EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/635814/2015
Procedure Management and Committees Support Division

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

Rotarix

human rotavirus, live attenuated

Procedure no: EMEA/H/C/000639/P46/084

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Further review of the submitted data, the rapporteur is of the opinion that the data support the requirement for a variation and should not be assessed as a PAM.

Therefore the MAH is requested to submit a variation. (in this case no need for assessment of the data).

1.1. Steps taken for the assessment

Submission date:	26/06/2015
Start of procedure:	26/07/2015
CHMP Rapporteur's preliminary assessment report circulated on:	25/08/2015
CHMP Rapporteur's updated assessment report circulated on:	n/a
CHMP opinion:	24/09/2015

2. Assessment of the post-authorisation measure PAM P46 083 and 084

2.1. Information on the development program

The MAH stated that studies DTPa-HBV-IPV/HibMenC-TT002 and DTPa-HBV-IPV/HibMenC-TT003 are stand alone studies.

The experimental DTPa-HBV-IPV/Hib-MenC-TT vaccine is a 7-valent paediatric vaccine containing the following antigens: diphtheria and tetanus toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN), recombinant hepatitis B surface antigen (HBsAg), poliovirus types 1, 2, 3, polyribosyl-ribitol phosphate (PRP) and meningococcal serogroup C (MenC).

The main objective of the studies was to investigate the safety and immunogenicity of the experimental 7-valent vaccine in two vaccine schedules (2, 3, 4 and 2, 4, 12 months of age) and in co-administration with *Synflorix* or *Prevenar 13* and/or *Rotarix*.

2.2. Information on the pharmaceutical formulation used in the study

The lyophilised and liquid formulations of *Rotarix* were used in this study.

2.2.1. Introduction

The MAH submitted a final report for:

- **DTPa-HBV-IPV/HibMenC-TT002**, a phase II, open-label, randomised, multicentre study in 9 study sites in Poland to evaluate the safety and immunogenicity of the experimental DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with 10-valent pneumococcal conjugate vaccine (*Synflorix*)

in healthy infants when administered as a three-dose primary vaccination course at 2, 3 and 4 months of age.

All subjects received Rotarix at 2 and 3 months of age. However, Rotarix was not specifically studied in this study.

- **DTPa-HBV-IPV/HibMenC-TT003**, a phase II, open-label, randomised, multicentre study in 33 study sites in Canada, France and Germany to evaluate the safety and immunogenicity of the experimental DTPa-HBV-IPV/Hib-MenC-TT vaccine, when given to healthy infants at 2, 4 and 12 months of age.

Rotarix administration was optional. The lyophilised and liquid formulations of Rotarix were used in this study. In France, Rotarix was not administered to the subjects.

2.2.2. Clinical study

DTPa-HBV-IPV/HibMenC-TT-002, Phase II, open-label, randomised, multicentre study to evaluate the safety and immunogenicity of the experimental DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with 10-valent pneumococcal conjugate vaccine (*Synflorix*) in healthy infants when administered as a three-dose primary vaccination course at 2, 3 and 4 months of age.

Description

This was a Phase II, open-label, randomised, multicentre study in 9 study sites in Poland.

Rotarix was one of the vaccines that were co-administered with the experimental 7-valent study vaccine at 2 and 3 months of age.

Booster vaccine doses will be provided at 16-18 months of age to all study participants as part of a separate clinical trial (113978 [DTPa-HBV-IPV-Hib-MenC-TT-004 BST 002]).

Methods

Objectives

Primary:

Immunogenicity

- To demonstrate that DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered PCV10 (*Synflorix*) is non-inferior to DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) co-administered with meningococcal serogroup C vaccine (*Menjugate*, Novartis), in terms of seroprotection to MenC one month after the third dose of primary vaccination.

  Criteria for non-inferiority: 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 ≤ 10%.

- To demonstrate that DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with PCV10 (*Synflorix*), is non-inferior to DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) co-administered with PCV10 (*Synflorix*), in terms of seroprotection to Hib one month after the third dose of primary vaccination.

