugate	All	-	-	-	-	-	272	86	31.6	26.1	37.5	-	-	-	-	-
		>20	-	-	-	-	-	272	2	0.7	0.1	2.6	-	-	-	-	-
	Synflorix	All	417	127	30.5	26.1	35.1	-	-	-	-	-	420	141	33.6	29.1	38.3
		>20	417	4	1.0	0.3	2.4	-	-	-	-	-	420	8	1.9	0.8	3.7
Swelling (mm)	Total	All	417	116	27.8	23.6	32.4	410	99	24.1	20.1	28.6	420	138	32.9	28.4	37.6
		>20	417	28	6.7	4.5	9.6	410	22	5.4	3.4	8.0	420	30	7.1	4.9	10.0
	DTPa-HBV-IPV/Hib-MenC-TT	All	417	94	22.5	18.6	26.9	-	-	-	-	-	-	-	-	-	-
		>20	417	16	3.8	2.2	6.2	-	-	-	-	-	-	-	-	-	-
	Infanrix hexa	All	-	-	-	-	-	410	86	21.0	17.1	25.2	420	122	29.0	24.7	33.6
		>20	-	-	-	-	-	410	17	4.1	2.4	6.6	420	13	3.1	1.7	5.2
	Menjugate	All	-	-	-	-	-	272	53	19.5	14.9	24.7	-	-	-	-	-
		>20	-	-	-	-	-	272	7	2.6	1.0	5.2	-	-	-	-	-
	Synflorix	All	417	92	22.1	18.2	26.4	-	-	-	-	-	420	109	26.0	21.8	30.4
		>20	417	24	5.8	3.7	8.4	-	-	-	-	-	420	22	5.2	3.3	7.8

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom

Total : n (%) = number (percentage) of subjects/doses with at least one local symptom whatever the number of injections; 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 33.

Table 10. Incidence of solicited general symptoms reported during the 8-day (Days 0-7) post-vaccination period overall by dose

		Hepta					HexaMnC					HexaPn				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	417	184	44.1	39.3	49.0	410	169	41.2	36.4	46.2	420	196	46.7	41.8	51.6
	Grade 3	417	4	1.0	0.3	2.4	410	12	2.9	1.5	5.1	420	6	1.4	0.5	3.1
	Related	417	167	40.0	35.3	44.9	410	157	38.3	33.6	43.2	420	178	42.4	37.6	47.3
Irritability	All	417	223	53.5	48.6	58.3	410	190	46.3	41.4	51.3	420	251	59.8	54.9	64.5
	Grade 3	417	22	5.3	3.3	7.9	410	24	5.9	3.8	8.6	420	34	8.1	5.7	11.1
	Related	417	204	48.9	44.0	53.8	410	171	41.7	36.9	46.6	420	234	55.7	50.8	60.5
Loss of appetite	All	417	107	25.7	21.5	30.1	410	103	25.1	21.0	29.6	420	127	30.2	25.9	34.9
	Grade 3	417	3	0.7	0.1	2.1	410	4	1.0	0.3	2.5	420	1	0.2	0.0	1.3
	Related	417	96	23.0	19.1	27.4	410	92	22.4	18.5	26.8	420	121	28.8	24.5	33.4
Temperature (Axillary) (°C)	All	417	84	20.1	16.4	24.3	410	48	11.7	8.8	15.2	420	92	21.9	18.0	26.2
	>38	417	14	3.4	1.8	5.6	410	16	3.9	2.2	6.3	420	27	6.4	4.3	9.2
	>38.5	417	4	1.0	0.3	2.4	410	6	1.5	0.5	3.2	420	8	1.9	0.8	3.7
	>39	417	0	0.0	0.0	0.9	410	1	0.2	0.0	1.4	420	0	0.0	0.0	0.9
	Related	417	77	18.5	14.9	22.5	410	40	9.8	7.1	13.0	420	84	20.0	16.3	24.2

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 34.

Table 11. Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period

		Hepta N = 419				HexaMnC N = 411				HexaPn N = 421			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		4	1.0	0.3	2.4	3	0.7	0.2	2.1	0	0.0	0.0	0.9
Blood and lymphatic system disorders (10005329)	Thrombocytopenia (10043554)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
Infections and infestations (10021881)	Pneumonia (10035664)	0	0.0	0.0	0.9	1	0.2	0.0	1.3	0	0.0	0.0	0.9
	Rhinitis (10039083)	0	0.0	0.0	0.9	1	0.2	0.0	1.3	0	0.0	0.0	0.9
	Upper respiratory tract infection (10046306)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Urinary tract infection (10046571)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Viral infection (10047461)	0	0.0	0.0	0.9	1	0.2	0.0	1.3	0	0.0	0.0	0.9

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 35.

