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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/P46/097

Note

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

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1. Introduction

On 5 December 2019, the MAH submitted a completed paediatric study for Rota-090 (etrack 201663, EudraCT 2016-003210-27), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Rota-090 is a phase IIIA, randomised, single-blind, multi-centric study to evaluate the immunogenicity, reactogenicity and safety of 3 doses of Pediarix, Hiberix and Prevenar 13 when co-administered with 2 doses of the Porcine circovirus (PCV)-free liquid formulation of GSK Biologicals' oral live attenuated Human Rotavirus (HRV) vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in healthy infants 6-12 weeks of age. Note that 'PCV-free' is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used. The end of study (EoS) was defined in the protocol as last testing results released for samples collected at Visit 4. If the last testing results had become available before the Last Subject Last Visit (LSLV), i.e., before the Extended Safety Follow-Up (ESFU), then the EoS would have been defined as the LSLV. As the last testing results for this study were available after the LSLV, EoS is defined as the last testing results released for samples collected at Visit 4. EoS occurred on 6 June 2019. Therefore, the deadline for submission under Art 46 was 6 December 2019.

A short critical expert overview was also provided.

2. Scientific discussion

In 2008, the Rotarix SmPC was updated with data from the second-year follow-up from a clinical study (ROTA-036) that evaluated the efficacy, immunogenicity, reactogenicity and safety of two doses of Rotarix in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the HRV vaccine. The efficacy results showed that sufficient protection against gastroenteritis caused by the serotypes G1P 8 , G2P 4 , G3P 8 , G4P 8 and G9P 8 continues in the second year of life, although the data for some of the serotypes indicate a certain waning immunity over time. No interference of Rotarix on immune response to antigens contained in coadministered childhood vaccines (Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec) could be observed in this study. The safety data for the second year was comparable with data from the first year in this study and did not raise any further concerns.

Also, based on a coadministration study of Rotarix with other vaccines, including oral polio vaccine (OPV), the wording of the SmPC was updated to reflect that, although concomitant administration of OPV may slightly reduce the immune response to Rotarix, it was shown that the protection against severe rotavirus gastro-enteritis is maintained.

Section 4.5 of the SmPC of Rotarix approved on the date of this report states:

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.

Concomitant administration of Rotarix and oral polio vaccine (OPV) does not affect the immune response to the polio antigens.

Although concomitant administration of OPV may slightly reduce the immune response to rotavirus vaccine, clinical protection against severe rotavirus gastro-enteritis was shown to be maintained in a clinical trial involving more than 4,200 subjects who received Rotarix concomitantly with OPV.

The Marketing Authorisation Holder submitted the final Study Report, including 6-month safety follow-up data, of study Rota-090 (etrack 201663, EudraCT 2016-003210-27) to comply with the requirements of Art 46 of the regulation (EC) No 1901/2006 (LEG, stand-alone PAM [P46]).

Immunogenicity and safety results of ROTA-090 are in line with the approved PI for Rotarix in the EU. No changes to the SmPC are needed, see also Section 3.

2.1. Clinical aspects

2.1.1. Clinical study etrack 201663, EudraCT 2016-003210-27

Description

A phase IIIA, randomized, single-blind, multi-centric study to evaluate the immunogenicity, reactogenicity and safety of 3 doses of *Pediarix, Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid formulation of GSK Biologicals' oral live attenuated HRV vaccine as compared to the currently licensed lyophilized formulation of the HRV vaccine in healthy infants 6-12 weeks of age. Note that 'PCV-free' is defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.

Methods

Objective(s)

Co-Primary objectives

☐ To demonstrate the non-inferiority of the immune responses to 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with 2 doses of the *Porcine circovirus* (PCV)-free liquid HRV vaccine, as compared to when co-administered with the currently licensed lyophilized HRV vaccine, 1 month after Dose 3 of routine infant vaccines.