  Criteria for non-inferiority: 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 ≤ 10%.

Secondary:

Immunogenicity

- To demonstrate that DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with PCV10 (*Synflorix*), is non-inferior to DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) co-administered with PCV10 (*Synflorix*), 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 ≤ 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.

Safety

- To assess the safety and reactogenicity of the DTPa-HBV-IPV/Hib-MenC-TT vaccine coadministered with PCV10 (*Synflorix*) in terms of solicited, unsolicited, local and general symptoms and serious adverse events.

Assessor's comment

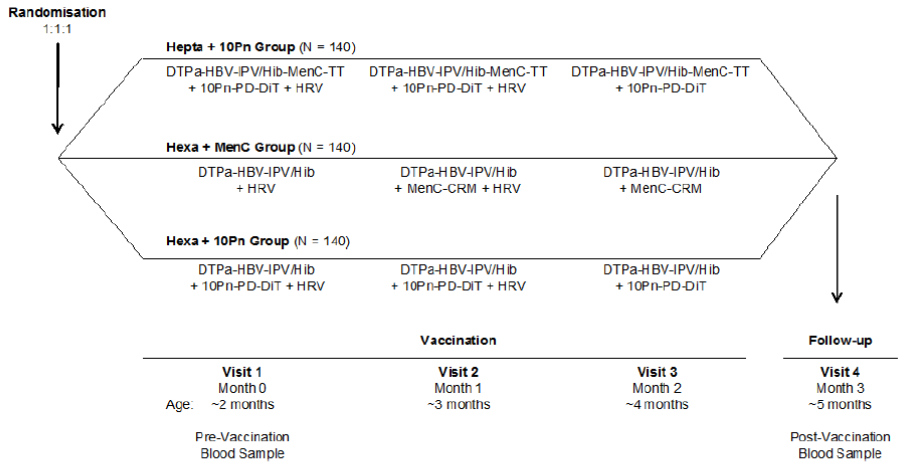
No immunogenicity results were generated for *Rotarix* in this study. The immunogenicity study objectives were not related to *Rotarix* and will therefore not be assessed within this procedure.

Study design

Subjects were randomized into 3 study groups in a 1:1:1 ratio.

Blood samples were collected from all subjects at the following time points:

- "Pre" (2 mL), at study Visit 1, just before the administration of the first vaccine dose.
- "Post" (5 mL), at study Visit 4, approximately one month after the third vaccine dose.



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

HRV: Human rotavirus vaccine (*Rotarix*)

Study population /Sample size

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.

A total of 420 subjects (140 per treatment group) were planned to be enrolled in order to have at least 378 evaluable subjects (approximately 126 subjects in each treatment group) at the time of the analysis.

Blinding

This study was conducted in an open manner due to the difference in the visual aspects of the Hib and Hib-MenC-TT vaccine vials and due to the different number of injections across the study groups (only two doses of *Menjugate* in the HexaMnC group). The laboratory in charge of the serology testing was blinded to the treatment, and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Treatments

Study vaccine: A candidate 7-valent paediatric vaccine similar to the 6-valent *Infanrix hexa*, but containing 5 µg PRP (Hib-antigen) and 5 µg Neisseria meningitidis serogroup C capsular polysaccharide conjugated to tetanus toxoid (MenC-antigen) instead of 10 µg PRP (Hib-antigen) in *Infanrix hexa*.

Similar to *Infanrix hexa*, the DTPa-HBV-IPV component is presented as a turbid white suspension in a pre-filled syringe. The lyophilised Hib-MenC component is presented as a white pellet in a glass vial; it must be reconstituted before use with the liquid DTPa-HBVIPV component.

Active control vaccines:

The following licensed vaccines were used as active controls:

- GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*),
- Novartis' meningococcal serogroup C vaccine (*Menjugate*).