Table 12. Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period

Primary System Organ Class (CODE)	Preferred Term (CODE)	Hepta N = 419				HexaMnC N = 411				HexaPn N = 421			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
At least one symptom		9	2.1	1.0	4.0	2	0.5	0.1	1.7	5	1.2	0.4	2.7
Blood and lymphatic system disorders (10005329)	Thrombocytopenia (10043554)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Diarrhoea (10012735)	1	0.2	0.0	1.3	1	0.2	0.0	1.3	3	0.7	0.1	2.1
	Flatulence (10016766)	2	0.5	0.1	1.7	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Haematochezia (10018836)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Regurgitation (10067171)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
	Vomiting (10047700)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	1	0.2	0.0	1.3
General disorders and administration site conditions (10018065)	Injection site reaction (10022095)	0	0.0	0.0	0.9	0	0.0	0.0	0.9	1	0.2	0.0	1.3
Infections and infestations (10021881)	Upper respiratory tract infection (10046306)	1	0.2	0.0	1.3	0	0.0	0.0	0.9	0	0.0	0.0	0.9
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	1	0.2	0.0	1.3	1	0.2	0.0	1.3	0	0.0	0.0	0.9

Hepta = DTPa-HBV-IPV/Hib-MenC-TT + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

HexaMnC = DTPa-HBV-IPV/Hib at 2, 3, 4 months, MenC-CRM at 3, 4 months and HRV at 2, 3 months of age.

HexaPn = DTPa-HBV-IPV/Hib + 10Pn-PD-DiT at 2, 3, 4 months and HRV at 2, 3 months of age.

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-002, Table 36.

Serious adverse events

No deaths were reported during this study. Non-fatal SAEs were reported for a total of 14 subjects during the entire study period. Among these, five subjects belonged to the Hepta group, six subjects were from the HexaMnC group and three were from the HexaPn group. One of these SAEs belonging to the Hepta group was considered to be potentially related to vaccination by the investigator. Eight days after the third dose of the DTPa-HBV-IPV/Hib-MenC-TT and *Synflorix* vaccines and 39 days after the second dose of *Rotarix*, this subject developed thrombocytopenia. On 22 Nov 2009 the subject experienced blood in stools. A few days later the subject developed mild purpuric rash. The subject was treated with immunoglobulins and steroids and the event was reported as resolved 116 days after the onset of symptoms. No SAE was still ongoing at the end of the study.

One subject in the Hepta group had an SAE that led to premature discontinuation of the study vaccines.

Assessor's comment

The frequency of AEs reported was approximately the same among the treatment groups (Hepta, HexaMnC and HexaPn). Overall, all the vaccines in the present study seem to have a tolerable safety profile.

The SAE reported for one subject, i.e. thrombocytopenia, was considered to have a potential causal relationship to the vaccination. As the subject received multiple vaccines, it is difficult to assess the causal relationship of the SAE to individual vaccines, but rather as related to vaccination in general. As the affected subject received *Synflorix*, it can not be excluded that this was the reason behind the SAE. An increased reactogenicity has previously been seen when *Infanrix* is co-administered with *Synflorix* compared to *Infanrix* given without *Synflorix*. However, as this was a single event which was resolved with proper treatment, and considering the fact that no causal relationship to a specific vaccine can be established, no new safety concerns are raised based on these results.

Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002

A phase II, open-label, multicentre study to evaluate the safety and immunogenicity of GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine as a booster dose in children aged 12 to 18 months, previously primed with the same vaccine in the primary vaccination study DTPa-HBV-IPV=Hib-MenC-TT-002 (112157).

Description

Methods

Objectives

Primary

- To demonstrate that GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine is non-inferior to *Menjugate* co-administered with *Infanrix hexa* in terms of seroprotection to MenC one month after the booster dose.

Non-inferiority would be demonstrated if the upper limit of the 95% CI on the group difference [MnC-CRM group minus Hepta group] in the percentage of subjects with rSBA-MenC titres $\geq 1:8$ is $\leq 10\%$.

- To demonstrate that GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine is non-inferior to *Infanrix hexa* co-administered with NeisVac-C in terms of seroprotection to PRP and MenC, one month after the booster dose.

Non-inferiority would be demonstrated if the upper limit of the 95% CI on the group difference [MnC-TT group minus Hepta group] in the percentage of subjects with anti-PRP concentrations $\geq 0.15 \mu\text{g/ml}$ is $\leq 10\%$.

and

Non-inferiority would be demonstrated if the upper limit of the 95% CI on the group difference [MnC-TT group minus Hepta group] in the percentage of subjects with rSBA-MenC titres $\geq 1:8$ is $\leq 10\%$.

Secondary

- To demonstrate that GSK Biologicals' DTPa-HBV-IPV/Hib-MenC-TT vaccine is non-inferior to *Infanrix hexa* co-administered with NeisVac-C in terms of seroprotection to diphtheria, tetanus, hepatitis B, and poliovirus types 1, 2 and 3, and in terms of antibody GMCs to pertussis antigens one month after the booster dose.

