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SCIENCE MEDICINES HEALTH

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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/P46/095

Note

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

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1. Introduction

On the 14th May 2019, the MAH submitted the final study report, including 6-month safety follow-up data, for the study Rota-081 (etrack 115461, EudraCT 2016-000598-19) to comply with the requirements of Art 46 of the regulation (EC) No 1901/2006.

Rota-081 is a phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of 3 production lots of the Porcine circovirus (PCV)-free liquid formulation of GlaxoSmithKline Biologicals'(GSK) oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK's HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a 2-dose vaccination in healthy infants starting at age 6-12 weeks. 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'.

A short critical expert overview is also provided.

2. Scientific discussion

2.1. Information on the development program

GSK has reviewed the immunogenicity and safety results of Study Rota-081 (etrack 115461, EudraCT 2016-000598-19) to comply with the requirements of Art 46 of the regulation (EC) No 1901/2006.

GSK plans to submit a Type II variation, composed of quality and clinical sections, to license the PCV-free manufacturing process of *Rotarix* and to meet the last part of the condition of the *Rotarix* Marketing Authorisation (EU Product Information Annex II, Part D, Obligation to conduct post-authorisation measures):

"In order to address the presence of porcine circovirus type 1(PCV-1) in Rotarix, the MAH commits to:

- *Provide, on a 6-month basis, updates on the progress being made on the activities set out in the implementation plan for the development of a PCV-free vaccine, as agreed by CHMP on 15 September 2016: every June and December until the PCVfree Rotarix application.Submit an application at the latest in 2020 to amend the particulars of the marketing authorisation in order to render the medicinal product PCV-free".*

The Rota-081 study results will be part of this variation to demonstrate the clinical comparability between the current and PCV-free *Rotarix* vaccines, on top of the technical comparability data.

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

2.3.2. Clinical study

Rota-081 (etrack 115461, EudraCT 2016-000598-19)

Description

A phase IIIA, randomised, observer-blind, multi-centre study to evaluate the clinical consistency of 3 production lots of the *Porcine circovirus* (PCV)-free liquid formulation of GlaxoSmithKline Biologicals'(GSK) oral live attenuated human rotavirus (HRV) vaccine and to evaluate the PCV-free liquid formulation of GSK's HRV vaccine as compared to the currently licensed lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety when administered as a 2-dose vaccination in healthy infants starting at age 6-12 weeks.

The study was conducted at 66 centres in 8 countries: 2 in Costa Rica, 10 in Finland, 6 in Germany, 7 in Japan, 6 in Republic of Korea, 9 in Spain, 6 in Taiwan and 20 in the US.

Methods

Objectives

Co-Primary objectives :

☐To demonstrate the lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-rotavirus (RV) immunoglobulin A (IgA) antibody concentrations 1-2 months after Dose 2.

Consistency was demonstrated if, for all pairs of lots, the 2-sided 95% confidence interval (CI) for the ratio of anti-RV IgA antibody geometric mean concentrations (GMCs), 1-2 months after Dose 2, was within the (0.5, 2) clinical limit interval.

☐To demonstrate the immunological non-inferiority of PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates 1-2 months after Dose 2.

Non-inferiority was demonstrated if the lower limit of the 2-sided asymptotic standardised 95% CI for the difference in seroconversion rate between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and licensed lyophilised HRV vaccine was greater than or equal to -10%.

☐To demonstrate the non-inferiority of the PCV-free liquid HRV vaccine to that of the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations 1-2 months after Dose 2.

Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI for the ratio of anti-RV IgA antibody GMCs, 1-2 months after Dose 2 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and the lyophilised HRV vaccine was greater than or equal to 0.67.

Secondary objectives:

Reactogenicity and safety

☐To evaluate the reactogenicity of the liquid HRV vaccine and currently licensed lyophilised HRV vaccine in terms of solicited adverse events (AEs) during the 8 days (Day 1-Day 8) follow-up period after each vaccination.

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

Immunogenicity

☐To assess the immunogenicity of the PCV-free liquid HRV vaccine and the currently licensed lyophilised HRV vaccine, in terms of percentage of subjects with anti-RV IgA antibody concentrations ≥90 U/mL, 1-2 months after Dose 2.

Methodology

Experimental design: Phase IIIA, observer-blind, randomised (1:1:1:1), controlled, multi-centre study, with 4 parallel groups and a staggered enrolment (Part A and Part B).

☐ Primary completion date (PCD): Visit 3 (Month 2-4).

☐ End of study (EoS): Last testing results released of samples collected at Visit 3 or last subject last visit (LSLV) (Follow up contact at Month 7-8).

☐ Study groups:

- ☐ PCV-free HRV liquid formulation lot A (also referred to as Liq_A group)
- ☐ PCV-free HRV liquid formulation lot B (also referred to as Liq_B group)
- ☐ PCV-free HRV liquid formulation lot C (also referred to as Liq_C group)
- ☐ GSK's currently licensed lyophilised HRV formulation (also referred to as Lyo_group)

☐ Control: Active control-lyophilised HRV vaccine

☐ Vaccination schedule: Two oral doses of the HRV vaccines were administered according to 1-month or 2-months interval, as per the RV vaccination schedule in participating countries.

☐ Concomitant administration of routine childhood vaccines was allowed according to the local immunisation practices in each participating country.

☐ Treatment allocation: Randomised 1:1:1:1 using GSK's central randomisation system on internet (SBIR).

☐ Blinding: Observer-blind

☐ Sampling schedule: Blood samples were collected from all subjects at Visit 1 and Visit 3 to measure serum anti-RV IgA antibody concentrations using enzyme linked immunosorbent assay (ELISA).

☐ Recording of gastroenteritis (GE) episodes: GE episodes occurring from Dose 1 of HRV vaccine up to Visit 3 were recorded for all subjects in the diary card.

☐ Parents/legally acceptable representatives (LARs) were instructed to collect stool sample(s) if the subject developed GE during this period. A stool sample had to be collected as soon as possible after illness began and preferably not later than 7 days after the start of GE symptoms. Two occurrences of diarrhoea were classified as separate episodes if there were 5 or more diarrhoea-free days between the episodes.

☐ Type of study: self-contained

☐ Data collection: Electronic case report form

☐ Safety monitoring: An Independent Data Monitoring Committee (IDMC) comprising clinical experts and a biostatistician, reviewed the cumulative, unblinded safety data on a regular basis during the study. Since no safety concerns were raised, the study continued as planned.

Number of subjects (planned and analysed):

The target enrolment was 1600 subjects (400 subjects in each group) to obtain at least 1280 evaluable subjects (320 subjects in each group) for the evaluation of the co-primary objectives, assuming that approximately 20% of the enrolled subjects were not evaluable. The actual number of subjects who received at least 1 dose of HRV vaccine was 1600 (400 subjects in Liq_A, 396 subjects in Liq_B, 402 subjects in Liq_C and 402 subjects in Lyo groups), comprising the Exposed set (ES).

Diagnosis and main criteria for inclusion:

The study was conducted in healthy male or female infants as established by medical history and clinical examination, who were 6-12 weeks of age at the time of first vaccination, born full-term (i.e. between a gestation period of 37 weeks 0 days and 41 weeks 6 days). Written informed consent was obtained from the parent(s)/LAR(s) of the subjects at the time of study entry.

Exclusion criteria essentially consisted of administration of vaccines not foreseen by the study protocol, previous vaccination against RV, administration of immunoglobulins, immune-modifying drugs or immunosuppressant medications, a potential reaction or hypersensitivity to the HRV vaccine components and significant history of chronic gastrointestinal disease or uncorrected gastrointestinal malformation or intussusception (IS). Subjects with previous confirmed occurrence of RV GE or with GE within 7 days preceding the study vaccine administration were excluded.

Duration of study:

The duration of the study, per subject, was approximately 7-8 months including the 6 months of extended safety follow-up period after the last dose of HRV vaccine.

Criteria for evaluation:

Primary endpoints

☐ Evaluation of immunogenicity in terms of anti-RV antibody concentrations.

☐ Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in each of the HRV liquid formulation groups (Liq_A, Liq_B and Liq_C).

☐ Anti-RV IgA antibody seroconversion rate* 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

☐ Serum anti-RV IgA antibody concentrations expressed as GMCs 1-2 months after Dose 2 in the lyophilised and pooled liquid groups.

*Seroconversion rate is defined as the percentage of subjects who were initially seronegative (i.e. with anti-RV IgA antibody concentration <20 U/mL prior the first dose of HRV vaccine) and developed anti-RV IgA antibody concentration ≥20 U/mL at Visit 3.