Concomitant vaccines:

The following licensed vaccines were used as co-administered vaccines:

- GSK Biologicals' 10Pn-PD-DiT (*Synflorix*),
- GSK Biologicals' Human Rotavirus Vaccine (*Rotarix*).

Outcomes/endpoints

Since no immunogenicity results were generated for *Rotarix* in this study, only the safety endpoints are described here.

Safety:

- Occurrence of solicited local and general symptoms during the 8-day (Day 0- Day 7) follow-up period after each vaccination.
- Occurrence of unsolicited symptoms during the 31-day (Day 0- Day 30) follow-up period after each vaccination.
- Occurrence of serious adverse events (SAEs) from Dose 1 up to study end.

Results

Recruitment/ Number analysed

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 and percentage of subjects who received study vaccine doses by vaccine (Total enrolled cohort)

	Hepta N=141						HexaMnC N = 139						HexaPn N = 141					
	DTPa-HBV-IPV/Hib-MenC-TT		Synflorix		Rotarix		Infanrix hexa		Menjugate		Rotarix		Infanrix hexa		Synflorix		Rotarix	
Total number of doses received	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0
1	2	1.4	2	1.4	2	1.4	3	2.2	0	0.0	4	2.9	1	0.7	1	0.7	1	0.7
2	0	0.0	0	0.0	139	98.6	0	0.0	136	97.8	135	97.1	0	0.0	0	0.0	140	99.3
3	139	98.6	139	98.6	0	0.0	136	97.8	0	0.0	0	0.0	140	99.3	140	99.3	0	0.0
Any	141	100	141	100	141	100	139	100	136	97.8	139	100	141	100	141	100	141	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 = number of subjects in each group included in the considered cohort
n (%) = number (percentage) of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

HRV: Human rotavirus vaccine (*Rotarix*)

Safety results

Table 2. Incidence and nature of symptoms (solicited and unsolicited) reported during the 8-day (Days 0-7) post-vaccination period overall by dose (Total vaccinated cohort)

		Any symptom			95% CI		General symptoms			95% CI		Local symptoms			95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
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

Summary of safety according to co-administration vaccine regimen. *Rotarix* was co-administered in each group at 2 and 3 months of age.

- **Irritability** was the most frequently reported solicited general symptom in each group (incidences ranging from 46.3% of doses in HexaMnC group to 59.8% of doses in the HexaPn group).
- There was no report of grade 3 **fever** (> 39.0°C axillary temperature) in the Hepta and the HexaPn groups and one report of grade 3 fever in the HexaMnC group.
- Unsolicited symptoms judged as possibly causally related to vaccination were reported following a maximum of 9 (2.1%) doses in a given group. **Diarrhoea** (following 3 [0.7%] doses in the HexaPn group, 1 [0.2%] dose in the Hepta group and 1 [0.2%] dose in the HexMnC group) and **flatulence** (following 2 [0.5%] doses in the Hepta group and none in the other groups) were the most frequent unsolicited symptoms considered possibly related to vaccination.
- 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, for subject number 383 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.

Assessor's comment

The safety profile is judged acceptable. Diarrhoea and flatulence could have occurred as a result of *Rotarix* vaccination. Irritability is also a known adverse reaction associated with *Rotarix*. Since *Rotarix* was co-administered with other vaccines in the study, the safety analysis performed in this study does not relate to administration of *Rotarix* alone. The overall safety conclusion was that the experimental 7-valent vaccine was well tolerated.

The MAH concluded that no changes to the product information are needed since no specific data on *Rotarix* were obtained in this study, which is accepted.

DTPa-HBV-IPV/HibMenC-TT003, a phase II, open-label, randomised, multicentre study to evaluate the safety and immunogenicity of the experimental DTPa-HBV-IPV/Hib-MenC-TT vaccine, when given to healthy infants at 2, 4 and 12 months of age.