Non-inferiority for diphtheria, tetanus, hepatitis B and poliovirus would be demonstrated if the upper limit of the 95% CI on the group difference [MnC-TT Group minus Hepta Group] in the percentage of seroprotected subjects is $\leq 10\%$

and

Non-inferiority for pertussis antigens would be demonstrated if the UL of the 95% CI on the GMC ratio [MnC-TT Group divided by Hepta Group] is ≤ 1.5 .

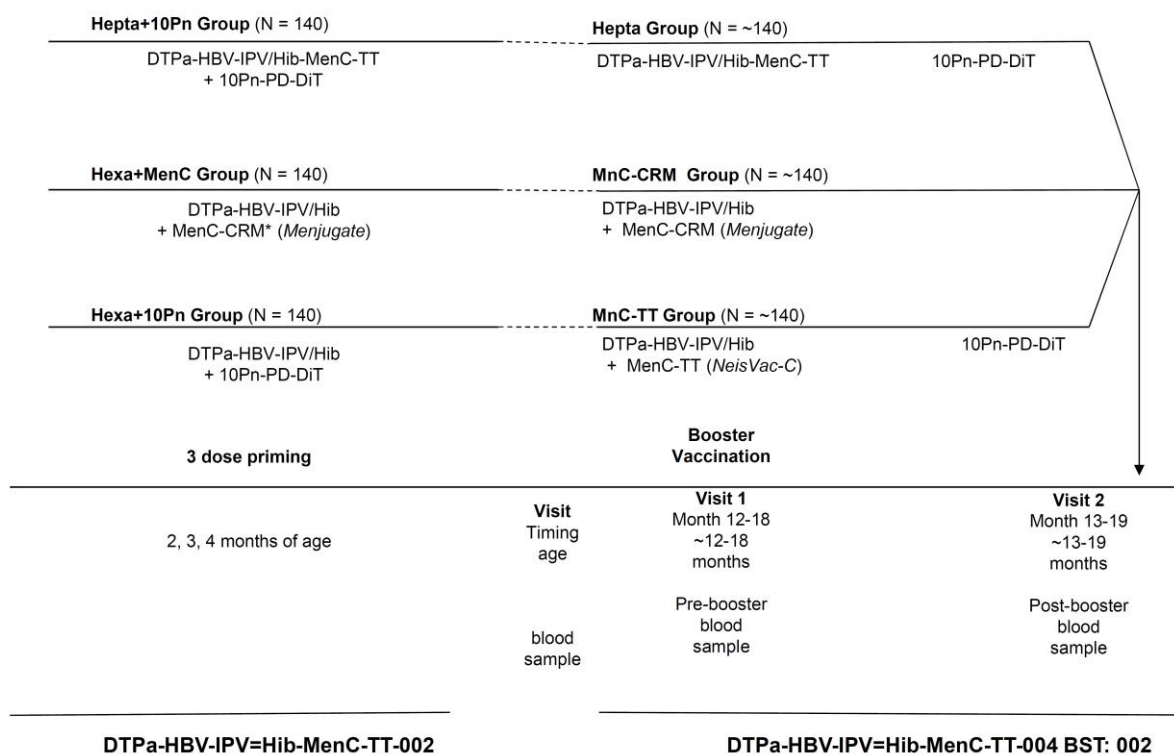
- To assess the persistence of the immune response to the study vaccines in terms of seroprotection/seropositivity rates and geometric mean concentrations/titres (GMCs/Ts) for all antigens, before the booster dose.
- To assess the immune response to the study vaccines in terms of seroprotection/seropositivity, GMCs/Ts to all antigens, in terms of booster response to pertussis antigens and GMC fold change in rSBA-MenC titres and anti-PRP concentrations.
- To assess the safety and reactogenicity of the study vaccines in terms of solicited, unsolicited, local and general symptoms and serious adverse events.

Study design

This was an open-label, controlled, multi-centre study with three parallel groups. It was a booster study following primary vaccination study 112157 (DTPA-HBV-IPV=HIB-MENC-TT-002):

- **Hepta Group** (subjects who received the DTPa-HBV-IPV/Hib-MenC-TT vaccine and *Synflorix* in the primary study) - received a booster dose of DTPa-HBV-IPV/Hib-MenC-TT vaccine.
- **MnC-CRM Group** (subjects who received *Infanrix hexa* co-administered with *Menjugate* in the primary study) – received a booster dose of *Infanrix hexa* co-administered with *Menjugate*.
- **MnC-TT Group** (subjects who received *Infanrix hexa* and *Synflorix* in the primary study) – received a booster dose of *Infanrix hexa* co-administered with *NeisVac-C*.

Synflorix was administered at Visit 2 to subjects in the Hepta and MnC-TT groups to complete the vaccination schedule started in the primary study but no study endpoints were associated with this vaccine. Blood samples were drawn for all subjects: just before the administration of the booster dose, and approximately one month after the booster dose.