Secondary endpoints

☐ Solicited AEs

☐ Occurrence of each solicited general AE within the 8 days (Day 1-Day 8) follow-up period after each dose of the lyophilised and PCV-free HRV liquid vaccine

☐ Unsolicited AEs.

☐ 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.

☐ SAEs

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

☐ Evaluation of immunogenicity in terms of anti-RV antibody concentrations.

☐ Serum anti-RV IgA antibody concentrations ≥90 U/mL 1-2 months after Dose 2in the lyophilised and pooled liquid groups.

Statistical methods:

Analyses were performed as planned in the protocol amendment 1 (dated 9 March 2017) and the Statistical Analysis Plan (SAP) Amendment 1 (dated 5 February 2018).

Analysis sets

☐ ES

☐ Per-protocol analysis set (PPS) of immunogenicity

Analysis of immunogenicity

The primary analysis was based on the PPS for analysis of immunogenicity. As the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity was 5% or more, a second analysis based on the ES was performed to complement the PPS analysis.

Between groups assessment

To control risk of concluding erroneously due to the multiple co-primary objectives, a hierarchical procedure was used with a 2.5% type I error.

☐ The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between any pair of the 3 lots of the HRV liquid vaccine was computed (first co-primary objective).

☐ The asymptotic standardised 95% CI for the difference in seroconversion rate at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine was computed (second co-primary objective conclusive only if the first co-primary objective was reached).

☐ The 95% CI for the ratio of anti-RV IgA antibody GMCs at Visit 3 between the PCV-free liquid HRV vaccine (pooled HRV liquid groups) and lyophilised HRV vaccine was computed (third co-primary objective conclusive only if the second co-primary objective was reached).

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. Further details on the statistical methods and derivations are available in the SAP.

Demographics

Synopsis Table 3 Study population (Exposed set)

	Liq_A N=400	Liq_B N=396	Liq_C N=402	Lyo N=402	Total N=1600
Number of subjects					
Planned, N	400	400	400	400	1600
Randomised, N	400	396	402	402	1600
Completed, n (%)	386 (96.5)	383 (96.7)	385 (95.8)	391 (97.3)	1545 (96.6)
Demographics					
N	400	396	402	402	1600
Females: Males	208:192	198:198	205:197	203:199	814:786
Mean age, weeks (SD)	8.5 (1.5)	8.4 (1.5)	8.4 (1.6)	8.5 (1.5)	8.4 (1.5)
Median age, weeks (minimum, maximum)	9.0 (6,12)	8.0 (6,12)	9.0 (6,12)	8.5 (6,13)	9.0 (6,13)
2 Most Frequent Races					
White (percentage)	263 (65.8)	258 (65.2)	262 (65.2)	262 (65.2)	1045 (65.3)
Asian (percentage)	95 (23.8)	96 (24.2)	98 (24.4)	95 (23.6)	384 (24.0)

Liq_A=HRV vaccine liquid formulation Lot A
Liq_B=HRV vaccine liquid formulation Lot B
Liq_C=HRV vaccine liquid formulation Lot C
Liq_Pool=Pooled HRV vaccine liquid formulation
Lyo=HRV vaccine lyophilised formulation
SD=Standard deviation

Results

Immunogenicity results:

Primary objectives

All primary confirmatory objectives were met.

☐ Lot-to-lot consistency was demonstrated between the 3 PCV-free liquid HRV vaccine lots.

☐ In terms of anti-RV IgA antibody seroconversion rates and GMCs, the PCV-free liquid HRV vaccine was shown to be non-inferior to the currently licensed lyophilised HRV vaccine based on the pre-defined criteria for non-inferiority.

Secondary objectives

☐ There was no evidence of difference between PCV-free liquid HRV vaccine and lyophilised HRV vaccine groups with respect to percentage of subjects with anti-RV IgA antibody concentrations equal to or above 90 U/mL, 1-2 months after Dose 2.