Description

This was a Phase II, open-label, randomised, multicentre study in 33 study sites in Canada, France and Germany. The study evaluated the safety and immunogenicity of the combined DTPa-HBV-IPV/Hib-MenC-TT vaccine when administered at 2, 4 and 12 months of age (2+1 schedule) as compared to the concomitant administration of the licensed hexavalent DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) with the monovalent MenC vaccine *Menjugate*.

Two doses of *Rotarix* were offered to the study participants, except if there is an advice of the local authorities in the participating country not to do so. Since Rotavirus vaccination is not mandatory in the participating countries and since *Rotarix* is not expected to impact the immunogenicity of any of the other study vaccines, the decision to administer *Rotarix* was at the discretion of the investigator in consultation with the parents/LARs.

Rotarix was offered at Visit 1 (8-12 weeks of age) and Visit 2 (about 4 months of age).

Methods

Objectives

Primary:

Immunogenicity

- To demonstrate that DTPa-HBV-IPV/Hib-MenC-TT vaccine co-administered with pneumococcal conjugate vaccine (*Prevenar 13*) (Combo group) was non-inferior to DTPa-HBV-IPV/Hib vaccine

(*Infanrix hexa*) co-administered with meningococcal serogroup C vaccine (*Menjugate*), and *Prevenar 13* (Control group), in terms of immune response to Hib and MenC antigens, one month after the second vaccine dose.

Criteria for non-inferiority: Non-inferiority in terms of response to PRP was demonstrated if the upper limit of the standardised asymptotic 95% confidence interval (CI) on the group difference [Control minus Combo] in percentage of subjects with anti-PRP antibody concentrations ≥ 0.15µg/ml was ≤ 10%. Non-inferiority in terms of response to MenC was demonstrated if the upper limit of the standardised asymptotic 95% CI on the group difference [Control minus Combo] in percentage of subjects with rSBA-MenC titres ≥ 8 was ≤ 10%.

Secondary:

Immunogenicity

No secondary immunogenicity endpoints related to *Rotarix*, and therefore not discussed.

Safety

- To assess the safety and reactogenicity of the study vaccines as a three-dose vaccination course, in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Assessor's comment

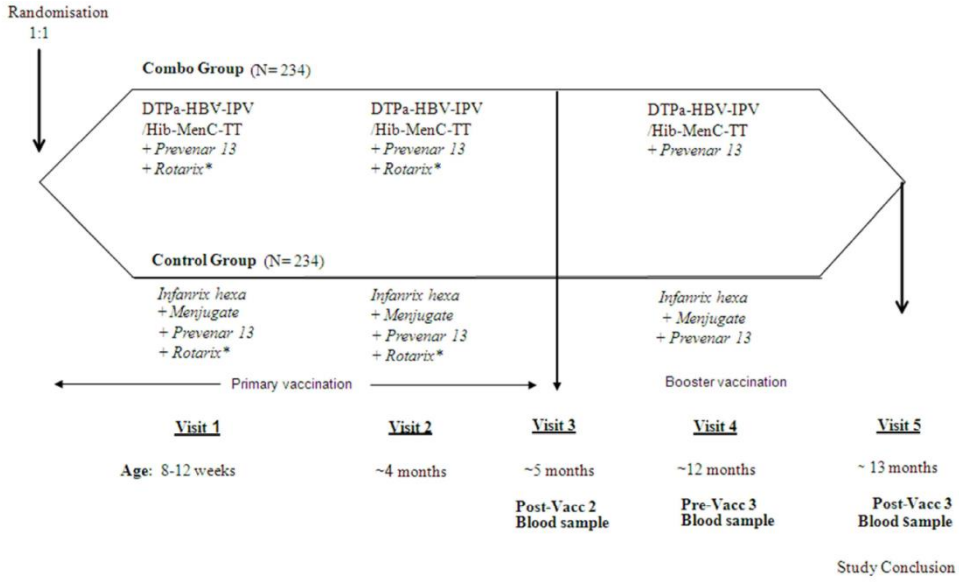
No immunogenicity results were generated for *Rotarix* in this study. The immunogenicity study objectives were not related to *Rotarix* and will therefore not be assessed within this procedure.