* 2 doses of MenC-CRM given at 3 and 4 months of age

N = number of subjects

Study population

Number of subjects:	Hepta	HexaMnC	HexaPn	Total
<i>Planned</i>	140	140	140	420
<i>Enrolled & vaccinated (=Total vaccinated cohort)</i>	137	133	121	391
<i>Safety: Booster Total Vaccinated cohort</i>	137	132	121	390
<i>Immunogenicity: Booster according-to-protocol (ATP) cohort for immunogenicity</i>	134	126	114	374

Diagnosis and criteria for inclusion

A male or female between, and including, 12 and 18 months of age at the time of booster vaccination who completed the full three-dose primary vaccination course according to their group allocation in the primary study 112157 (DTPa-HBV-IPV=HIB-MENC-TT- 002).

Treatments

A total of 421 subjects were enrolled in the primary vaccination study 112157 (DTPa-HBV- IPV=HIB- MENC-TT-002) and were expected to participate in this booster vaccination study.

Randomization remained the same as in the primary study 112157 (DTPA-HBV-IPV= HIB-MENC-TT-002).

Outcomes/endpoints

Primary endpoints

Immune response to the study vaccine antigens. One month after the booster dose:

- Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/ml}$,
- rSBA-MenC antibody titres ≥ 8 .

Secondary endpoints

- Immune response to the study vaccine antigens. One month after the booster dose:
 - rSBA-MenC antibody titres ≥ 128 and antibody titres,
 - anti-PSC antibody concentrations $\geq 0.3 \mu\text{g/ml}$, $\geq 2 \mu\text{g/ml}$ and antibody concentrations,
 - anti-PRP antibody concentrations $\geq 1 \mu\text{g/ml}$ and antibody concentrations,
 - anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/ml}$ and antibody concentrations,
 - anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/ml}$ and antibody concentrations,
 - anti-HBs antibody concentrations $\geq 3.3 \text{ mIU/ml}$, $\geq 10 \text{ mIU/ml}$, $\geq 100 \text{ mIU/ml}$ and antibody concentrations,
 - anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8 and antibody titres,
 - anti-PT, anti-FHA and anti-PRN antibody concentrations $\geq 5 \text{ EL.U/ml}$ and antibody concentrations,
- Persistence of antibodies to the study vaccine antigens. Before the booster dose:
 - rSBA-MenC antibody titres ≥ 8 , ≥ 128 and antibody titres,
 - anti-PSC antibody concentrations $\geq 0.3 \mu\text{g/ml}$, $\geq 2 \mu\text{g/ml}$ and antibody concentrations,
 - anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/ml}$ $\geq 1 \mu\text{g/ml}$ and antibody concentrations,
 - anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/ml}$ and antibody concentrations,
 - anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/ml}$ and antibody concentrations,
 - anti-HBs antibody concentrations 3.3 mIU/ml , $\geq 10 \text{ mIU/ml}$ and antibody concentrations,
 - anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8 and antibody titres,
 - anti-PT, anti-FHA and anti-PRN $\geq 5 \text{ EL.U/ml}$ and antibody concentrations.
- Solicited local and general symptoms.
 - Occurrence of solicited local and general symptoms during the 8-day (Day 0-7) follow-up period following the booster dose.
- Unsolicited adverse events.
 - Occurrence of unsolicited symptoms during the 31-day (Day 0-30) follow-up period following the booster dose.
- Serious adverse events.
 - Occurrence of serious adverse events after the booster dose of the study vaccine up to the study end.

Recruitment/ Number analysed

Of the 421 subjects who completed the primary vaccination course in the 112157 [DTPA-HBV-IPV=HIB-MENC-TT-002] study a total of 391 subjects were enrolled in the booster vaccination study after having been checked for the inclusion and exclusion criteria: 137 subjects in the Hepta group, 133 subjects in the MnC-CRM group and 121 subjects in the MnC-TT group.

Of the 391 subjects vaccinated in this study, 390 subjects completed the study. One subject from the MnC-TT group was lost to follow up after the first study visit.

Baseline data

The summary of demographic characteristics for the Booster ATP cohort for immunogenicity is presented in Table 13.

Table 13. Summary of demographic characteristics (Booster ATP cohort for immunogenicity)

Characteristics	Parameters or Categories	Hepta N = 134		MnC-CRM N = 126		MnC-TT N = 114		Total N = 374	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (months) at booster vaccination	Mean	13.7	-	13.9	-	13.7	-	13.8	-
	SD	0.72	-	0.73	-	0.77	-	0.74	-
	Median	14.0	-	14.0	-	14.0	-	14.0	-
	Minimum	12	-	12	-	12	-	12	-
	Maximum	16	-	16	-	15	-	16	-
Gender	Female	70	52.2	77	61.1	54	47.4	201	53.7
	Male	64	47.8	49	38.9	60	52.6	173	46.3
Geographic Ancestry	White - Caucasian / European Heritage	134	100	126	100	114	100	374	100

Hepta = 4 doses of DTPa-HBV-IPV/Hib-MenC-TT at 2, 3, 4 and 12-18 months of age

MnC-CRM = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + 3 doses of *Menjugate* at 3, 4 and 12-18 months of age

MnC-TT = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + single dose of *NeisVac-C* at 12-18 months of age

N = total number of subjects n (%) = number (percentage) of subjects in a given category

Value = value of the considered parameter

SD = standard deviation

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 17.

