16 March 2015
EMA/178957/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P46 069

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION[1]

The data from this study do not warrant any changes in the SmPC and PL.

III. INTRODUCTION

On 02/09/2011, the MAH submitted a completed paediatric study for Rotarix to comply with the requirements of Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The study has not been conducted in accordance with an agreed paediatric investigation plan. The Food and Drug Administration of Taiwan had requested GSK to conduct this study as a post-approval commitment to collect local clinical data on the immunogenicity and safety of Rotarix when administered to healthy Taiwanese infants who had received hepatitis B immunoglobulin (HBIG) within 24h after birth.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Rotarix and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

Vaccine name	Vaccine	Formulation	Presentation	Volume	Number of doses
HRV vaccine	GSK Biologicals' HRV lyophilised vaccine	**Active substance** RIX4414 HRV strain at least $10^{6.0}$ CCID50 **Excipients** Dulbecco's Modified Eagle Medium (DMEM) 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg **In liquid diluent** Calcium carbonate 60mg Xanthan 2.5 mg Water for Injection q.s. ad 1ml	Lyophilised vaccine in a monodose glass vial Diluent (calcium carbonate buffer) supplied separately.	1ml	1

$CCID_{50}$: median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
DMEM: Dulbecco's Modified Eagle Medium
The HRV vaccine was purchased by the subject's parents/LARs

[1] *The recommendation from section V can be copied in this section*

Clinical aspects

1. Introduction

The MAH submitted the final report for study 114351 (Rota-077 PMS), a phase IV, open, multi-centre study to assess the immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy Taiwanese infants who received hepatitis B immunoglobulin after birth.

Assessors' comment

This study was planned to be conducted at multiple centres in Taiwan. However, all the subjects were enrolled at one centre.

2. Clinical study

- **Methods**

- Objective(s)

Primary:

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody seroconversion rate, 2 months post-Dose 2 (i.e. at Visit 3) of the HRV vaccine.

Secondary:

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 2 months post-Dose 2 (i.e. at Visit 3) of the HRV vaccine.
- To assess the reactogenicity of GSK Biologicals' HRV vaccine in terms of occurrence of solicited adverse events (AEs) within the 8-day (Day 0 to Day 7) follow-up period after each dose of the HRV vaccine.
- To assess the safety of GSK Biologicals' HRV vaccine in terms of unsolicited AEs within 31 days after any dose of the HRV vaccine and SAEs, from Dose 1 of the HRV vaccine up to Visit 3 (Month 4).
- To assess the presence of RV in gastroenteritis (GE) stools collected from Dose 1 of HRV vaccine up to Visit 3 (Month 4)

- Study design

Phase IV, open-label, single centre, single group. All subjects received two doses of HRV vaccine at Visit 1 (Day 0) and Visit 2 (Month 2) (at 2, 4 months of age). Blood samples were collected at Visit 1 and at Visit 3 (Month 4). Stool samples were collected in case of GE occurring from Dose 1 of the HRV vaccine up to study end (Visit 3). Cf. Figure below.

