28 January 2016
EMA/105868/2016
Committee for Medicinal Products for Human Use (CHMP)

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

Rotarix

International non-proprietary name: rotavirus vaccine, live

Procedure No. EMEA/H/C/000639/P46 085

Note

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

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Rapporteur's Assessment Report for the Post-Authorisation Measure P46 085

Rotarix

International non-proprietary name: human rotavirus, live

Procedure No. EMEA/H/C/P46 085

Marketing authorisation holder: GlaxoSmithKline Biologicals S.A

Date of this report:	05/01/2016
Deadline for comments:	18/01/2016

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Abbreviations

EPI	Expanded Program on Immunization
HRV	Human Rotavirus Vaccine
SCID	Severe combined immunodeficiency
RVGE	Rotavirus Gastro-Entiritis
GMC	Geometric Mean Concentration
HRV	Human Rotavirus Vaccine
RV1	Rotarix mono-valent Vaccine

1. Introduction

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

ROTARIX final report for study 10PN-PD-DIT-034 (A phase III, open, controlled study in South Africa to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine (Synflorix) administered as a 3-dose (6, 10, 14 weeks) primary immunization course in HIV infected infants, HIV exposed uninfected infants and HIV unexposed uninfected infants followed by a booster vaccination at 9-10 months of age.) in accordance with Article 46 of Regulation (EC) No 1901/2006, in which *Rotarix* is coadministered.

1.1. Steps taken for the assessment

Submission date:	23/10/2015
Start of procedure:	30/11/2015
CHMP Rapporteur's preliminary assessment report circulated on:	04/01/2016
CHMP Rapporteur's updated assessment report circulated on:	21/01/2016
CHMP opinion:	28/01/2016

2. Assessment of the post-authorisation measure PAM EMEA-H-C-639-P46 085

The applicant submitted to the EMA the final report for study 10PN-PD-DIT-034 (A phase III, open, controlled study in South Africa to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT, *Synflorix*) administered as a 3-dose (6, 10, 14 weeks) primary immunization course in HIV infected infants, HIV exposed uninfected infants and HIV unexposed uninfected infants followed by a booster vaccination at 9-10 months of age. (EudraCT: 2011-002077-35)) in accordance with Article 46 of Regulation (EC) No 1901/2006, in which *Rotarix* is coadministered at 10 and 14 weeks of age.

Methods

Objectives (relevant to Rotarix)

Primary objective

Immunogenicity

The primary objective of the study 10PN-PD-DIT-034 was to evaluate and characterize the immune response to the 10Pn-PD-DiT vaccine one month following a 3-dose (6, 10 and 14 weeks of age) primary vaccination course according to the EPI-schedule in HIV infected infants, HIV exposed uninfected infants and HIV unexposed uninfected infants.

Secondary objective

Immunogenicity

Secondary objectives included assessment of the immune response to *Synflorix* and co-administered Tritanrix-Hepb-HiB, *Rotarix* and measles vaccine at different timepoints (post-primary, prior to and after booster).

Safety

As one of the secondary objectives, this study meant to evaluate immunogenicity, safety and reactogenicity of Rotarix one month following a 2-dose (10 and 14 weeks of age) vaccination course in all groups.

To evaluate the safety and reactogenicity of GSK Biologicals' HRV vaccine in all groups.

Study population

Inclusion criteria

The study included 3 populations defined by the HIV status of both the mother and the infant:

· Infants born from a HIV-positive mother and confirmed as being HIV infected, as documented by a positive HIV DNA-PCR at screening and by a positive HIV viral load test at Visit 1, were referred to as **HIV+/+**.

· Infants born from a HIV-positive mother and confirmed as being HIV exposed uninfected, as documented by a negative HIV DNA-PCR result at screening, were referred to as **HIV+/-**.

· Infants born from a HIV negative mother* and confirmed as HIV unexposed uninfected, as documented by a negative HIV ELISA result at Visit 1, are referred to as **HIV-**.

*As documented by both a negative HIV ELISA test performed on blood from the mother after 24 weeks of gestation and the absence of clinical signs of an acute seroconversion syndrome thereafter until delivery.

HIV testing was performed as follows :

For infants born from a HIV infected mother:

– **HIV screening visit (at 4-8 weeks of age)**: The HIV status of infants born from a HIV positive mother was determined by **HIV DNA-PCR**. Note: Infants with a documented HIV DNA-PCR test performed at other facilities were eligible for the study without additional HIV screening tests.

For infants with a positive HIV DNA-PCR result at screening and for infants referred to the study with a documented positive HIV DNA-PCR result:

– HIV viral load test at Visit 1 (Month 0 [Pre]) and Visit 10 (Month 23 [Post IV]) by using a HIV RNA PCR.

– CD4 count at Visit 1 (Month 0 [Pre]), Visit 5 (Month 8 [Post III]), Visit 8 (Month 14 [Post IV]) and Visit 10 (Month 23 [Post IV]).

HIV exposed uninfected infants (with a negative HIV DNA-PCR result at screening):

– HIV DNA-PCR 2 months post-cessation of breastfeeding.

– HIV ELISA at Visit 10 (Post IV [M23]).

For infants born from a HIV uninfected mother:

– HIV ELISA at Visit 1 (Month 0 [Pre]) and Visit 10 (Month 23 [Post IV/Post III]).

– Infants with a positive ELISA test at Visit 1 (Month 0 [Pre]) had a confirmatory HIV DNA-PCR test and were excluded from the According-To-Protocol (ATP) statistical analyses.

For all study participants:

– Additional HIV testing was to be performed if clinically indicated.

Exclusion criteria

- Subjects were to be free of any known or suspected health problems that would contraindicate the initiation of routine immunizations outside a clinical trial context (except for subjects in the HIV infected group).
- HIV infected infants with **moderately and severely symptomatic infection** (stages III and IV, respectively) according to the prevailing version of the WHO classification (version 2007) were excluded from the study.
- Babies with a family history of hereditary immunodeficiency other than HIV infection and babies whose weight for age using standard growth charts was <3rd percentile at Visit 1, except for HIV infected infants for which the decision of enrolment was left to the investigator's discretion, were also excluded from the study.

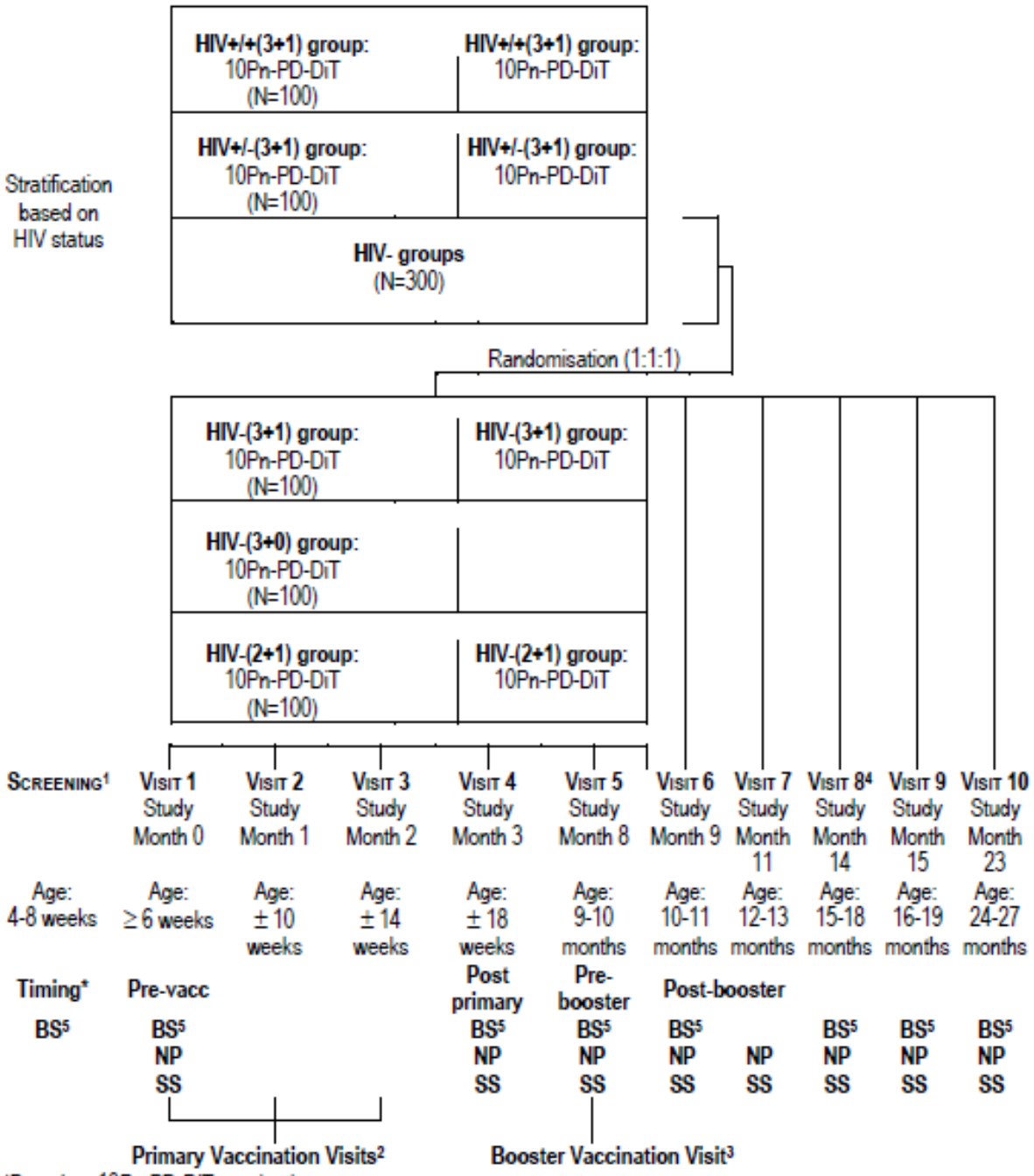
One of the elimination criteria from safety and immunogenicity ATP analyses was a positive HIV DNA-PCR test during the study for the HIV unexposed uninfected infants and HIV exposed uninfected infants.

Sample size

A total of 497 subjects were enrolled and 350 subjects received at least one dose of Rotarix.

Study design

The study design was a single-centre, open, partially randomized, controlled study.



*Based on 10Pn-PD-DiT vaccination

[1] Applicable for children born from a HIV infected mother. Infants with a documented HIV DNA-PCR test performed at other facilities were also eligible for the study without additional HIV analysis.

[2] All groups were to receive DTPw-HBV/Hib at 6, 10, and 14 weeks of age (primary vaccination) according to the nationally recommended immunization schedule and HRV at 10 and 14 weeks of age (primary vaccination).

[3] The HIV-(3+0) group did not receive a booster vaccine dose of 10Pn-PD-DiT.

[4] All groups were to receive DTPw-HBV/Hib at 15-18 months of age (booster vaccination) according to the nationally recommended immunization schedule.

[5] Refer to Table 9 and Table 10 for details.

BS = Blood Sample, NP = Nasopharyngeal Swab, SS = Salivary sample

The study included 5 parallel groups:

· **Group HIV+/+**(3+1) (referred to as 'HIV+/+' hereafter): subjects were to receive 3 primary doses and one booster dose of 10Pn-PD-DiT;

· **Group HIV+/-**(3+1) (referred to as 'HIV+/-' hereafter): subjects were to receive 3 primary doses and one booster dose of 10Pn-PD-DiT;

HIV unexposed uninfected infants were randomized into 3 sub-groups with a 1:1:1 ratio:

· **Group HIV-**(3+1) (referred to as 'HIV-(3+1)' hereafter): subjects were to receive 3 primary doses and one booster dose of 10Pn-PD-DiT;

· **Group HIV-**(3+0) (referred to as 'HIV-(3+0)' hereafter): subjects were to receive 3 primary doses of 10Pn-PD-DiT without a booster dose;

· **Group HIV-**(2+1) (referred to as 'HIV-(2+1)' hereafter): subjects were to receive 2 primary doses and one booster dose of 10Pn-PD-DiT.

Treatment allocation was done by stratification according to the HIV status of the infant and randomization in the HIV unexposed uninfected group with a 1:1:1 ratio. This study included an HIV screening visit for infants between 4-8 weeks of age born from an HIV infected mother; infants with a documented HIV DNA-PCR test performed at other facilities were also eligible for the study without additional HIV analysis.

For each subject, the duration of the study was approximately 24 months and at least 20 months for subjects in the according-to-protocol (ATP) cohort for immunogenicity (primary objective).

Endpoints

Primary endpoint

Immunogenicity

- Anti-pneumococcal vaccine serotype antibody concentrations ≥ 0.2 mcg/mL, one month after primary immunization.

Secondary endpoints (relevant to Rotarix)

Immunogenicity

- Concentration of antibodies induced by the co-administered HRV vaccine, one month after the administration of the second vaccine dose: Anti-rotavirus IgA antibody concentration.