Immunogenicity results

The analysis of immunogenicity was performed on the Booster ATP cohort for immunogenicity. Since, for any vaccine group, not more than 5% of the vaccinated subjects with serological results were eliminated from the Booster ATP cohort for immunogenicity, no analyses were performed on the Booster total vaccinated cohort.

Since not all objectives in the primary study (DTPA-HBV-IPV=HIB-MENC-TT-002) were met, formal conclusions on the inferential objectives of the present (booster) study cannot be made. The below sections describe whether the results observed in this study were within the limits for non-inferiority pre-specified in the protocol.

Primary Objectives (Non-inferiority in terms of rSBA-MenC and anti-PRP response)

One month post-booster vaccination

- The upper limit of the standardised asymptotic 95% CI on the group difference (*MnC-CRM* group minus Hepta group) in terms of MenC seroprotection rates was below 10%, the pre-defined clinical limit for non-inferiority.
- The upper limit of the standardised asymptotic 95% CI on the group difference (*MnC-TT* group minus Hepta group) in terms of MenC seroprotection rates was below 10%, the pre-defined clinical limit for non-inferiority.
- The upper limit of the standardised asymptotic 95% CI on the group difference (*MnC-TT* group minus Hepta group) in terms of PRP seroprotection rates was below 10%, the predefined clinical limit for non-inferiority.

Assessor's comment

The primary objectives regarding seroprotection rates of MenC and PRP showed non-inferiority of the study vaccine to the control groups.

Secondary objectives (Non-inferiority in terms of anti-tetanus, anti-diphtheria, anti-pertussis, anti-HBs and anti-poliovirus types 1, 2 and 3 response)

One month post-primary vaccination:

- For diphtheria, tetanus, hepatitis B and poliovirus types 1, 2 and 3, the upper limits of the standardised asymptotic 95% CI on the group difference (*MnC-TT* group minus Hepta group) for the percentage of seroprotected subjects were all below 10%, the pre-defined clinical limit for non-inferiority.
- *For hepatitis B, the upper limit of the standardised asymptotic 95% CI on the group difference (MnC-TT group minus Hepta group) for the percentage of subjects with post-vaccination anti-HBs concentrations ≥ 100 mIU/mL as measured by ELISA was below 10%, the pre-defined clinical limit for non-inferiority. (Note that this is a post-hoc analysis, which is not part of the primary analysis.)* (Amended: 14 January 2014)
- The upper limit of the 95% CI on the GMC ratio (*MnC-TT* group GMC divided by Hepta group GMC) was below 1.5, the pre-defined clinical limit for non-inferiority, for anti-PT and anti-FHA GMCs but not for anti-PRN GMCs.

Assessor's comment

Regarding the secondary objectives, the predefined non-inferiority criteria for diphtheria, tetanus, hepatitis B, the three poliovirus types, and the pertussis components PT (pertussis toxoid) and FHA (filamentous haemagglutinin) were reached. Regarding the third pertussis component PRN (pertactin), pre-defined non-inferiority criteria was not met.

No further regulatory action regarding *Synflorix* is required based on these results.

Immunogenicity conclusions

Since not all the secondary objectives of the primary vaccination trial [112157 (DTPa- HBV-IPV=Hib-MenC-TT-002)] were met, formal conclusions based on the results of the present booster trial could not be made.

- The pre-defined non-inferiority criteria for the primary objectives in terms of immune response to MenC and PRP were met.
- The pre-defined non-inferiority criteria linked to the secondary endpoints of diphtheria, tetanus, hepatitis B, poliovirus types 1, 2 and 3 and PT and FHA were met. The pre-defined non-inferiority criterion for PRN was not met.
- Following the booster dose of the DTPa-HBV-IPV/Hib-MenC-TT vaccine (Hepta group), all* subjects were seroprotected against MenC, PRP, diphtheria, tetanus, hepatitis B and the three poliovirus types; and all subjects were seropositive for anti-PT, FHA and PRN antibodies.

**For one subject from the Hepta group, the results of anti-HBs retesting were below 10 mIU/mL suggesting that the subject might not be seroprotected (Amended: 14 January 2014).*

Assessor's comment

The immunogenicity results are generally in accordance with what has been reported from other booster studies. It is not possible to draw any specific conclusions on the immunogenicity of *Synflorix* based on the results of the present study, as no endpoints regarding this vaccine were included.

Safety results

All 391 enrolled subjects in this study received the booster dose of their allocated vaccine.

The safety analysis was performed on the Booster total vaccinated cohort since less than 5% of subjects in each group were eliminated for the ATP cohort for safety.

The overall incidence of symptoms (solicited and unsolicited, local and general) reported during the 8-day follow-up period after vaccination is presented in Table 14. None of the subjects experienced an adverse event that led to premature discontinuation of the study vaccine or withdrawal of the subject from the study.