For the anti-RV IgA antibody seroconversion rates and GMCs assessed by gender, race and country, comparable immune responses were observed between the PCV-free liquid HRV vaccine and lyophilised HRV vaccine groups

Synopsis Table 4 Lot-to-lot consistency of the PCV-free liquid HRV vaccine in terms of immunogenicity as measured by serum anti-RV IgA antibody concentrations, 1-2 months after the second dose of HRV vaccine (Per-protocol set)

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Liq_A	332	156.1	Liq_B	326	145.9	Liq_A/Liq_B	1.07	0.79	1.44
Liq_A	332	156.1	Liq_C	326	177.1	Liq_A/Liq_C	0.88	0.65	1.19
Liq_B	326	145.9	Liq_C	326	177.1	Liq_B/Liq_C	0.82	0.61	1.11

Source: Table 14.2.1.1
Liq_A=HRV vaccine liquid formulation Lot A
Liq_B=HRV vaccine liquid formulation Lot B
Liq_C=HRV vaccine liquid formulation Lot C
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 (Liq_A, Liq_B and Liq_C) and the country as fixed effects).
LL=lower limit
UL=upper limit
Success criterion: for all pairs of lots, the 2-sided 95% confidence intervals for the lot-to-lot GMC ratio are within [0.5, 2] interval.

Synopsis Table 5 Non-inferiority of the PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of seroconversion rates, 1-2 months after the second dose of HRV vaccine (Per-protocol set)

								Difference in seroconversion rate			
										95% CI	
Group	N	n	%	Group	N	n	%	Difference	%	LL	UL
Liq_Pool	984	780	79.27	Lyo	329	269	81.76	Liq_Pool-Lyo	-2.49	-7.15	2.63

Source: Table 14.2.1.2
Liq_Pool=pooled HRV vaccine liquid formulation
Lyo=HRV vaccine lyophilised formulation
N=number of subjects who were seronegative at baseline
n=number of subjects who seroconverted at Visit 3
%=percentage of subjects who seroconverted at Visit 3
95% CI=asymptotic standardised 95% confidence interval
LL=lower limit
UL=upper limit
Success criterion: the lower limit of the 2-sided asymptotic standardised 95% CI for the group difference (Liq_Pool-Lyo) is greater than or equal to -10%

Synopsis Table 6 Non-inferiority of the PCV-free liquid HRV vaccine as compared to the currently licensed lyophilised HRV vaccine in terms of serum anti-RV IgA antibody concentrations, 1-2 months after the second dose of HRV vaccine (Per-protocol set)

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Liq_Pool	984	159.5	Lyo	329	152.8	Liq_Pool/Lyo	1.04	0.82	1.33

Source: Table 14.2.1.3
Liq_Pool=pooled HRV vaccine liquid formulation
Lyo=HRV vaccine lyophilised 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 (Liq_Pool and Lyo) and the country as fixed effects).
LL=lower limit
UL=upper limit
Success criterion: the lower limit of the 2-sided 95% CI for the group GMC ratio (Liq_Pool/Lyo) is greater than or equal to 0.67

Safety results

Overall (solicited and unsolicited) incidence of AEs

☐ The percentage of subjects reporting at least 1 solicited or unsolicited AE was 78.5% in the PCV-free liquid HRV pooled group and 78.9% in the lyophilised HRV vaccine group.

☐ The percentage of subjects reporting grade 3 solicited or unsolicited AE was 12.6% in the PCV-free liquid HRV pooled group and 11.2% in the lyophilised HRV vaccine group.

☐ The percentage of subjects reporting any solicited or unsolicited AEs considered causally related to vaccination was 47.2% in the PCV-free liquid HRV pooled group and 48.5% in the lyophilised HRV vaccine group.

☐ The percentage of subjects reporting any grade 3 solicited or unsolicited AEs considered causally related to vaccination was 7.0% in the PCV-free liquid HRV pooled group and 7.7% in the lyophilised HRV vaccine group.

☐ The percentage of subjects reporting solicited or unsolicited AEs leading to medical attention was 15.1% in the PCV-free liquid HRV pooled group and 17.7% in the lyophilised HRV vaccine group.

☐ The 3 individual PCV-free liquid HRV vaccine groups showed comparable safety profile across groups which was also similar to the lyophilised HRV vaccine group.

Solicited general adverse events

☐ Overall/subject, irritability/fussiness was the most frequently reported solicited general AE in the PCV-free liquid HRV pooled group (66.9%) and in the lyophilised HRV vaccine group (64.9%).

☐ Overall/subject, irritability/fussiness was also the most frequently reported grade 3 solicited general AE, AE considered causally related to vaccination, and grade 3 AE considered causally related to vaccination. The percentage of subjects reporting irritability/fussiness was similar in the PCV-free liquid HRV pooled group and the lyophilised HRV vaccine group.

☐ Overall/subject, cough/runny nose was the most frequently medically attended solicited general AE with similar percentage of subjects in the PCV-free liquid HRV pooled group and the lyophilised HRV vaccine group.

☐ Overall/subject the 3 individual PCV-free liquid HRV vaccine groups showed comparable safety profile across groups which was also similar to the lyophilised HRV vaccine group.

☐ For the safety analysis for solicited general AEs performed by gender, race and country, overall, no significant group differences were observed in the PCV-free liquid HRV pooled group compared to the lyophilised HRV vaccine group.

Unsolicited adverse events

☐ Upper respiratory tract infection (reported in 8.0% of subjects in the PCV-free liquid HRV pooled group and 7.5% of subjects in the lyophilised HRV vaccine group) and nasopharyngitis (reported in 7.1% of subjects in the PCV-free liquid HRV pooled group and 7.2% of subjects in the lyophilised HRV vaccine group) were the most frequently reported unsolicited AEs.

☐ Grade 3 unsolicited AEs were reported in 3.3% of subjects in the PCV-free liquid HRV pooled group and 2.0% of subjects in the lyophilised HRV vaccine group.

☐ Unsolicited AEs considered causally related to vaccination were reported in 6.7% of subjects each in the PCV-free liquid HRV pooled and the lyophilised HRV vaccine groups.

☐ Grade 3 unsolicited AEs considered causally related to vaccination were reported in 4 subjects in the PCV-free liquid HRV pooled group (abdominal pain, constipation, flatulence and diaper dermatitis) and 2 subjects in the lyophilised HRV vaccine group (vomiting and diaper dermatitis).

☐ Unsolicited AEs requiring medical attention were reported in 35% of subjects in the PCV-free liquid HRV pooled group and 33.1% of subjects in the lyophilised HRV vaccine group.

☐ For the safety analysis for unsolicited AEs performed by country, overall, no significant group differences were observed in the PCV-free liquid HRV pooled group compared to the lyophilised HRV vaccine group.

Serious adverse events

☐ There was no death reported in this study.

☐ All SAEs reported during the study (reported in 5.0% of subjects in the PCV-free liquid HRV pooled group and 4.5% of subjects in the lyophilised HRV vaccine group) were not considered causally related to vaccination by the investigator.

☐ Of the reported SAEs, 2 SAEs resolved with sequelae (myelitis and subdural hygroma reported for 1 subject in Liq_A group) and 3 SAEs were not resolved at the end of the study (milk allergy reported for a subject in Liq_A group and metastases to liver and neuroblastoma reported for a subject in Liq_B group).

☐ One subject in Liq_C group reported IS 132 days after receiving the second dose of vaccination. The event resolved and was not considered as causally related to vaccination by the investigator.[1]

☐ There were no dropouts due to AEs or SAEs.

2.3.3. Discussion on clinical aspects

This phase IIIA, randomised, controlled, observer-blind, multi-country study demonstrated the lot-to-lot consistency of 3 production lots of the PCV-free liquid formulation of GSK's oral live attenuated HRV vaccine and its non-inferiority compared to current licensed lyophilised formulation in terms of immunogenicity.

In addition, the study showed that the administration of PCV-free liquid and current licensed lyophilised formulation did not raise any safety concerns and that PCV-free liquid and current licensed lyophilised formulation have a similar reactogenicity and safety profile.

The Assessor has reviewed the immunogenicity and safety results of Study Rota-081 based on the dossier submitted and has concluded that the data do not influence the benefit-risk balance and are in line with the approved Product Information for *Rotarix* in the EU. Therefore, no changes to the current SmPC i.e. Annex I of the EU Product Information, for *Rotarix* are considered necessary.
<Rapporteur's><CHMP> overall conclusion and recommendation

[1] **Serious Adverse Event: Intussusception**
Subject received 2 doses of the PCV-free liquid HRV vaccine. At 8 months of age, 132 days after receiving the second dose of vaccination, the subject experienced frequent vomiting, and was hospitalised the following day. The subject was diagnosed with moderate IS (Grade 2 SAE). The subject was treated with high-pressure enema, followed by intravenous administration of a combination of glucose, potassium chloride, sodium chloride, sodium lactate, and a combination of calcium chloride, glucose, potassium chloride, sodium acetate, and sodium chloride. The subject was discharged from the hospital 134 days after receiving the second dose of vaccination. In the opinion of the investigator, IS was considered not related to the study vaccine. The SAE was considered resolved, with an outcome of recovery on Day 134, after the second dose of vaccination.

☒ Fulfilled:

No regulatory action required.