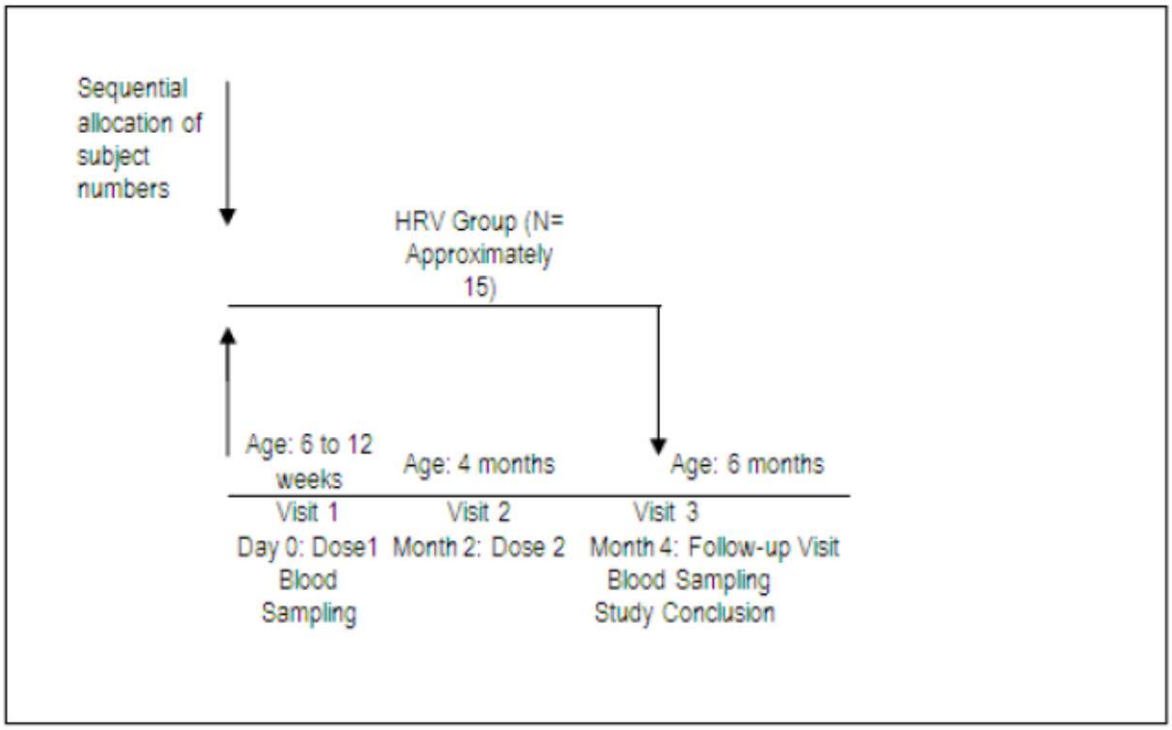
- Study population /Sample size

Healthy infants between, and including, 6 and 12 weeks of age at the time of first vaccination. Subjects who had received a previous dose of hepatitis B immunoglobulin (HBIG) after birth were included in the study. 15 subjects were planned and enrolled in the study.

- Treatments

Two doses of HRV vaccine to be administered at 2, 4 months of age. All subjects will receive routine childhood vaccinations according to the local immunisation practice.

Study design



N = number of subjects

- Outcomes/endpoints

Immunogenicity: Serum anti-rotavirus IgA antibody concentrations in samples collected at Visit 1 and at Visit 3 using an in-house Enzyme Linked ImmunoSorbent Assay (ELISA).

Safety and reactogenicity: Recording of solicited symptoms (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine. Recording of unsolicited symptoms occurring during the 31-day follow-up period (Day 0 – Day 30) after any dose of HRV vaccine. Recording of serious adverse events (SAEs) occurring during the entire study period (from Dose 1 of HRV vaccine up to Visit 3).

Evaluation of RV in GE stool samples: Recording of any GE (diarrhoea with or without vomiting) occurring from Dose 1 of HRV vaccine up to Visit 3.

- Statistical methods, sample size

The sample size was pre-defined as per the regulatory request. Using a sample size of 15 subjects a 90.0% seroconversion rate (exact 95% CI 63.7%; 99.3%) was expected.

Analysis of demography: The mean, range and standard deviation (SD) of height (in cm) and weight (in kg) at Visit 1 was calculated. The mean, range and SD of age in weeks at each dose of HRV vaccine were also calculated. The racial and gender composition were tabulated.