Table 14. Incidence and nature of symptoms (solicited and unsolicited) reported during the 8-day (Days 0-7) post-booster vaccination period

Group	Any symptom					General symptoms					Local symptoms				
	N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
Hepta	137	113	82.5	75.1	88.4	137	88	64.2	55.6	72.2	137	82	59.9	51.1	68.1
MnC-CRM	133	114	85.7	78.6	91.2	133	84	63.2	54.4	71.4	133	96	72.2	63.7	79.6
MnC-TT	121	100	82.6	74.7	88.9	121	84	69.4	60.4	77.5	121	82	67.8	58.7	76.0

Hepta = 4 doses of DTPa-HBV-IPV/Hib-MenC-TT at 2, 3, 4 and 12-18 months of age

MnC-CRM = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + 3 doses of *Menjugate* at 3, 4 and 12-18 months of age

MnC-TT = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + single dose of *NeisVac-C* at 12-18 months of age

N = number of subjects with the administered dose

N (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 36.

Local symptoms

The overall incidence of local symptoms (solicited and unsolicited) by vaccine administration site, reported during the 8-day follow-up period after vaccination is presented in Table 15.

Table 15. Incidence and nature of local symptoms (solicited and unsolicited) reported for each vaccine during the 8-day (Days 0-7) post-booster vaccination period

	DTPa-HBV-IPV/Hib-MenC-TT					Infanrix hexa					Menjugate					NeisVac-C				
	95% CI					95% CI					95% CI					95% CI				
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Hepta	137	82	59.9	51.1	68.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MnC-CRM	-	-	-	-	-	133	93	69.9	61.4	77.6	133	77	57.9	49.0	66.4	-	-	-	-	-
MnC-TT	-	-	-	-	-	121	80	66.1	57.0	74.5	-	-	-	-	-	121	64	52.9	43.6	62.0

Hepta = 4 doses of DTPa-HBV-IPV/Hib-MenC-TT at 2, 3, 4 and 12-18 months of age

MnC-CRM = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + 3 doses of *Menjugate* at 3, 4 and 12-18 months of age

MnC-TT = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + single dose of *NeisVac-C* at 12-18 months of age

N = number of subjects with the administered dose

N (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 37.

- Redness at the injection site was the most frequently reported local reaction in the three groups (incidence of redness was 50.7%, 57.9% and 57.5% in the Hepta, MnCCRM and MnC-TT groups, respectively). Redness was also the most common grade 3 symptom (reported for 14%, 15% and 14.2% of the vaccinees in the Hepta, MnCCRM and MnC-TT groups, respectively).
- Large injection site reactions (either localized large swelling at the injection site or diffuse swellings not involving the adjacent joint) were reported for 11 subjects (five in the Hepta group, four in the MnC-CRM group and two in the MnC-TT group). All these reactions were limited to the immediate injection area; with a size of 60 to 100 mm. Functional impairment was reported for only one subject (in the MnC-CRM group). This was of intensity 1 (easily tolerated, causing minimal discomfort and not interfering with everyday activities). All subjects recovered without sequelae.

Solicited general adverse events

The incidence of solicited general symptoms reported during the 8-day follow-up period after booster vaccination, for the Booster total vaccinated cohort is presented in Table 16.

- Irritability was the most frequently reported general symptom across groups, observed in 47.8%, 48.9% and 55% of subjects in the Hepta, MnC-CRM and MnCTT groups, respectively.
- The most common grade 3 solicited general symptom in the Hepta and MnC-TT groups was irritability reported for 4.4% and 5.8% of subjects, respectively. In the MnC-CRM group,

irritability of grade 3 intensity was reported for 1.5% of the subjects. Drowsiness was the second most frequently reported grade 3 adverse event.

- The majority of solicited general symptoms following booster dose in the three groups were considered by the investigator to be causally related to vaccination.

Table 16. Incidence of solicited general symptoms reported during the 8-day (Days 0-7) post-booster vaccination period