Study design

Subjects were randomized into 2 study groups in a 1:1 ratio.

Blood sampling: Blood samples (5 ml) were collected from all subjects at the following time points:

- "Post-Vacc 2", at study Visit 3, approximately one month after the administration of the second vaccine dose;
- "Pre-Vacc 3", at study Visit 4, just before the administration of the third vaccine dose;
- "Post-Vacc 3", at study Visit 5, approximately one month after the third vaccine dose.



Study population /Sample size

Healthy male or female infants between, and including, 8 and 12 months of age at the time of first vaccination and born after a gestation period between 36 and 42 weeks were enrolled in the study. Written informed consent was obtained from the parent(s)/legally acceptable representative(s) of the subject. Subjects with evidence of previous diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib, pneumococcal and MenC vaccination or disease at any time during the study period were not included in the study.

A total of 468 subjects (234 per treatment group) were planned to be enrolled in order to have at least 420 evaluable subjects (approximately 210 subjects in each treatment group) at the time of the analysis.

Blinding

This study was conducted in an open manner as the number of vaccines to be administered per visit differed between the groups. The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Treatments

Study vaccine: A candidate 7-valent paediatric vaccine similar to the 6-valent *Infanrix hexa*, but containing 5 µg PRP (Hib-antigen) and 5 µg Neisseria meningitidis serogroup C capsular polysaccharide conjugated to tetanus toxoid (MenC-antigen) instead of 10 µg PRP (Hib-antigen) in *Infanrix hexa*.

Similar to *Infanrix hexa*, the DTPa-HBV-IPV component is presented as a turbid white suspension in a pre-filled syringe. The lyophilised Hib-MenC component is presented as a white pellet in a glass vial; it must be reconstituted before use with the liquid DTPa-HBV-IPV component.

Active control vaccines:

The following licensed vaccines were used as active controls:

- GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*),

- Novartis' meningococcal serogroup C vaccine (*Menjugate*).

Concomitant vaccines:

The following licensed vaccines were used as co-administered vaccines:

- Wyeth Lederle' s 13-valent pneumococcal conjugate vaccine (*Prevenar 13*),
- GSK Biologicals' Human Rotavirus Vaccine (*Rotarix*).

Outcomes/endpoints

Since no immunogenicity results were generated for *Rotarix* in this study, only the safety endpoints are described here.

Safety:

- Occurrence of solicited local and general symptoms during the 8-day (Day 0- Day 7) follow-up period after each vaccination.
- Occurrence of unsolicited symptoms during the 31-day (Day 0- Day 30) follow-up period after each vaccination.
- Occurrence of serious adverse events (SAEs) from Dose 1 up to study end.

Results

Recruitment/ Number analysed

Of the 480 subjects vaccinated in this study, 474 subjects completed the primary vaccination series (2 and 4 months of age) and 453 subjects completed the primary and booster series (2, 4 and 12 months of age).

None of the withdrawals was due to a serious adverse event.

One withdrawal was due to a non-serious adverse event.

Safety results

A total of 301 subjects received at least one dose of *Rotarix*: 150 subjects in the study vaccine group ("Combo") and 151 subjects in the control group.

Table 3. Incidence and nature of symptoms (solicited and unsolicited) reported during the 8-day (Days 0-7) post-vaccination period following each dose, overall by dose and overall by subject (Total vaccinated cohort)