Safety

- Occurrence of each solicited adverse event (AE) within 4 days after each vaccination.
  - Local (any, grade 3) AEs.
  - General (any, grade 3, related) AEs.
- Occurrence of unsolicited AEs within 31 days after each vaccination.
- Occurrence of SAEs following screening or after the first vaccination, as applicable, up to study end.

Statistical Methods

Analyses were performed as per protocol and Statistical Analysis Plan except for the following:

• The safety analysis according to WHO HIV clinical staging at study entry was not performed as planned because all enrolled HIV +/+ subjects were in WHO stage 1 (Asymptomatic Persistent generalized lymphadenopathy) at study entry.

• The immunogenicity analysis for HIV infected infants was performed according to CD4 percentage categories and viral load categories in addition to the analysis per CD4 count.

Analysis of demography was performed as follows :

• CD4 cell counts and CD4 percentages were summarized for HIV+/+ subjects (mandatory at Visits 1, 5, 8, 10 + if clinically indicated) and for HIV+/- and HIV- subjects (if clinically indicated).

• For HIV+/+ subjects:

– WHO clinical staging (at Visits 1, 5, 8 and 10) and viral load (at Visits 1 and 10) were summarized.

– Changes in WHO clinical staging, CD4 cell count, CD4 percentage and viral load (at Visits 5, 8 and 10 as compared with baseline) were also tabulated in a descriptive way.

• For the HIV+/- subjects, summary of breastfeeding cessation was tabulated.

• For the HIV uninfected subjects, anti-HIV antibodies test results (ELISA) were summarised at Visits 1 and 10.

• HIV DNA response were summarised up to 2 months after breastfeeding cessation and when clinically indicated for the HIV+/- subjects and only when clinically indicated for the HIV- subjects.

Results

Immunogenicity results

Following one month after 2 doses of *Rotarix*, the GMCs for Anti-Rotavirus antibodies IgA calculated on seropositive subjects were 169.8 (58,6%), 201.9 (78%), 282.7 (80,3%), 241.3 (69,7%) and 212.0 (65,7%) in the HIV+/+, HIV+/-, HIV-(3+1), HIV-(3+0) and HIV-(2+1) groups, respectively. Please refer to the Tables 146 & 147 for the ATP cohorts and to the Tables 219 & 220 for the TVC cohorts.

For the subjects who did receive 2 doses of HRV, the seropositivity rates at first study visit (approx. 6 weeks of age) were 23.3%, 30.4%, 35.8%, 23.9% and 31.8% in the HIV+/+, HIV+/-, HIV-(3+1), HIV-(3+0) and HIV-(2+1) groups, respectively.

For the subjects who did not receive any dose of HRV, the seropositivity rates at first study visit (approx. 6 weeks of age) were 73.3%, 46.2%, 77.8%,67.2% and 51.7% in the HIV+/+, HIV+/-, HIV-(3+1), HIV-(3+0) and HIV-(2+1) groups, respectively. There is a higher background seropositivity rates in the subjects who did not receive any doses of HRV compared to the subjects who received 2 doses.

All the subjects who did not receive HRV dose did their visit between 19/02/2009 and 08/03/2009 whereas for the subjects receiving the 2 doses, it was between 26/05/2009 and 24/08/2010. Rotavirus infections in South-Africa are known to be seasonal and occur during the cool, dry winter months and usually run from March to August; however the RotaVirus season in 2009 started earlier [Iyaloo, 2013]. This might be an explanation for the higher background seropositivity rates in the subjects who did not receive any doses of HRV.

Table 146-147. Results of Immunogenicity responses to *Rotarix* 1 month post the 2 dose schedule (at approximatively 18 weeks of age) for the ATP cohort.

Table 146 Seropositivity rates and anti-rotavirus IgA antibody GMCs - by HRV vaccination status (ATP cohort for immunogenicity)

					≥ 20 U/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-ROTA IGA	2 doses of HRV	HIV+/+	PRE	52	13	25.0	14.0	38.9	18.7	13.2	26.4
			PIII(M3)	58	34	58.6	44.9	71.4	52.6	33.8	81.8
		HIV+/-	PRE	61	19	31.1	19.9	44.3	21.2	15.0	29.9
			PIII(M3)	59	46	78.0	65.3	87.7	104.1	66.3	163.5
		HIV-(3+1)	PRE	65	24	36.9	25.3	49.8	27.0	18.3	39.6
			PIII(M3)	66	53	80.3	68.7	89.1	146.4	94.2	227.4
		HIV-(3+0)	PRE	65	15	23.1	13.5	35.2	16.7	12.9	21.7
			PIII(M3)	66	46	69.7	57.1	80.4	92.0	60.0	141.0
		HIV-(2+1)	PRE	66	21	31.8	20.9	44.4	25.6	17.2	38.2
			PII(M3)	67	44	65.7	53.1	76.8	74.3	47.5	116.3
	1 dose of HRV	HIV-(3+1)	PRE	1	0	0.0	0.0	97.5	10.0	-	-
			PIII(M3)	1	1	100	2.5	100	25.0	-	-
		HIV-(3+0)	PRE	1	0	0.0	0.0	97.5	10.0	-	-
			PIII(M3)	1	0	0.0	0.0	97.5	10.0	-	-
	No HRV dose	HIV+/+	PRE	11	8	72.7	39.0	94.0	31.7	17.9	56.0
			PIII(M3)	11	5	45.5	16.7	76.6	54.8	13.1	229.2
		HIV+/-	PRE	25	12	48.0	27.8	68.7	32.2	17.8	58.2
			PIII(M3)	27	13	48.1	28.7	68.1	54.0	21.3	136.8
		HIV-(3+1)	PRE	23	20	87.0	66.4	97.2	136.2	68.1	272.2
			PIII(M3)	25	17	68.0	46.5	85.1	63.1	34.8	114.5
		HIV-(3+0)	PRE	25	17	68.0	46.5	85.1	55.3	29.2	104.8
			PIII(M3)	24	16	66.7	44.7	84.4	47.5	26.5	85.3
		HIV-(2+1)	PRE	26	14	53.8	33.4	73.4	30.7	18.3	51.5
			PII(M3)	28	15	53.6	33.9	72.5	41.7	22.3	78.1

Table 147 GMCs for anti-rotavirus IgA antibodies calculated on seropositive subjects for subjects having received the 2 doses of HRV vaccine (ATP cohort for immunogenicity)

				GMC		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
ANTI-ROTA IGA	HIV+/+	PRE	52	122.2	58.6	255.0
		PIII(M3)	58	169.8	111.3	259.0
	HIV+/-	PRE	61	111.5	58.9	211.0
		PIII(M3)	59	201.9	135.1	301.7
	HIV-(3+1)	PRE	65	146.9	81.2	265.9
		PIII(M3)	66	282.7	195.9	408.1
	HIV-(3+0)	PRE	65	92.2	52.5	161.9
		PIII(M3)	66	241.3	173.6	335.5
	HIV-(2+1)	PRE	66	192.7	96.3	385.8
		PII(M3)	67	212.0	139.3	322.7

HIV+/+ = HIV infected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV+/- = HIV exposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(3+1) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(3+0) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(2+1) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 2 primary doses at 6-14 weeks of age and booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
GMC = geometric mean antibody concentration
N = number of seropositive subjects (with concentration ≥ 20 U/mL)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = prior to dose 1

Table 219-220. Results of Immunogenicity responses to *Rotarix* 1 month post the 2 dose schedule (at approximatively 18 weeks of age) for the TVC cohort.

Table 219 Seropositivity rates and anti-rotavirus IgA antibody GMCs - by HRV vaccination status (Total vaccinated cohort)

					≥ 20 U/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-ROTA IGA	2 doses of HRV	HIV+/+	PRE	60	14	23.3	13.4	36.0	18.2	13.3	25.1
			PIII(M3)	65	39	60.0	47.1	72.0	60.9	39.2	94.7
		HIV+/-	PRE	69	21	30.4	19.9	42.7	20.7	15.1	28.4
			PIII(M3)	66	51	77.3	65.3	86.7	102.5	66.8	157.3
		HIV-(3+1)	PRE	67	24	35.8	24.5	48.5	26.2	18.0	38.1
			PIII(M3)	68	55	80.9	69.5	89.4	151.3	98.4	232.6
		HIV-(3+0)	PRE	67	16	23.9	14.3	35.9	17.7	13.3	23.5
			PIII(M3)	67	46	68.7	56.2	79.4	89.0	58.1	136.3
		HIV-(2+1)	PRE	66	21	31.8	20.9	44.4	25.6	17.2	38.2
			PII(M3)	67	44	65.7	53.1	76.8	74.3	47.5	116.3
	1 dose of HRV	HIV-(3+1)	PRE	1	0	0.0	0.0	97.5	10.0	-	-
			PIII(M3)	1	1	100	2.5	100	25.0	-	-
		HIV-(3+0)	PRE	2	0	0.0	0.0	84.2	10.0	10.0	10.0
			PIII(M3)	1	0	0.0	0.0	97.5	10.0	-	-
	No HRV dose	HIV+/+	PRE	15	11	73.3	44.9	92.2	36.2	21.6	60.5
			PIII(M3)	14	7	50.0	23.0	77.0	58.7	18.5	186.7
		HIV+/-	PRE	26	12	46.2	26.6	66.6	30.8	17.3	54.7
			PIII(M3)	27	13	48.1	28.7	68.1	54.0	21.3	136.8
		HIV-(3+1)	PRE	27	21	77.8	57.7	91.4	104.4	53.2	204.8
			PIII(M3)	28	19	67.9	47.6	84.1	67.8	37.3	123.5
		HIV-(3+0)	PRE	28	19	67.9	47.6	84.1	51.3	28.7	91.8
			PIII(M3)	24	16	66.7	44.7	84.4	47.5	26.5	85.3
		HIV-(2+1)	PRE	29	15	51.7	32.5	70.6	28.4	17.7	45.6
			PII(M3)	29	15	51.7	32.5	70.6	39.7	21.6	73.2

Table 220 GMCs for anti-rotavirus IgA antibodies calculated on seropositive subjects for subjects having received the 2 doses of HRV vaccine (Total vaccinated cohort)

				GMC		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
ANTI-ROTA IGA	HIV+/+	PRE	60	131.7	65.8	263.7
		PIII(M3)	65	203.3	134.7	306.7
	HIV+/-	PRE	69	109.8	61.3	196.8
		PIII(M3)	66	203.3	138.7	297.8
	HIV-(3+1)	PRE	67	146.9	81.2	265.9
		PIII(M3)	68	287.6	201.8	409.9
	HIV-(3+0)	PRE	67	108.8	57.9	204.6
		PIII(M3)	67	241.3	173.6	335.5
	HIV-(2+1)	PRE	66	192.7	96.3	385.8
		PII(M3)	67	212.0	139.3	322.7

HIV+/+ = HIV infected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV+/- = HIV exposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(3+1) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age and a booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(3+0) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 3 primary doses at 6, 10 and 14 weeks of age, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
HIV-(2+1) = HIV unexposed uninfected children receiving 10Pn-PD-DiT as 2 primary doses at 6-14 weeks of age and booster dose at age of 9-10 months, and receiving DTPw-HBV/Hib at 6, 10 and 14 weeks of age with a booster dose at age of 15-18 months
GMC = geometric mean antibody concentration
N = number of seropositive subjects (with concentration ≥ 20 U/mL)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = prior to dose 1
PIII(M3)/PII(M3) = one month after primary vaccination

Safety results

In this study, the 10Pn-PD-DiT vaccine as well as the co-administered DTPw-HBV/Hib, HRV and measles vaccines were generally well-tolerated in HIV-exposed infected, HIV-exposed uninfected and HIV-unexposed uninfected infants when administered according to different vaccination schedules. The safety analysis performed in this study does not relate to the administration of HRV alone.

Regarding the safety of the 10Pn-PD-DiT vaccine when administered in HIV-negative and HIV-positive subjects starting at 6 weeks of age, similar reporting rates of symptoms among the study groups were observed. However, the number of SAEs reported in HIV positive infants was higher than in the HIV-exposed uninfected and HIV- unexposed uninfected infants, which was expected given their impaired health status.

Fatal Serious adverse events (SAEs) were reported for 11 subjects during the post-primary phase [5 in the HIV+/+ group , 3 in the HIV+/- group and 3 in the HIV-(3+0) group] and for one subject during the post-booster phase [in the HIV+/- group]. Among these fatal SAEs, 2 were assessed by the investigator to be causally related to vaccination: sudden infant death syndrome in the HIV+/- group occurring 3 days after administration of study vaccine dose 1 [BP1]and sudden death in the HIV-(3+0) group occurring one day after administration of study vaccine dose 1[BP2]. Both events were assessed by the investigator as causally related to vaccination given the time interval between vaccination and the onset of the event.

During the course of the study, at least one non-fatal SAE was reported for 111 subjects (31 in the HIV+/+ group, 25 in the HIV+/- group, 20 in each of the HIV-(3+1) and HIV- (2+1) groups and 15 in the HIV-(3+0) group). Of these, 4 non-fatal SAEs (gastroenteritis in the HIV+/+ group, 2 events of febrile convulsion [one in the HIV-(3+1) group and one in the HIV-(2+1) group] and injection site abscess in the HIV-(3+0) group) were assessed by the investigator to be causally related to vaccination and were recovered/resolved.

At study end, 5 of these non-fatal SAEs were not recovered/not resolved (Kwashiorkor in a subject in the HIV+/+ group, cerebral palsy in a subject in the HIV+/- group, HIV infection in a subject in the HIV-(3+1) group, asthma in a subject in the HIV-(2+1) group and trisomy 21 in a subject in the HIV-(2+1) group), one SAE was recovering/resolving (pulmonary tuberculosis in a subject in the HIV+/+ group [subject moved out of study area and no more information was available]) and one SAE recovered/resolved with sequelae (meningitis tuberculous in a subject in the HIV-(3+1) group). Note that the subject in the HIV+/+ group who suffered from Kwashiorkor died of sudden death later (30 days post-dose 3 of study vaccines). Note that the safety analysis performed in this study does not relate to the administration of RV1 alone.

No intussusception cases were reported.

Conclusions

The MAH submitted the final report for study 10PN-PD-DIT-034 in accordance with Article 46 of Regulation (EC) No 1901/2006, in which *Rotarix* is coadministered. This study was a phase III, open, controlled study in South Africa to assess the immunogenicity, safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine administered as a 3-dose (6, 10, 14 weeks) primary immunization course in HIV infected infants, HIV exposed uninfected infants and HIV unexposed uninfected infants followed by a booster vaccination at 9-10 months of age.

Immune responses to the *Rotarix* vaccine were observed in HIV-infected, HIV-exposed uninfected infants and HIV unexposed/uninfected [HIV-(3+1), HIV-(3+0), HIV-(2+1)] one month after a 2-dose primary vaccination course (10 and 14 weeks of age) in respectively 58,6%, 78,0%, 80,3%, 69,7%

and 65,7%. This is in line with what could be expected of the immune responses in HIV-infected compared to the uninfected subjects.

Regarding the safety of the 10Pn-PD-DiT vaccine as well as the co-administered DTPw-HBV/Hib, RV1 and measles vaccines, when given in HIV-negative and HIV-positive subjects starting at 6 weeks of age, similar reporting rates of symptoms among the study groups were observed. The safety analysis performed in this study did not relate to the administration of *Rotarix* alone. However, the number of SAEs reported in HIV-positive infants was higher than in the HIV-exposed uninfected and HIV-unexposed uninfected infants, which was expected given their impaired health status. Note that HIV infected infants with moderately and severely symptomatic infection (stages III and IV, respectively) according to the prevailing version of the WHO classification (version 2007) were excluded from the study.

Overall, the 10Pn-PD-DiT vaccine, when co-administered with the DTPw- HBV/Hib, RV1 and measles vaccines, had a positive benefit/risk profile in HIV-exposed infected, HIV-exposed uninfected and HIV-unexposed uninfected infants when administered according to different vaccination schedules.

The MAH has concluded that no changes are needed to the PI of *Rotarix* since the data are aligned with the known immunogenicity profile and do not impact the B/R profile.

The current wordings in the *Rotarix* SmPC are as follows :

> ***4.4 Special warnings and precautions for use***
>
> *Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of Rotarix. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems (see section 4.8).*
>
> *Administration of Rotarix to infants who have known or suspected immunodeficiency should be based on careful consideration of potential benefits and risks.*
>
> ***4.5 Interaction with other medicinal products and other forms of interaction***
>
> *Rotarix can be given concomitantly with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTPa-HBV-IPV/Hib)]: diphtheria-tetanus-whole cell pertussis vaccine (DTPw), diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. Clinical studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.*
>
> ***4.8 Undesirable effects***
>
> *Other special populations*
>
> *Safety in infants with human immunodeficiency (HIV) infection*
>
> *In a clinical study, 100 infants with HIV infection were administered Rotarix lyophilised formulation or placebo. The safety profile was similar between Rotarix and placebo recipients.*
>
> ***5.1 Pharmacodynamic properties***
>
> *Immune response*
>
> *The immunologic mechanism by which Rotarix protects against rotavirus gastro-enteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastro-enteritis has not been established.*

The following table shows the percentage of subjects initially seronegative for rotavirus (IgA antibody titres < 20 U/ml) (by ELISA) with serum anti-rotavirus IgA antibody titers ≥ 20U/ml one to two months after the second dose of vaccine or placebo as observed in different studies.

Schedule	Studies conducted in	Vaccine		Placebo	
		N	% ≥ 20U/ml [95% CI]	N	% ≥ 20U/ml [95% CI]
2, 3 months	France, Germany	239	82.8 [77.5;87.4]	127	8.7 [4.4;15.0]
2, 4 months	Spain	186	85.5 [79.6;90.2]	89	12.4 [6.3;21.0]
3, 5 months	Finland, Italy	180	94.4 [90.0;97.3]	114	3.5 [1.0;8.7]
3, 4 months	Czech Republic	182	84.6 [78.5;89.5]	90	2.2 [0.3;7.8]
2, 3 to 4 months	Latin America; 11 countries	393	77.9% [73.8;81.6]	341	15.1% [11.7;19.0]
10, 14 weeks and 6, 10, 14 weeks (Pooled)	South Africa, Malawi	221	58.4 [51.6;64.9)	111	22.5 [15.1;31.4]

3. CHMP's overall conclusion

In this study, immune responses to the *Rotarix* vaccine were observed in HIV-infected, HIV-exposed uninfected infants and HIV unexposed/uninfected [HIV-(3+1), HIV-(3+0), HIV-(2+1)] one month after a 2-dose primary vaccination course (10 and 14 weeks of age) in respectively 58,6%, 78,0%, 80,3%, 69,7% and 65,7%. This is in line with what could be expected of the immune responses in HIV-infected compared to the uninfected subjects.

Live oral rotavirus vaccines have shown modest efficacy among children in African countries for reasons that are not completely understood. However, since the incidence of severe rotavirus disease is significantly higher in high child mortality settings, the numbers of severe disease cases and deaths averted by vaccines in these settings are likely to be higher than in low mortality settings, despite the lower vaccine efficacy.

Regarding the safety of the 10Pn-PD-DiT vaccine as well as the co-administered DTPw-HBV/Hib, RV1 and measles vaccines, when given in HIV-negative and HIV-positive subjects starting at 6 weeks of age, similar reporting rates of symptoms among the study groups were observed. The safety analysis performed in this study did not relate to the administration of *Rotarix* alone. However, the number of SAEs reported in HIV-positive infants was higher than in the HIV-exposed uninfected and HIV-unexposed uninfected infants, which was expected given their impaired health status.

In immunocompromised patients, natural rotavirus infection is not regularly associated with severe diarrhoea or systemic disease, although shedding of the virus may be prolonged. However, individuals with severe combined immunodeficiency (SCID) such as congenital immunodeficiency, bone marrow transplantation or solid organ transplantation sometimes experience severe, prolonged and even fatal gastro-entiritis (RVGE) (Clarck- In:Plotkin - 2013). In South Africa, the estimated incidence of acute RVGE was 2.3 fold (95% confidence interval: 1.8–2.9) higher in HIV-infected than in non-infected individuals (Groome, 2012).

A small RCT that enrolled a total of 100 asymptomatic or mildly symptomatic HIV-positive infants aged 6–10 weeks in South Africa found that 3 doses of *Rotarix* were well tolerated and elicited a satisfactory immune response without aggravating the immunologic or HIV condition (Steele, 2011).

Nevertheless, administration of *Rotarix* to infants who have known or suspected immunodeficiency should be based on careful consideration of potential benefits and risks (SmPC *Rotarix* 2015). As a reminder, contraindications for using rotavirus vaccines are severe hypersensitivity to any of their components and severe immunodeficiency including SCID.

Overall, the 10Pn-PD-DiT vaccine, when co-administered with the DTPw- HBV/Hib, RV1 and measles vaccines, had a positive benefit/risk profile in HIV-exposed infected, HIV-exposed uninfected and HIV-unexposed uninfected infants when administered according to different vaccination schedules. The MAH has concluded that no changes are needed to the PI of *Rotarix* since the data are aligned with the known immunogenicity profile and do not impact the B/R profile.

The CHMP endorses the conclusions of the MAH.

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

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

References

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