Symptom	Type	Hepta					MnC-CRM					MnC-TT				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
Drowsiness	All	136	40	29.4	21.9	37.8	133	39	29.3	21.8	37.8	120	39	32.5	24.2	41.7
	Grade 3	136	4	2.9	0.8	7.4	133	4	3.0	0.8	7.5	120	2	1.7	0.2	5.9
	Related	136	34	25.0	18.0	33.1	133	35	26.3	19.1	34.7	120	28	23.3	16.1	31.9
	Grade 3*Related	136	4	2.9	0.8	7.4	133	4	3.0	0.8	7.5	120	1	0.8	0.0	4.6
	Medical advice	136	0	0.0	0.0	2.7	133	0	0.0	0.0	2.7	120	2	1.7	0.2	5.9
Irritability	All	136	65	47.8	39.2	56.5	133	65	48.9	40.1	57.7	120	66	55.0	45.7	64.1
	Grade 3	136	6	4.4	1.6	9.4	133	2	1.5	0.2	5.3	120	7	5.8	2.4	11.6
	Related	136	54	39.7	31.4	48.4	133	51	38.3	30.1	47.2	120	49	40.8	32.0	50.2
	Grade 3*Related	136	6	4.4	1.6	9.4	133	2	1.5	0.2	5.3	120	4	3.3	0.9	8.3
	Medical advice	136	2	1.5	0.2	5.2	133	0	0.0	0.0	2.7	120	3	2.5	0.5	7.1
Loss of appetite	All	136	31	22.8	16.0	30.8	133	32	24.1	17.1	32.2	120	43	35.8	27.3	45.1
	Grade 3	136	1	0.7	0.0	4.0	133	3	2.3	0.5	6.5	120	3	2.5	0.5	7.1
	Related	136	25	18.4	12.3	25.9	133	24	18.0	11.9	25.6	120	29	24.2	16.8	32.8
	Grade 3*Related	136	1	0.7	0.0	4.0	133	3	2.3	0.5	6.5	120	1	0.8	0.0	4.6
	Medical advice	136	1	0.7	0.0	4.0	133	0	0.0	0.0	2.7	120	2	1.7	0.2	5.9
Temperature (Axillary) (°C)	All	136	34	25.0	18.0	33.1	133	30	22.6	15.8	30.6	120	31	25.8	18.3	34.6
	≥ 37.5	136	34	25.0	18.0	33.1	133	30	22.6	15.8	30.6	120	31	25.8	18.3	34.6
	> 38.0	136	11	8.1	4.1	14.0	133	11	8.3	4.2	14.3	120	12	10.0	5.3	16.8
	> 38.5	136	1	0.7	0.0	4.0	133	4	3.0	0.8	7.5	120	6	5.0	1.9	10.6
	> 39.0	136	1	0.7	0.0	4.0	133	2	1.5	0.2	5.3	120	2	1.7	0.2	5.9
	Related	136	24	17.6	11.6	25.1	133	24	18.0	11.9	25.6	120	18	15.0	9.1	22.7
	> 39.0*Related	136	1	0.7	0.0	4.0	133	1	0.8	0.0	4.1	120	1	0.8	0.0	4.6
	Medical advice	136	1	0.7	0.0	4.0	133	0	0.0	0.0	2.7	120	4	3.3	0.9	8.3

Hepta = 4 doses of DTPa-HBV-IPV/Hib-MenC-TT at 2, 3, 4 and 12-18 months of age

MnC-CRM = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + 3 doses of *Menjugate* at 3, 4 and 12-18 months of age

MnC-TT = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + single dose of *NeisVac-C* at 12-18 months of age

N = number of subjects with the administered dose

N (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 40.

Unsolicited adverse events

The percentage of subjects with grade 3 unsolicited symptoms and unsolicited symptoms with a causal relationship to vaccination classified by the MedDRA Preferred Term during the 31-day follow-up period after vaccination, for the Booster total vaccinated cohort is presented in Table 17.

- Grade 3 unsolicited symptoms were infrequent (a maximum of four subjects [3% in the MnC-CRM group]) and none were considered related to the vaccination.

- Unsolicited symptoms judged to be causally related to vaccination were reported for a maximum of three (2.2%) subjects per group.

Table 17. Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-booster vaccination period

		Hepta N = 137				MnC-CRM N = 133				MnC-TT N = 121			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	2.2	0.5	6.3	0	0.0	0.0	2.7	1	0.8	0.0	4.5
Blood and lymphatic system disorders (10005329)	Lymphadenopathy (10025197)	1	0.7	0.0	4.0	0	0.0	0.0	2.7	0	0.0	0.0	3.0
General disorders and administration site conditions (10018065)	Injection site reaction (10022095)	0	0.0	0.0	2.7	0	0.0	0.0	2.7	1	0.8	0.0	4.5
Infections and infestations (10021881)	Respiratory tract infection (10062352)	1	0.7	0.0	4.0	0	0.0	0.0	2.7	0	0.0	0.0	3.0
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	1	0.7	0.0	4.0	0	0.0	0.0	2.7	0	0.0	0.0	3.0

Hepta = 4 doses of DTPa-HBV-IPV/Hib-MenC-TT at 2, 3, 4 and 12-18 months of age

MnC-CRM = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + 3 doses of *Menjugate* at 3, 4 and 12-18 months of age

MnC-TT = 4 doses of DTPa-HBV-IPV/Hib at 2, 3, 4 and 12-18 months of age + single dose of *NeisVac-C* at 12-18 months of age

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with the administered dose

N (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 42.

Serious adverse events

SAEs were reported for seven subjects (three in the Hepta group, two in the MnC-CRM group and two in the MnC-TT group) during the entire study period (Table 18). None of the SAEs were considered to be potentially related to vaccination by the investigator. No SAE was ongoing at the end of the study. No deaths were reported during this study.