		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
Dose 1	Combo	238	215	90.3	85.9	93.8	238	202	84.9	79.7	89.2	238	145	60.9	54.4	67.2
	Control	242	218	90.1	85.6	93.5	242	205	84.7	79.5	89.0	242	163	67.4	61.1	73.2
Dose 2	Combo	237	203	85.7	80.5	89.9	237	195	82.3	76.8	86.9	237	144	60.8	54.2	67.0
	Control	241	216	89.6	85.1	93.2	241	204	84.6	79.5	89.0	241	161	66.8	60.5	72.7
Dose 3	Combo	228	211	92.5	88.3	95.6	228	191	83.8	78.3	88.3	228	165	72.4	66.1	78.1
	Control	233	213	91.4	87.1	94.7	233	200	85.8	80.7	90.0	233	175	75.1	69.0	80.5
Overall/dose	Combo	703	629	89.5	87.0	91.6	703	588	83.6	80.7	86.3	703	454	64.6	60.9	68.1
	Control	716	647	90.4	88.0	92.4	716	609	85.1	82.2	87.6	716	499	69.7	66.2	73.0
Overall/subject	Combo	238	232	97.5	94.6	99.1	238	232	97.5	94.6	99.1	238	198	83.2	77.8	87.7
	Control	242	238	98.3	95.8	99.5	242	234	96.7	93.6	98.6	242	207	85.5	80.5	89.7

Combo = DTPa-HBV-IPV/Hib-MenC-TT + *Prevenar 13* at 2, 4 and 12 months of age
Control = *Infanrix hexa* + *Menjugate* + *Prevenar 13* at 2, 4 and 12 months of age
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
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

Summary of safety according to co-administration vaccine regimen. *Rotarix* was co-administered in each group at about 2-3 months of age, and at 4 months of age.

- **Irritability** was the most frequently reported solicited general symptom (reported for 87.4% of subjects in the Combo group and 85.9% of subjects in the Control group). It was also the most frequently reported grade 3 solicited general symptom.
- There was no report of grade 3 **fever** (> 39.0°C axillary temperature).
- At least one unsolicited symptom was reported for 62.2% of subjects in Combo group and 65.3% of subjects in Control group during the 31-day (Days 0-30) follow up period. Unsolicited symptoms of grade 3 intensity were reported for 6.7% of subjects in the Combo group and 10.7% of subjects in the Control group. Two subjects in the Control group reported unsolicited symptoms (**flatulence** and persistent crying) of grade 3 intensity that were assessed by the investigator to be causally related to vaccination.
- No deaths were reported during this study.
- SAEs were reported for 12 subjects (5.0%) in the Combo group and 15 subjects (6.2%) in Control group during the entire study period. No SAE was considered by the investigator as causally related to the vaccinations. All SAEs were resolved by the end of the study.

Assessor's comment

The safety profile is judged acceptable. Flatulence could have occurred as a result of *Rotarix* vaccination. Irritability is also a known adverse reaction associated with *Rotarix*.

Since *Rotarix* was co-administered with other vaccines in the study, the safety analysis performed in this study does not relate to administration of *Rotarix* alone. The overall safety conclusion was that the experimental 7-valent vaccine was well tolerated.

The MAH concluded that no changes to the product information are needed since no specific data on *Rotarix* were obtained in this study, which is accepted.

2.2.3. Discussion on clinical aspects

The concomitant use of *Rotarix* with hexavalent DTPa-HBV-IPV/Hib, pneumococcal and meningococcal serogroup C (MenC) vaccines has been documented previously in clinical studies demonstrating that the immune responses and the safety profiles of the administered vaccines were unaffected.

The current studies investigated an experimental 7-valent paediatric vaccine with *Rotarix* being one of several concomitant vaccines. The immune response and the safety profile of *Rotarix* co-administration was, however, not specifically studied. No conclusion can therefore be drawn as to the influence of co-administering *Rotarix* with the new 7-valent vaccine in combination with pneumococcal vaccines PCV10 or PCV13.

The safety profile in these limited study populations (410 and 301 *Rotarix* recipients, respectively) do not give rise to new safety concerns and are consistent with the documented safety profile of *Rotarix*.

No further regulatory action is considered necessary.

3. Rapporteur's overall conclusion

The article 46 paediatric submission is considered fulfilled and no further regulatory action is needed. The provided data do not cause concern regarding the safety of *Rotarix*.

The benefit/risk balance of *Rotarix* therefore remains positive.

☒ PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: