EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

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

Rotarix

rotavirus vaccine, live

Procedure no: EMEA/H/C/000639/P46/091

Note

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

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Table of contents

1. Introduction

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

Final study report for the study Rota-079 in accordance with Article 46 of Regulation (EC) No 1901/2006, in which Rotarix and a DTaP-IPV vaccine are coadministered.

Study Rota-079 is a phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine (Squarekids, Kitasato Daiichi Sankyo Vaccine Co., Ltd) when co-administered with Rotarix in healthy Japanese infants aged 6-12 weeks at the time of the first dose of HRV vaccination.

Rotarix liquid formulation is licensed in Japan since 1 July 2011.

No changes to the Product Information (PI) of Rotarix are proposed by the MAH.

1.1. Steps taken for the assessment

Submission date:	16/05/2018
Start of procedure:	25/06/2018
CHMP Rapporteur's preliminary assessment report circulated on:	13/07/2018
CHMP Rapporteur's updated assessment report circulated on:	n/a
CHMP opinion:	23/08/2018

2. Assessment of the post-authorisation measure PAM P46 091

Study ROTA-079 (114720) is a Study Rota-079 was conducted upon request of the Pharmaceuticals and Medical Devices Agency (PMDA) to evaluate the immunogenicity and safety of diphtheria, tetanus, pertussis (DTP) vaccine, made by a Japanese domestic manufacturer, as routine vaccine when co-administered with Rotarix.

The end of study was defined in the protocol as the last testing results released of samples collected at Visit 7. Since this occurred on 20 November 2017, the deadline for submission is 20 May 2018.

The study was initiated on 16-September-2016 and completed on 29-May-2017 and was conducted at 11 sites in Japan.

Squarekids is a DTaP-IPV vaccine containing BP>=4Unit; DT>=14IU; TT>=9IU; Inactivated Poliovirus type 1=40DU; Inactivated Poliovirus type 2=8DU; Inactivated Poliovirus type 3=32DU; Sodium hydrate=210µg; Trisodium phosphate=810µg; Aluminium chloride=900µg 0.5 mL. It is administered subcutaneously as a 3-dose primary vaccination schedule.

Rotarix is administered orally as a 2-dose primary vaccination schedule, either concomitantly or staggered.

Methods

Primary objective

Immunogenicity

- To demonstrate that the immunogenicity to the antigens contained in DPT-IPV vaccine was not impaired by the co-administration with liquid HRV vaccine (Rotarix).

Criteria for non-inferiority (one month after the third dose of DPT-IPV vaccine at Visit 7):

- Lower limits of the standardised asymptotic 95% confidence intervals (CIs) on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective concentrations ≥0.1 IU/mL for anti-diphtheria antibodies and concentrations ≥0.1 IU/mL for anti-tetanus antibodies were ≥-10% (clinical limit for non-inferiority),
- Lower limits of the 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with concentrations ≥10 IU/mL for antibodies against the pertussis toxoid (PT) and filamentous hemagglutinin (FHA) antigens (anti-PT and anti-FHA) were ≥-10% (clinical limit for non-inferiority),
- Lower limits of the standardised asymptotic 95% CIs on the differences (Co-administered group minus Staggered group) in the percentages of subjects with seroprotective titres (≥8 ED50) for each of anti-poliovirus serotypes 1, 2 and 3 antibodies were ≥-10% (clinical limit for non-inferiority).

Secondary objectives

Immunogenicity

- To assess the immunogenicity of the liquid HRV vaccine in terms of serum anti-RV IgA antibody seropositivity and geometric mean concentrations (GMCs) in a sub-cohort of subjects, one month after the second dose of the liquid HRV vaccine.
- To assess the immunogenicity to all the antigens contained in the DPT-IPV vaccine in terms of GMCs/geometric mean antibody titres (GMTs), one month after the third dose of the DPT-IPV vaccine.

Safety/Reactogenicity

- To assess reactogenicity and safety after each dose of liquid HRV vaccine and first dose of DPT-IPV vaccine in terms of solicited symptoms during the 8-day follow-up period and unsolicited symptoms during the 31-day follow-up period.
- To assess safety in terms of serious adverse events (SAEs) from the first dose of study vaccine up to study end.

CHMP comment

Immunogenicity data for Rotarix were generated in a sub-cohort.

Safety data was generated for Rotarix in the staggered administration group, and for Rotarix and DTP-IPV co-administration in the concomitant group.

Study population

Healthy Japanese male or female infants, 6-12 weeks of age at the time of first dose.

CHMP comment

The study protocol was correct in defining the main contra-indications of Rotarix as exclusion criteria (history of intussusception, history of uncorrected congenital malformation of the gastrointestinal tract that would have predisposed the infant to intussusception, history of Severe Combined Immunodeficiency Disease (SCID), acute disease at time of enrolment meaning a rectal temperature of ≥ 38°C.)

Sample size

The target enrolment was at least 292 subjects (146 subjects approximately in each group), in order to have 262 evaluable subjects (131 in each study group) for the immunogenicity analyses corresponding to the primary confirmatory objective. The first 146 subjects enrolled were to be allocated to the HRV immunogenicity sub-cohort.

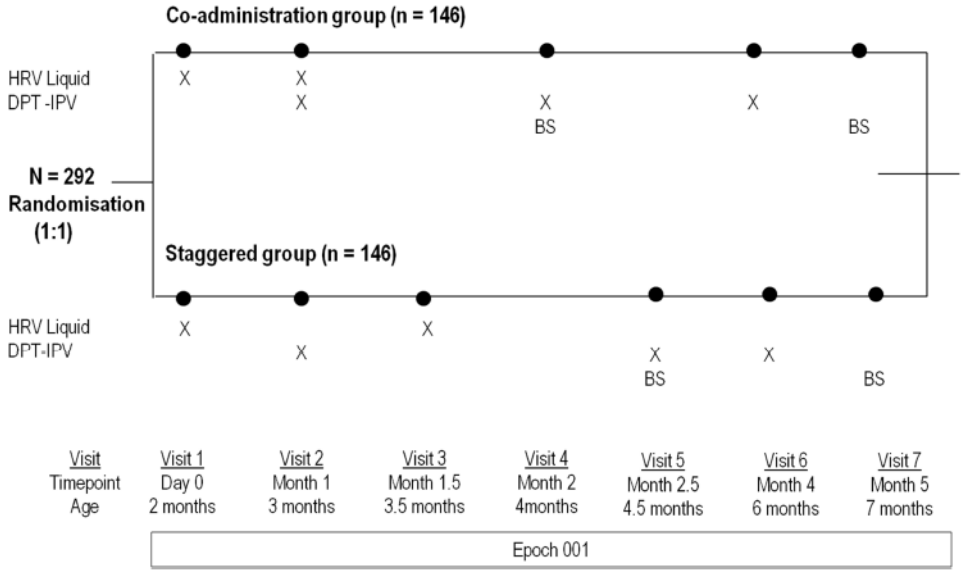
	Total			Co-administered		Staggered	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	292			147		145	
Total vaccinated cohort	292		100	147		145	
Study vaccine dose not administered according to protocol (code 1070)	2	2		1	1	1	1
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	6	6		3	3	3	3
Non-compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	1	1		0	0	1	1
Essential serological data missing (code 2100)	3	7		2	4	1	3
ATP cohort for immunogenicity	280		95.9	141		139	

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
Note: Subjects may have more than one elimination code assigned
n=number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s=number of subjects with the elimination code assigned
%=percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Study design

The study design was a Phase IV, open-label, 1:1 randomised, controlled, multicentre, single-country study with two parallel groups:

- **Co-administered group**: Subjects were administered the DPT-IPV vaccine according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule. The co-administration of study vaccines was to be performed only once, when the infant was approximately 3 months old.
- **Staggered group**: Subjects were administered the DPT-IPV vaccine according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule.



N=Number of subjects enrolled; n=Number of subjects in each group; BS=Blood Sampling.
Visit 3 and Visit 5 were applicable only for subjects in the Staggered group. Visit 4 was applicable only for subjects in the Co-administered group.

Study vaccines

Type of contact and time point	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 1 (Day 0)	1.5 mL	Co-administered group, Staggered group	*Rotarix*	O	Not applicable	Not applicable
Visit 2 (Month 1)	1.5 mL	Co-administered group	*Rotarix*	O	Not applicable	Not applicable
Visit 2 (Month 1)	0.5 mL	Co-administered group, Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 3 (Month 1.5)	1.5 mL	Staggered group	*Rotarix*	O	Not applicable	Not applicable
Visit 4 (Month 2)	0.5 mL	Co-administered group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 5 (Month 2.5)	0.5 mL	Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-
Visit 6 (Month 4)	0.5 mL	Co-administered group, Staggered group	*Squarekids*	SC	Upper arm, or Upper thigh	-

[1]Oral (O)/subcutaneous (SC)

Endpoints

Primary endpoint

Immunogenicity

Immunogenicity with respect to components of the DPT-IPV vaccine one month after administration of the third dose of the vaccine (Visit 7):

- anti-diphtheria antibody concentrations ≥0.1 IU/mL,
- anti-tetanus antibody concentrations ≥0.1 IU/mL,

- anti-PT and anti-FHA antibody concentrations ≥10 IU/mL,
- anti-poliovirus serotypes 1, 2 and 3 antibody titres ≥8 ED50.

Secondary endpoints:

Immunogenicity

- Serum anti-RV IgA antibody concentration and seropositivity in a sub-cohort of subjects, one month after the second dose of the liquid HRV vaccine.
- Serum GMCs/GMTs for anti-diphtheria, anti-tetanus, anti-poliovirus serotypes 1, 2 and 3, anti-PT and anti-FHA antibodies, one month after the third dose of the DPT-IPV vaccine.

Safety/Reactogenicity

- Occurrence of solicited general symptoms during the 8-day (Days 0-7) follow-up period after each dose of liquid HRV vaccine.
- Occurrence of solicited local and general symptoms during the 8-day (Days 0-7) follow-up period after the first dose of DPT-IPV vaccine (Note: the general symptoms solicited for the DPT-IPV vaccine were different from those solicited for the HRV vaccine).
- Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each dose of the liquid HRV vaccine and the first dose of DPT-IPV vaccine, according to the medical dictionary for regulatory activities (MedDRA) classification.
- Occurrence of SAEs from the first dose of the study vaccine up to study end (Visit 7).

Immunological correlates of protection

- Antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus): a threshold of 0.1 IU/mL (ELISA), provided a conservative estimate of the percentage of subjects deemed to be protected
- Antibodies against poliovirus types 1, 2 and 3 were determined by a virus micro-neutralisation test adapted from the World Health Organization (WHO) Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. The lowest dilution at which serum samples were tested was 1:8, from which a test was considered positive. Titres were expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. Antibody titres greater than or equal to this value were considered as protective.
- No correlate of protection had been defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT and FHA were measured by an ELISA technique developed in-house. The assay cut-off for anti-PT was 2.693 IU/mL and for anti-FHA was 2.046 IU/mL.
- No immunological correlate of protection had been demonstrated so far for the antigen used as part of the HRV vaccine. However, a publication indicated that post-vaccination anti-RV IgA seropositivity (antibody concentration ≥20 U/mL) could serve as a useful correlate of vaccine efficacy in clinical trials of Rotarix (Cheuvart, 2014).

CHMP comment

The endpoints are acceptable.

The study is powered to assess the primary endpoints. Safety and immunogenicity of the HRV

vaccine were secondary endpoints. Immunogenicity was determined in a subset of the first 146 subjects enrolled. Safety endpoints are descriptive.

Results

Immunogenicity results

The primary objective was met as the non-inferiority was demonstrated hierarchically.

The lower limits of the standardised asymptotic 95% CIs on the differences (Co-administered group minus Staggered group) were ≥-10% for all antigens (anti-diphtheria, anti-tetanus, anti-FHA, anti-PT, anti-poliovirus type 1, 2 and 3).

- Anti-diphtheria and anti-tetanus antibodies (ATP cohort for immunogenicity)

								Difference in percentage (Co-administered minus Staggered)		
		Co-administered			Staggered				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
anti-diphtheria antibody	0.1 IU/mL	141	141	100	137	137	100	0.00	-2.66	2.74
anti-tetanus antibody	0.1 IU/mL	141	139	98.6	138	137	99.3	-0.69	-4.39	2.71

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
N=number of subjects with available results
n/%=number/percentage of subjects with concentration within the specified range
95% CI=Standardised asymptotic 95% confidence interval; LL=lower limit, UL=upper limit

- Anti-PT and anti-FHA (ATP cohort for immunogenicity)

								Difference in percentage (Co-administered minus Staggered)		
		Co-administered			Staggered				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
anti-PT antibody	10 IU/mL	141	135	95.7	138	128	92.8	2.99	-2.70	9.12
anti-FHA antibody	10 IU/mL	141	141	100	138	138	100	0.00	-2.66	2.72

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
N=number of subjects with available results
n/%=number/percentage of subjects with concentration within the specified range
95% CI=Standardised asymptotic 95% confidence interval; LL=lower limit, UL=upper limit

- Anti-poliovirus 1, 2 and 3 (ATP cohort for immunogenicity)

								Difference in percentage (Co-administered minus Staggered)		
		Co-administered			Staggered				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
anti-poliovirus 1	8 ED_{50}	140	140	100	137	137	100	0.00	-2.68	2.74
anti-poliovirus 2	8 ED_{50}	128	128	100	127	127	100	0.00	-2.92	2.95
anti-poliovirus 3	8 ED_{50}	132	132	100	123	122	99.2	0.81	-2.04	4.47

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
N=number of subjects with available results
n/%=number/percentage of subjects with titre within the specified range
95% CI=Standardised asymptotic 95% confidence interval; LL=lower limit, UL=upper limit

- Anti-RV IgA (HRV immunogenicity sub-cohort)

Anti-RV IgA antibody concentrations were ≥13 U/mL (assay cut-off) in at least 95.7% of subjects in the two groups. At least 92.5% of subjects were seropositive i.e. with anti-RV IgA antibody concentrations ≥20 U/mL in the two groups. The GMCs of anti-RV IgA antibodies were similar in the two groups.

				Assay cut-off				≥20 U/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-RV IgA antibody	Co-administered	PI(D60)	69	66	95.7	87.8	99.1	64	92.8	83.9	97.6	350.1	223.3	548.8
	Staggered	PII(D75)	67	66	98.5	92.0	100	62	92.5	83.4	97.5	362.5	251.0	523.5

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
PI(D60)=One month after the second dose of the liquid HRV vaccine in the co-administered group (Visit 4)
PII(D75)=One month after the second dose of the liquid HRV vaccine in the staggered group (Visit 5)
Assay cut-off=anti-RV of 13 U/mL
GMC=geometric mean antibody concentration calculated on all subjects
Seropositivity rate=Anti-RV concentration ≥20 U/mL
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=lower limit, UL=upper limit

CHMP comment

No immune interferences with co-administered antigens were observed.

The seropositivity rate for HRV vaccine is high and comparable to previous clinical trials (see SmPC).

Safety results

- Total vaccinated cohort (n = 292)

The analyses for safety were performed on the TVC. The primary analysis of solicited symptom was performed by the administered dose, regardless of whether a solicited symptom had been documented as present/absent.

	Co-administered DPT-IPV N=147		Co-administered *Rotarix* N=147		Staggered DPT-IPV N=145		Staggered *Rotarix* N=145	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0	0	0.0	0	0.0	1	0.7	0	0.0
1	1	0.7	0	0.0	0	0.0	0	0.0
2	0	0.0	147	100	0	0.0	145	100
3	146	99.3	0	0.0	144	99.3	0	0.0
Any	147	100	147	100	144	99.3	145	100

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
N=number of subjects in each group included in the considered cohort
n/%=number/percentage of subjects receiving the specified total number of doses

- Occurrence of solicited general symptoms (Days 0-7)

Some of the solicited general symptoms are different for the HRV and the DPT-IPV vaccines.

Solicited general symptoms collected for the HRV vaccine are cough, diarrhoea, irritability/fussiness, loss of appetite, temperature and vomiting.

Solicited general symptoms collected for the DPT-IPV vaccine are drowsiness, irritability/fussiness, loss of appetite and temperature.

The analysis of each solicited symptom was limited to the symptoms specific to each vaccine.

As a consequence, different general symptoms were solicited overall after the co-administration of first DPT-IPV vaccine dose with the second HRV vaccine dose (7 symptoms) as compared to when the first DPT-IPV vaccine dose (4 symptoms) and the second HRV vaccine dose (6 symptoms) were administered alone. This potentially leads to an artefactual increased total incidence of general symptoms in the Co-administered group. Therefore, caution must be exercised when assessing the rates of solicited symptoms in each of the groups.

In overall per subject analysis, irritability/fussiness and cough were the most frequently reported solicited general symptoms in the two groups.

– Irritability/fussiness was reported in 63.3% and 54.5% of subjects in the Co-administered and the Staggered groups, respectively.

– Cough was reported in 46.3% of subjects in the Co-administered group and 49.7% of subjects in the Staggered group.

– Cough, diarrhoea, irritability/fussiness and vomiting, were the most frequently reported Grade 3 solicited general symptom with a maximum incidence of 1.0% of doses and 2.1% of subjects.

– The incidence of all solicited general symptoms (i.e. cough, diarrhoea, irritability/fussiness, loss of appetite, vomiting and fever) did not show any clinically relevant difference between the groups.

- Occurrence of solicited local and general symptoms (Days 0-7)

Redness was the most frequently reported solicited local symptom in the two groups.

– Redness was reported in 57.8% of subjects in the Co-administered group and 58.3% of subjects in the Staggered group.

- Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each dose of the liquid HRV vaccine and the first dose of DPT-IPV vaccine

For the HRV vaccine, at least one unsolicited symptom was reported in 59.9% of subjects in the Co-administered group and 55.9% of subjects in the Staggered group.

By preferred term, the most frequently reported unsolicited symptoms were:

– Nasopharyngitis (Co-administered group: 15.0% of subjects; Staggered group: 21.4% of subjects)

– Upper respiratory tract inflammation (Co-administered group: 12.2% of subjects; Staggered group: 13.1% of subjects)

– The incidence of the unsolicited symptoms was similar in the two groups.

No records of grade 3 unsolicited symptoms with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period after any dose of liquid HRV vaccine.

- Occurrence of SAEs from the first dose of the study vaccine up to study end (Month 5).

All SAEs reported were recovered and resolved and were not causally related to the vaccination.

No fatal SAEs were reported.

		Co-administered N=147					Staggered N=145				
					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL
At least one symptom		4	4	2.7	0.7	6.8	5	5	3.4	1.1	7.9
Infections and infestations (10021881)	Hand-foot-and-mouth disease (10019113)	0	0	0.0	0.0	2.5	1	1	0.7	0.0	3.8
	Nasopharyngitis (10028810)	0	0	0.0	0.0	2.5	1	1	0.7	0.0	3.8
	Pneumonia respiratory syncytial viral (10035732)	0	0	0.0	0.0	2.5	1	1	0.7	0.0	3.8
	Respiratory syncytial virus bronchiolitis (10038718)	0	0	0.0	0.0	2.5	1	1	0.7	0.0	3.8
	Respiratory syncytial virus infection (10061603)	2	2	1.4	0.2	4.8	0	0	0.0	0.0	2.5
	Viral infection (10047461)	0	0	0.0	0.0	2.5	1	1	0.7	0.0	3.8
Respiratory, thoracic and mediastinal disorders (10038738)	Fibrinous bronchitis (10051011)	1	1	0.7	0.0	3.7	0	0	0.0	0.0	2.5
Vascular disorders (10047065)	Kawasaki's disease (10023320)	1	1	0.7	0.0	3.7	0	0	0.0	0.0	2.5

Co-administered=DPT-IPV vaccine administered according to a 3, 4, 6-month schedule and the liquid HRV vaccine according to a 2, 3-month schedule
Staggered=DPT-IPV vaccine administered according to a 3, 4.5, 6-month schedule and the liquid HRV vaccine according to a 2, 3.5-month schedule
At least one symptom=at least one symptom experienced (regardless of the MedDRA Preferred Term)
N=number of subjects with at least one administered dose
n*=number of events reported
n/%=number/percentage of subjects reporting the symptom at least once
95% CI=exact 95% confidence interval; LL=lower limit, UL=upper limit

Kawasaki disease

Narrative: This 3-month-old male subject was enrolled in an open label study titled A phase IV, randomised, open-label, controlled study to assess the immunogenicity and safety of the diphtheria, tetanus, pertussis and inactivated poliovirus (DPT-IPV) vaccine Squarekids when co-administered with GSK Biologicals' oral live attenuated HRV liquid vaccine Rotarix in healthy Japanese infants aged 6–12

weeks at the time of the first dose of HRV vaccination. The subject received the 2nd dose of Rotarix liquid formulation (oral) 1.5 ml on 18th November 2016, for prophylaxis. The subject received the 1st dose of Squarekids (subcutaneous) 0.5 ml on 18th November 2016, for prophylaxis.

On 2nd December 2016, 14 days after receiving Rotarix liquid formulation and Squarekids, the subject developed severe - grade 3 kawasaki's disease. Serious criteria included hospitalization and GSK medically significant. Squarekids was continued with no change. The outcome of kawasaki's disease was recovered/resolved on 12th December 2016. The investigator considered that there was no reasonable possibility that the kawasaki's disease may have been caused by Rotarix liquid formulation and Squarekids.

CHMP comment

No records of grade 3 unsolicited symptoms with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period after any dose of liquid HRV vaccine.

All SAEs reported were recovered and resolved and were not causally related to the vaccination.

No fatal SAEs were reported.

This is a relatively small study (n = 292)

Conclusions

The primary objective was met as non-inferiority of the immune response was demonstrated hierarchically. Hence, the immunogenicity to the antigens contained in DPT-IPV vaccine was not impaired by the co-administration with Rotarix.

The anti-RV IgA seropositivity rates and GMCs one month after the second dose of the liquid HRV vaccine, and GMCs/GMTs for DPT-IPV antigens, one month after the third dose of the DPT-IPV vaccine were similar in the two groups.

No safety concerns were raised during the study. All SAEs reported were recovered and resolved and were not causally related to the vaccination. The safety results of this study indicate that the subjects receiving liquid HRV vaccine with DPT-IPV vaccine experienced a clinically acceptable safety profile.

The MAH concluded that no changes are needed to the PI of Rotarix since the data are aligned with the known safety profile, are aligned with the information already present in the PI related to concomitant administration of Rotarix with Hib monovalent or combination vaccines, and do not impact the B/R profile of the vaccine.

3. Rapporteur's overall conclusion

The data of study ROTA-079 (114720) confirm the information already presented in the current SmPC, i.e. that Rotarix can be given concomitantly with any of the following monovalent or combination vaccines, including hexavalent vaccines (DTPa-HBV-IPV/Hib), diphtheria-tetanus-acellular pertussis vaccine (DTPa), inactivated polio vaccine (IPV). Clinical studies demonstrate that the immune responses and the safety profiles of the administered vaccines were unaffected.

No new safety concerns that could be related to Rotarix were observed in this study.

The B/R profile of Rotarix therefore remains positive.

The Rapporteur endorses the conclusions of the MAH.

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