***Criteria for non-inferiority**:*

☐ *Lower limits of the 2-sided standardized asymptotic 95% confidence intervals (CIs) on the differences between groups [PCV-free liquid HRV vaccine group (HRV Liq group) minus lyophilized HRV vaccine (HRV Lyo group)] in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) for each of anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibodies were ≥-10% (clinical limit for non-inferiority),*

☐ *The lower limit of the 2-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with seroprotective concentration (≥10 mIU/mL) for antibodies against Hepatitis B surface antigen (anti-HBs) was ≥-10% (clinical limit for non-inferiority),*

☐ *Lower limits of the 2-sided standardized asymptotic 95% CIs on the differences between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with seroprotective titers [≥ 8 Median effective dose (ED50)] for each of anti-poliovirus serotypes 1, 2 and 3 antibodies were ≥-5% (clinical limit for noninferiority),*

☐ *Lower limits of the 2-sided 95% CIs on the geometric mean concentration (GMC) ratios (HRV Liq group over HRV Lyo group) for antibodies against each of the pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) antigens [anti-PT, anti-FHA and anti-PRN] were ≥0.67 (clinical limit for non-inferiority),*

☐ *Lower limits of the 2-sided 95% CIs on the GMC ratios (HRV Liq group over HRV Lyo group) for each of the 13 Streptococcus pneumoniae (S. pneumoniae) serotypes were ≥0.5 (clinical limit for non-inferiority),*

☐ *The lower limit of the 2-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with concentration of antibodies against polyribosyl-ribitol-phosphate antigen (anti-PRP) ≥0.15 µg/mL was ≥-5%,*

☐ *The lower limit of the 2-sided standardized asymptotic 95% CI on the difference between groups (HRV Liq group minus HRV Lyo group) in the percentages of subjects with concentration of antibodies against anti-PRP ≥1.0 µg/mL was ≥-10% (clinical limit for non-inferiority).*

To rule out a 10% decrease in seroresponse to PT, FHA and PRN antigen when *Pediarix* was co-administered with PCV-free liquid HRV vaccine compared to when *Pediarix* was co-administered with the currently licensed lyophilized HRV vaccine.

- Seroresponse was defined as the percentage of subjects showing an antibody concentration above a threshold that leads to 95% seroresponse in the control group (lyophilized HRV vaccine),
- p-value on the difference in seroresponse between groups is <2.5% for each PT, FHA and PRN antigen (p-value was computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the liquid group is <85% and the a-posteriori probability of the threshold in the lyophilized group).

Secondary objectives

Immunogenicity:

☐ To assess the immunogenicity of the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine in terms of serum anti-rotavirus (anti-RV) immunoglobulin A (IgA) antibody seropositivity rate at Visit 4, 3 months after Dose 2 of the HRV vaccine.

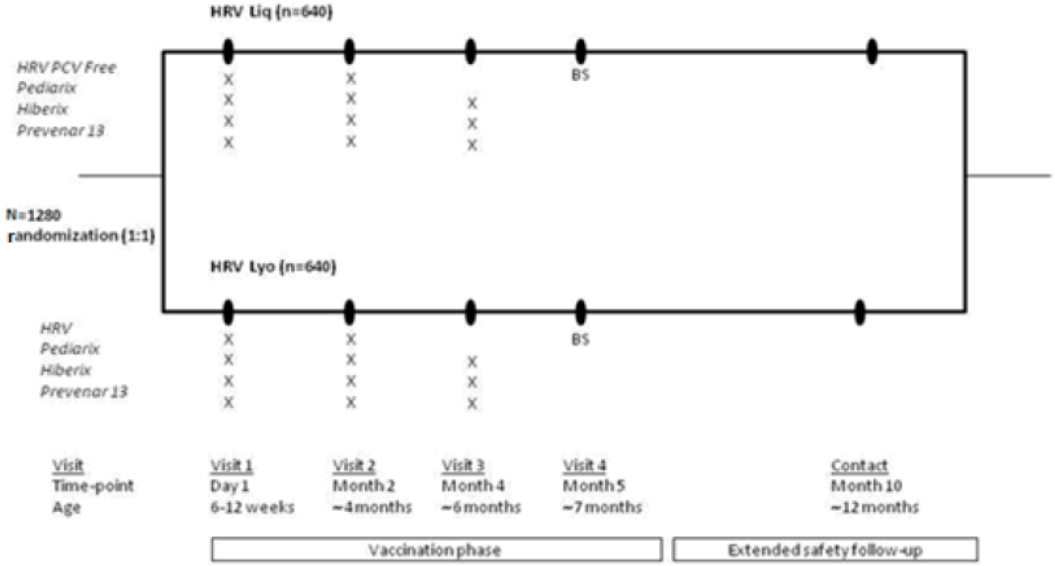
☐ To assess the immunogenicity of routine infant vaccines *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine at Visit 4, 1 month after Dose 3 of routine infant vaccines.