Table 18. Summary table of serious adverse events reported during the study period

Group	Sub. No.	Case Id	Age at onset (Month)	Sex	Verbatim	Preferred term	System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
Hepta			13	M	first/second degree skin burn	Thermal burn	Injury, poisoning and procedural complications	HO	1	22	8	2	N	Recovered/resolved
			14	F	Bronchopneumonia	Bronchopneumonia	Infections and infestations	HO	1	18	11	2	N	Recovered/resolved
			14		Gastroenteritis	Gastroenteritis	Infections and infestations	HO	1	18	6	2	N	Recovered/resolved
			14	M	Burns of the face, chest, left shoulder and stomach	Thermal burn	Injury, poisoning and procedural complications	HO	1	28	19	2	N	Recovered/resolved
			14	M	Diarrhoea	Diarrhoea	Gastrointestinal disorders	HO	1	33	6	1	N	Recovered/resolved
MnC-CRM			13	F	Pneumonia	Pneumonia	Infections and infestations	HO	1	21	12	2	N	Recovered/resolved
			14	M	Upper resp tract infection	Upper respiratory tract infection	Infections and infestations	HO	1	10	11	2	N	Recovered/resolved
			14		Urticaria	Urticaria	Skin and subcutaneous tissue disorders	HO	1	6	10	2	N	Recovered/resolved
MnC-TT			15	M	Pneumonia	Pneumonia	Infections and infestations	HO	1	23	11	2	N	Recovered/resolved
			14	M	Diarrhoea	Diarrhoea	Gastrointestinal disorders	HO	1	6	9	1	N	Recovered/resolved
			14		Urticaria	Urticaria	Skin and subcutaneous tissue disorders	HO	1	12	3	1	N	Recovered/resolved

Hepta = DTPa-HBV-IPV/Hib-MenC-TT at 12-18 months of age

MnC-CRM = DTPa-HBV-IPV/Hib + *Menjugate* at 12-18 months of age

MnC-TT = DTPa-HBV-IPV/Hib + *NeisVac-C* at 12-18 months of age

MED type = type of medical advice: HO/ER/MD: Hospitalization/Emergency Room/Medical Doctor

Dose = dose given prior to the serious adverse event

N/Y = No/Yes

Source: CSR Study DTPa-HBV-IPV=Hib-MenC-TT-004 BST:002, Table 44.

Assessor's comment

During the follow-up period of 31 days, at least one unsolicited AE was reported for 32.8%, 21.8% and 28.9% of the subjects in the Hepta, MnC-CRM and MnC-TT groups, respectively. *Synflorix* was administered at visit 2 to the subjects in Hepta and MnC-TT groups to complete the vaccination started in the primary study. The increased reactogenicity in these two groups might potentially be explained by the co-administration of *Synflorix*, which have been reported from previous studies.

No further regulatory action is required based on these results.

2.3.3. Discussion on clinical aspects

The submitted study DTPa-HBV-IPV=Hib-MenC-TT-002 was intended to assess the immunogenicity and safety following vaccination with a new combination vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib and group C meningococcal diseases. The results showed non-inferiority of this new combination vaccine (i.e. DTPa-HBV-IPV/hib-MenC-TT) to *Infanrix hexa* and *Menjugate* regarding immune response to PRP (Hib) and MenC (Meningococci group C). The study vaccine was also shown to be non-inferior to *Infanrix hexa* coadministered with *Synflorix* regarding seroprotection rates to tetanus and diphtheria. For the pertussis antigens, non-inferiority was not demonstrated as the results exceeded the pre-defined limit. Regarding hepatitis B and the three poliovirus types, non-inferiority could not be concluded, because of the sequential nature of the analysis and the higher ranking objective linked to anti-pertussis response which did not met the criteria for non-inferiority.

Concerning *Synflorix*, one month after the third dose, the vast majority of subjects reached acceptable antibody concentrations for the majority of the pneumococcal serotypes included in the vaccine. This

was true for both study groups where the subjects received *Synflorix* (i.e. Hepta and HexaPn groups, respectively). The results generally confirm what is already known regarding immunogenicity and safety of *Synflorix*. Consequently, no **amendments of the SPC or other** regulatory action considering *Synflorix* is required, based on the presented results.

The extension study DTPa-HBV-IPV=Hib-MenC-TT-004 was designed to assess the immunogenicity and reactogenicity of booster vaccination at 12-18 months of age with GSK Biologicals' investigational DTPa- HBV-IPV/Hib-MenC-TT vaccine in toddlers who had received the same vaccine in primary vaccination.

Whereas in the primary infant vaccination study (i.e. DTPa-HBV-IPV=Hib-MenC-TT-002), *Synflorix* was co-administered either with the combined DTPa-HBV-IPV/Hib-MenC-TT vaccine or with *Infanrix hexa*, no study endpoints were associated with the booster dose of *Synflorix* in the current study. Based on the submitted results, no regulatory actions regarding *Synflorix* are considered necessary.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

This article 46 submission is considered satisfactory and no further regulatory action regarding *Synflorix* is required.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

4. Member State Comments

Comments were received from member states that endorsed the AR and had no additional comments.