***Reactogenicity and Safety*:**

☐ To assess the reactogenicity of the PCV-free liquid HRV vaccine and currently licensed lyophilized HRV vaccine in terms of general solicited adverse events (AEs) during the 8-day (Day 1-Day 8) follow-up period after each dose of HRV vaccine.

☐ To assess the safety of the study vaccines in terms of unsolicited AEs during the 31- day (Day 1-Day 31) follow-up period after each dose of HRV vaccine and serious adverse events (SAEs) during the entire study period.

Study design



N = Number of subjects planned to be enrolled, n = Number of subjects planned in each study group, BS = blood sample, PCV-free = No detection of PCV-1 and PCV-2 according to the limit of detection of the tests used.
Contact (by telephone call) was carried out 6 months after Visit 3 for safety follow-up. An IDMC reviewed the unblinded safety data by treatment group periodically. Details of the review are described in an IDMC charter.

Study population /Sample size

	HRV Liq N=632	HRV Lyo N=640	Total N=1272
Number of subjects			
Planned, N	640	640	1280
Randomized, N	632	640	1272
Completed, n (%)	574 (90.8)	574 (89.7)	1148 (90.3)
Demographics			
N	632	640	1272
Females:Males	308:324	309:331	617:655
Mean Age, weeks (SD)	8.7 (1.1)	8.7 (1.1)	8.7 (1.1)
Median Age, weeks (minimum, maximum)	9.0 (6,12)	9.0 (6,12)	9.0 (6,12)
2 Most Frequent Races			
White (%)	468 (74.1)	471 (73.6)	939 (73.8)
Black or African American (%)	74 (11.7)	78 (12.2)	152 (11.9)

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation,
SD=Standard deviation,
N=total number of subjects
n/%=number of subjects in a given category
Source: Table 14.1.2 (09AUG2019 10:29 Greenwich Mean Time (GMT)) and Table 14.1.6.1 (09AUG2019 10:29 GMT)

Treatments

Test vaccine

Treatment name	Vaccine name	Formulation	Volume to be administered	Number of doses	Route	Lot numbers
HRV Liquid	HRV PCV-free	PCV-free HRV RIX4414* live attenuated $\geq 10^{6.0}$ $CCID_{50}$	1.5 mL	2	O	DROLA041A1

O= Oral, $CCID_{50}$: Median cell culture infective dose (quantity of virus causing infection in 50% of exposed cells)
* The typographical error in the strain number RIX4144 mentioned in the protocol has been corrected to RIX4414 in this report.

Other vaccines

Treatment name	Vaccine name	Formulation	Volume to be administered	Number of doses	Route	Lot numbers
HRV Lyophilized	HRV	HRV RIX4414* live attenuated $\geq 10^{6.0}$ $CCID_{50}$	1 mL	2	O	AROTVA342A
	HRV Diluent	$CaCO_3$=60 mg				AD05VB121B
Pediarix	DTPa-HBV-IPV	DT≥30 IU; TT≥40 IU; PT=25 µg; FHA=25 µg; PRN=8 µg; HBsAg=10 µg; Inactivated Poliovirus type 1 (Mahoney strain) =40 DU; Inactivated Poliovirus type 2 (MEF-1 strain) =8 DU; Inactivated Poliovirus type 3 (Saukett strain); Aluminium=700 µg Al3+	0.5 mL	3	IM (Right thigh)	AC21B636A
Hiberix	Hib	PRP=10 µg; TT≥25 µg	0.5 mL	3	IM (Right thigh)	AHIBVD203B
	NaCl	NaCl=150 mM				AD02B751AY, AD02B751AZ
Prevenar 13	*Prevenar 13*	PS1=2.2 µg CRM197; PS3=2.2 µg CRM197; PS4=2.2 µg CRM197; PS5=2.2 µg CRM197; PS6A=2.2 µg CRM197; PS6B=4.4 µg CRM197; PS7F=2.2 µg CRM197; PS9V=2.2 µg CRM197; PS14=2.2 µg CRM197; PS18C=2.2 µg CRM197; PS19A=2.2 µg CRM197; PS19F=2.2 µg CRM197; PS23F=2.2 µg CRM197; $AlPO_4$=125 µg Al3+	0.5 mL	3	IM (Left thigh)	DLOCA164A, DLOCA171A

HRV: Human rotavirus, DTPa: Diphtheria tetanus acellular pertussis, HBV: Hepatitis B virus, Hib- *Haemophilus* type b, IPV: Inactivated Poliovirus, DT: Diphtheria toxoid, TT: Tetanus toxoid, PT: Pertussis toxoid, FHA: Filamentous hemagglutinin, PRN: Pertactin; PRP: Polyribosyl-ribitol-phosphate, HBsAg-Hepatitis B surface antigen.
$CCID_{50}$: Median cell culture infective dose (quantity of virus causing infection in 50% of exposed cells), IM: Intramuscular, O: Oral, NaCl: Sodium Chloride, $CaCO_3$: Calcium carbonate, $AlPO_4$: Aluminium Phosphate, mL: milliliter; mg: milligrams,
* The typographical error in the strain number RIX4144 mentioned in the protocol has been corrected to RIX4414 in this report.

Outcomes/endpoints

Primary endpoints:

☐ Immunogenicity with respect to components of the routine infant vaccines, 1 month after Dose 3 of routine infant vaccines (Visit 4):

☐ Anti-D antibody concentration ≥0.1 IU/mL,

☐ Anti-T antibody concentration ≥0.1 IU/mL,

☐ Anti-HBs antibody concentrations ≥10 mIU/mL,

☐ Anti-poliovirus types 1, 2 and 3 antibody titers ≥8 ED50,

☐ Anti-PT, anti-FHA and anti-PRN antibody concentrations expressed as GMCs,

☐ Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations expressed as GMCs,

☐ Anti-PRP antibody concentrations ≥0.15 µg/mL,

☐ Anti-PRP antibody concentrations ≥1.0 µg/mL.

☐ Difference in seroresponse with respect to PT, FHA and PRN antigen components 1 month after Dose 3 of routine infant vaccines (Visit 4):

☐ #Seroresponse to PT, FHA and PRN.

Non-inferiority criteria

Antibody	Seroprotective concentration	Clinical limit of non-inferiority defined in ROTA-090 study (LL of 95% CI)
Anti-diphtheria (anti-D) (IU/mL)	≥0.1 IU/mL	≥-10%
Anti-tetanus (anti-T) (IU/mL)	≥0.1 IU/mL	≥-10%
Anti-hepatitis B surface (anti-HBs) (mIU/mL)	≥10 mIU/mL	≥-10%
Anti-poliovirus serotypes 1, 2 and 3		
Anti-poliovirus 1 (ED_{50})	≥8 ED_{50} (seroprotective titer)	≥-5%
Anti-poliovirus 2 (ED_{50})		
Anti-poliovirus 3 (ED_{50})		
Pertussis toxoid (PT), Filamentous hemagglutinin (FHA) and Pertactin (PRN) antigens		
Anti-Pertussis toxoid (PT) (IU/mL)		≥0.67 (GMC group ratio)
Anti-Filamentous hemagglutinin (FHA) (IU/mL)		
Anti-Pertactin (PRN) (IU/mL)		
Anti-*Streptococcus pneumoniae (S. pneumoniae)* (Anti-PnPS) (µg/mL) 13 serotypes		≥0.5 (GMC group ratio)
Anti-Polyribosyl-ribitol-phosphate antigen (anti-PRP) (µg/mL)	≥0.15 µg/mL	≥-5%
	≥1.0 µg/mL	≥-10%

Group differences in seroprotective concentrations were calculated for anti-D, anti-T, anti-HBs, anti-Polio (seroprotective titer) and anti-PRP antibodies
Group GMC ratios were calculated for PT, FHA and PRN antigens and 13 *S. pneumoniae* serotypes
GMC: Geometric Mean Concentration, mL: millilitre, IU: International Units, mIU: milli International Units,
ED50: Estimated dose 50%

Secondary endpoints:

☐ Serum anti-RV IgA antibody seropositivity 3 months after Dose 2 of HRV vaccine (Visit 4).

☐ *Serum anti-RV IgA antibody concentrations ≥20 U/mL and ≥90 U/mL.

☐ Immunogenicity with respect to components of the routine infant vaccines, 1 month after Dose 3 of routine infant vaccines (Visit 4).

☐ Anti-PT, anti-FHA and anti-PRN antibody concentrations ≥2.693 IU/mL, ≥2.046 IU/mL and ≥2.187 IU/mL, respectively.

☐ Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations ≥0.35 µg/mL for the Enzyme-Linked Immunosorbent Assay (ELISA).

☐ Anti-D, anti-T, anti-PRP and anti-HBs antibody concentrations expressed as GMCs and anti-poliovirus types 1, 2 and 3 antibody concentrations expressed as geometric mean titers (GMTs).

☐ Occurrence of general solicited AEs during the 8 days (Day 1-Day 8) follow-up period after each dose of HRV vaccine.

☐ Occurrence of unsolicited AEs within 31 days (Day 1-Day 31) after any dose of HRV vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

☐ Occurrence of SAEs from Dose 1 of study vaccines up to study end.

Note: The following clarifications have been made in the report compared to the protocol.

#Seroresponse to anti-PT, anti-FHA and anti-PRN, has been rephrased as Seroresponse to PT, FHA and PRN.

**Timepoint was erroneously presented as 1-2 months after Dose 2, the same has been corrected.*

Statistical Methods

The statistical analysis was performed as planned in the protocol (dated 27 October 2016) and the Statistical Analysis Plan (SAP) (dated 1 August 2017).

***Analysis sets*:** ES for analysis of safety and per-protocol set (PPS) for analysis of immunogenicity.

Analysis of immunogenicity:

Between group analysis:

For each treatment group, 1 month after Dose 3 of routine infant vaccines at Visit 4 (Month 5) time-point:

☐ Two-sided asymptotic standardized 95% CIs for the difference in the percentage of subjects with titer/concentration above or equal to pre-specified clinical thresholds were computed (PCV-free HRV Liq minus HRV Lyo).

☐ The 2-sided 95% CIs for the group GMC/GMT ratio (PCV-free HRV Liq over HRV Lyo) were computed using an Analysis of variance (ANOVA) model on the logarithm10 transformation of the concentrations.

☐ For the group comparison in PT, FHA, PRN seroresponse at 1 month post-dose 3, P value for testing H0: P≤85% vs. H1: P>85% (P= % of subjects in PCV-free HRV Liq with seroresponse (above a threshold that leads to 95% seroresponse in the HRV Lyo)) was computed. P-value was computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the HRV Lyo is <85% and the aposteriori probability of the threshold in the PCV-free HRV Liq.

***Analysis of safety*:** The ES was used for the analysis of safety. Descriptive summaries were generated via the percentage by group and associated exact 95% CI.

Results

Efficacy results

Co-primary confirmatory objectives

All the co-primary confirmatory objectives of the study were met.

☐ The immune response elicited by 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* was non-inferior when co administered with the 2 doses of the PCV-free liquid HRV vaccine versus when co-administered with the currently licensed lyophilized HRV vaccine, 1 month after Dose 3 of routine infant vaccines.

☐ A 10.0% decrease in seroresponse to PT, FHA and PRN antigens when *Pediarix* was co-administered with PCV-free liquid HRV vaccine compared to when *Pediarix* was co-administered with the currently licensed lyophilized HRV vaccine was ruled out as the p-values for anti-PT, anti-FHA, anti-PRN antibodies were less than the predefined criterion of 0.025.

Secondary objectives

☐ Three months after Dose 2 of the HRV vaccine, the percentage of subjects with anti- RV

antibody concentration ≥20 U/mL and ≥90 U/mL in both the vaccine groups was comparable.

☐ One month after Dose 3 of routine infant vaccines, the antibody concentrations against the routine infant vaccines in both the vaccine groups were comparable.

☐ The results of the analyses performed on the ES were consistent with results observed for PPS.

☐ In subgroup analyses performed by race and gender, comparable immune responses were observed between the PCV-free HRV Liq and HRV Lyo vaccine groups.

Table 2.5 **Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective concentrations (≥0.1 IU/mL) of anti-D and anti-T, 1 month after the third dose of the co-administered vaccines (Per-protocol set)**

							Difference in seroprotective concentration (HRV Liq - HRV Lyo)		
	HRV Liq			HRV Lyo				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
Anti-D (IU/mL)	478	478	100.0	486	486	100.0	-0.00	-0.80	0.79
Anti-T (IU/mL)	486	486	100.0	495	495	100.0	-0.00	-0.79	0.77

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
n/%=number/percentage of subjects with concentrations equal to or above the cut-off 1 month after the third dose of the co-administered vaccines
95% CI=asymptotic standardised 95% confidence interval; LL=lower limit; UL=upper limit
Success criterion: the lower limit of the 2-sided asymptotic standardized 95% CI for the group difference (HRV Liq - HRV Lyo) greater than or equal to -10%.
Source: Table 14.2.1.1 (09AUG2019 10:36 GMT)

Table 2.6 Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix, Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective concentrations (≥10 mIU/mL) of anti- HBs, 1 month after the third dose of the co-administered vaccines (Per-protocol set)

							Difference in seroprotective concentration (HRV Liq - HRV Lyo)		
	HRV Liq			HRV Lyo				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
Anti-HBs (mIU/mL)	460	457	99.3	471	471	100.0	-0.65	-1.90	0.16

HRV Liq=PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
n/%=number/percentage of subjects with concentrations equal to or above the cut-off 1 month after the third dose of the co-administered vaccines
95% CI=asymptotic standardised 95% confidence interval; LL=lower limit; UL=upper limit
Success criterion: the lower limit of the 2-sided asymptotic standardized 95% CI for the group difference (HRV Liq - HRV Lyo) greater than or equal to -10%.
Source: Table 14.2.1.2 (09AUG2019 10:36 GMT)

Table 2.7 Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix, Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group difference in percentage of subjects with seroprotective titers (≥8 ED_{50}) of anti-poliovirus, 1 month after the third dose of the co-administered vaccines (Per-protocol set)

							Difference in seroprotective concentration (HRV Liq - HRV Lyo)		
	HRV Liq			HRV Lyo				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
Anti-Poliovirus 1 (ED_{50})	477	477	100.0	487	486	99.8	0.21	-0.60	1.15
Anti-Poliovirus 2 (ED_{50})	464	463	99.8	479	478	99.8	-0.01	-1.02	0.98
Anti-Poliovirus 3 (ED_{50})	439	439	100.0	454	454	100.0	-0.00	-0.87	0.84

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
n/%=number/percentage of subjects with titers equal to or above the cut-off 1 month after the third dose of the co-administered vaccines
95% CI=asymptotic standardised 95% confidence interval; LL=lower limit; UL=upper limit
Success criterion: the lower limit of the 2-sided asymptotic standardized 95% CI for the group difference (HRV Liq - HRV Lyo) greater than or equal to -5%
Source: Table 14.2.1.3 (09AUG2019 10:36 GMT)

Table 2.8 Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group GMC ratio for anti-PT, anti-FHA and anti-PRN, 1 month after the third dose of the co-administered vaccines (Per-protocol set)

					GMC ratio (HRV Liq / HRV Lyo)		
	HRV Liq		HRV Lyo			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
Anti-PT (IU/mL)	486	51.0	495	54.2	0.94	0.86	1.03
Anti-FHA (IU/mL)	486	107.3	495	107.7	1.00	0.92	1.08
Anti-PRN (IU/mL)	486	55.0	495	56.6	0.97	0.86	1.10

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
GMC=geometric mean concentration estimated from the ANOVA model
95% CI=95% confidence interval for the adjusted GMC ratio (ANOVA model including the vaccine group as fixed effect).
LL=lower limit, UL=upper limit
Success criterion: the lower limit of the 2-sided 95% CI for the group GMC ratio (HRV Liq/HRV Lyo) ≥0.67.
Source: Table 14.2.1.4 (09AUG2019 10:36 GMT)

Table 2.9 Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of group GMC ratio for each of the 13 *S. pneumoniae* serotypes, 1 month after the third dose of the co-administered vaccines (Per-protocol set)

					GMC ratio (HRV Liq / HRV Lyo)		
	HRV Liq		HRV Lyo			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
Anti-PnPS 1 (µg/mL)	448	1.95	466	1.89	1.03	0.93	1.14
Anti-PnPS 3 (µg/mL)	448	0.53	466	0.53	1.00	0.91	1.11
Anti-PnPS 4 (µg/mL)	448	1.24	466	1.25	0.99	0.90	1.09
Anti-PnPS 5 (µg/mL)	441	1.28	459	1.22	1.05	0.94	1.17
Anti-PnPS 6A (µg/mL)	448	2.84	466	2.80	1.01	0.92	1.12
Anti-PnPS 6B (µg/mL)	448	1.93	465	2.00	0.96	0.83	1.12
Anti-PnPS 7F (µg/mL)	448	3.01	466	3.04	0.99	0.91	1.08
Anti-PnPS 9V (µg/mL)	447	1.68	466	1.63	1.03	0.93	1.14
Anti-PnPS 14 (µg/mL)	448	6.27	466	6.26	1.00	0.89	1.13
Anti-PnPS 18C (µg/mL)	448	1.81	466	1.76	1.03	0.92	1.14
Anti-PnPS 19A (µg/mL)	448	1.87	466	1.80	1.04	0.93	1.15
Anti-PnPS 19F (µg/mL)	448	2.94	466	2.85	1.03	0.95	1.12
Anti-PnPS 23F (µg/mL)	448	1.14	462	1.16	0.98	0.87	1.10

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
GMC=geometric mean concentration estimated from the ANOVA model
95% CI=95% confidence interval for the adjusted GMC ratio (ANOVA model including the vaccine group as fixed effect).
LL=lower limit, UL=upper limit
Success criterion: the lower limit of the 2-sided 95% CI for the group GMC ratio (HRV Liq/HRV Lyo) ≥ 0.5.
Source: Table 14.2.1.5 (09AUG2019 10:36 GMT)

Table 2.10 Confirmatory objectives: Non-inferiority of the immune responses to 3 doses of *Pediarix*, *Hiberix* and *Prevenar 13* when co-administered with 2 doses of the PCV-free liquid HRV vaccine, as compared to when co-administered with lyophilized HRV vaccine in terms of the group difference in seroprotective concentrations (≥0.15 µg/mL and 1.0 µg/mL) of anti-PRP, 1 month after the third dose of the co-administered vaccines (Per-protocol set)

								Difference in seroprotective concentration (HRV Liq - HRV Lyo)		
		HRV Liq			HRV Lyo				95% CI	
Antibody	Cut-off	N	n	%	N	n	%	%	LL	UL
Anti-PRP (µg/mL)	0.15	485	473	97.5	492	479	97.4	0.17	-1.94	2.28
Anti-PRP (µg/mL)	1	485	394	81.2	492	404	82.1	-0.88	-5.75	3.99

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
n/%=number/percentage of subjects with concentrations equal to or above the cut-off 1 month after the third dose of the co-administered vaccines
95% CI=asymptotic standardised 95% confidence interval; LL=lower limit; UL=upper limit
Success criterion 1: for the cut-off 0.15 the lower limit of the 2-sided asymptotic standardized 95% CI for the group difference (HRV Liq - HRV Lyo) ≥-5%.
Success criterion 2: for the cut-off 1 the lower limit of the 2-sided asymptotic standardized 95% CI for the group difference (HRV Liq - HRV Lyo) ≥-10%.
Source: Table 14.2.1.6 (09AUG2019 10:36 GMT).

Table 2.11 Confirmatory objectives: To rule out a 10% decrease in seroresponse to pertussis antigens, 1 month after the third dose of the co- administered vaccines (Per-protocol set)

		HRV Liq			HRV Lyo			
Antibody	Cut-off	N	n	%	N	n	%	P-value
Anti-PT (IU/mL)	18.566	486	440	90.5	495	470	94.9	<.0001
Anti-FHA (IU/mL)	35.711	486	466	95.9	495	470	94.9	<.0001
Anti-PRN (IU/mL)	11.034	486	455	93.6	495	470	94.9	<.0001

HRV Liq= PCV-free HRV vaccine liquid formulation; HRV Lyo=HRV vaccine lyophilized formulation
N=number of subjects with available results
n/%=number/percentage of subjects above the cut-off
Cut-off is the antibody level that leads to 95% response in the control group.
The p-value is computed by integrating on the p-values of one-sided tests (null hypothesis: HRV Liq < 85%) and the posterior probability of the cut-off in the control group. Success criterion: P-value below or equal to 0.025.
Source: Table 14.2.1.7 (09AUG2019 10:32 GMT)

Safety results

The safety profile of the PCV-free liquid HRV vaccine was comparable to the lyophilized HRV vaccine.

Overall incidence of AEs (solicited and unsolicited), 8 Days (Day 1- Day 8):

At least 1 solicited or unsolicited AE was reported in 88.4% and 89.8% of the subjects in the PCV-free HRV Liq and HRV Lyo groups, respectively. In both the vaccine groups, the incidence of the solicited or unsolicited AEs (grade 3, causally related, grade 3 causally related and AEs leading to medically attended visits) was comparable.

Solicited general adverse events, 8 days (Day 1-Day 8):

In both the vaccine groups, solicited general AEs were reported in similar percentages of subjects. Irritability/fussiness was the most frequently reported AE (82.8% and 81.6% of the subjects in the PCV-free HRV Liq and HRV Lyo groups, respectively). Cough/runny nose was the most frequently reported AE leading to medically attended visits (5.9% and 5.2% of the subjects in the PCV-free HRV Liq and HRV Lyo groups, respectively).

Unsolicited adverse events, 31 days (Day 1- Day 31):

At least 1 unsolicited AE was reported in 46.5% and 51.1% of the subjects in the PCV free HRV Liq and the HRV Lyo vaccine group, respectively. The most commonly reported grade 3 unsolicited AE was bronchiolitis in PCV-free HRV Liq group (0.8% of subjects) and upper respiratory tract infection in HRV Lyo group (0.6% of subjects). Upper respiratory tract infection was the most frequently reported unsolicited AE which was medically attended (9.0% and 9.5 % of the subjects in the PCV-free HRV Liq and HRV Lyo groups, respectively).

Deaths and Serious adverse events during the entire study period:

Deaths:

One fatal SAE (with diagnosis of Sudden Infant Death Syndrome) occurred on Day 68 of receiving the first dose of PCV-free HRV Liq vaccine. The SAE was assessed by the investigator as not causally related to the vaccination. No deaths were reported in the HRV Lyo group.

Serious Adverse Events:

A total of 39 subjects reported SAEs (20 and 19 subjects in the PCV-free HRV Liq and HRV Lyo groups, respectively). None of the SAEs in the PCV-free HRV Liq group was assessed as causally related to the vaccine. In the HRV Lyo group, after the second dose of vaccination, 2 SAEs (abdominal distension and intussusception) were reported in 2 subjects and were assessed by the investigator as causally related to the vaccine. Abdominal distension was reported on Day 48 and intussusception on Day 8. In both the cases, the events resolved within 2 days after the onset.

Withdrawals due to AE/SAE:

Five subjects were withdrawn from the study due to AE/SAE; 3 from the PCV-free HRV Liq group (1 SAE, 1 solicited AE and 1 unsolicited non-serious AE) and 2 from the HRV Lyo group (1 SAE and 1 unsolicited non-serious AE).

2.1.2. Discussion on clinical aspects

This phase IIIA, randomized, single-blind, multi-centric study demonstrated that the immunological response elicited to all the antigens in each of the routine infant vaccines *Pediarix, Hiberix* and *Prevenar 13* when co-administered with the PCV-free liquid HRV vaccine was non-inferior as compared to when co-administered with the currently licensed lyophilized HRV vaccine in healthy infants of 6-12 weeks of age. In addition, co-administration of routine infant vaccines with PCV-free liquid or currently licensed lyophilized HRV vaccine did not raise safety concerns. The reactogenicity and safety profile of the 2 groups was similar.

3. CHMP overall conclusion and recommendation

The Marketing Authorisation Holder submitted the final Study Report, including 6-month safety follow-up data, of study Rota-090 (etrack 201663, EudraCT 2016-003210-27) to comply with the requirements of Art 46 of the regulation (EC) No 1901/2006 (stand-alone PAM [P46 097]).

Immunogenicity and safety results of ROTA-090 are in line with the approved PI for Rotarix in the EU. No changes to the SmPC are needed.

☒ PAM Fulfilled:

No further regulatory action required.