Analysis of Immunogenicity: The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

Analysis of Reactogenicity and Safety: The safety analysis was performed on the total vaccinated cohort. The percentage of doses and of subjects with any symptom (solicited or unsolicited) reported

during the 8-day (Day 0 to Day 7) follow-up period and with each solicited symptom including those rated grade 3 in intensity, those assessed as related to vaccination and symptoms rated grade 3 in intensity and related to vaccination reported during the 8-day (Day 0 to Day 7) solicited follow-up period was tabulated by group with their exact 95% CIs. The verbatim reports of unsolicited symptoms were to be reviewed by a physician and the signs and symptoms were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Every verbatim term was matched with the appropriate Preferred Term (PT). The percentage of subjects with unsolicited symptoms occurring within 31 days (Day 0 to Day 30) after any dose, with its exact 95% CI was tabulated, and by PT. Similar tabulation was done for unsolicited symptoms with causal relationship to vaccination and for unsolicited AEs rated as grade "3". SAEs reported during the study period (i.e. from Dose 1 up to Visit 3) were summarised.

Analysis of Stool Samples: The analysis was performed on the total vaccinated cohort. The percentage of subjects reporting GE and RV GE episodes from Dose 1 of HRV vaccine up to Visit 3 was tabulated.

- **Results**

- Recruitment/ Number analysed

Analyses were performed as per protocol. None of the subjects were excluded from the ATP analyses. Hence, the total vaccinated cohort and the ATP cohort for immunogenicity consisted of all 15 enrolled subjects.

- Immunogenicity results (Table 11)

Table 11 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

			≥ 20 U/ml				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV	Pre	15	0	0.0	0.0	21.8	<20	-	-
	PII(M4)	15	15	100	78.2	100	254.7	145.0	447.7

HRV = Human Rotavirus Vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Pre = pre-vaccination
PII (M4) = blood sample taken two month after the second dose at Visit 3

- Safety results

  - The percentage of subjects reporting any AEs (solicited or unsolicited) during the 8-day (Day 0 – Day 7) follow-up period was 86.7%. There was no increase in the incidence of AEs (solicited or unsolicited) from Dose 1 to Dose 2 of the HRV vaccine.
  - The percentage of subjects reporting any AEs (solicited or unsolicited) rated as Grade 3 in intensity during the 8-day (Day 0 – Day 7) follow-up period was 20.0% and those assessed as causally related to vaccination was 60.0%. The vaccine related AEs reported in this study were solicited AEs as there were no reports of Grade 3 and vaccine related unsolicited AEs.
  - Irritability was the most frequently reported solicited AE after each dose; reported for 53.3% of subjects after Dose 1 and for 60.0% of subjects after Dose 2.
  - Irritability rated grade "3" in intensity was reported for 6.7% of subjects after each dose of HRV vaccine.
  - Grade "3" solicited AEs were reported in less than 6.7% of the subjects after each dose.
  - The percentage of subjects reporting at least one unsolicited AE classified by MedDRA SOC and PT during the 31-day (Day 0 – Day 30) follow-up period was 26.7%.
  - There were no reports of unsolicited AEs rated grade '3' in intensity and those assessed by the investigator to be causally related to vaccination during the study.

- One subject had a report of a SAE of “Bronchiolitis” classified by MedDRA SOC and PT during the study period. The subject experienced the SAE 17 days after receiving Dose 2 of HRV vaccine. The SAE lasted for 25 days and was assessed by the investigator as not causally related to vaccination. There were no AEs leading to premature discontinuation of the study vaccine and/or study.

- Concomitant medications

  - The percentage of subjects who started taking at least one concomitant medication from Day 0 to Day 7 was 20.0%. Antipyretic medications were received by 13.3% of subjects. None of the subjects received prophylactic antipyretic or any antibiotic from Day 0 to Day 7 after vaccination.
  - The percentage of subjects who started taking at least one concomitant medication during the study period was 40.0%. Antipyretic medications were received by 33.3% of subjects.
  - None of the subjects received prophylactic antipyretic or any antibiotic during the study.

- Rotavirus in stool samples

  - The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine up to Visit 3 was 13.3% (n=2).
  - There were two GE episodes reported between Dose 1 and before Dose 2 of HRV vaccine. Of the GE episodes reported, GE stool result was not available for 1 subject (50.0%) because GE stool sample was not collected from the subject.
  - There were no reports of RV GE episodes from Dose 1 of HRV vaccine up to Visit 3.

3. Discussion on clinical aspects

This study was conducted following the request from the FDA of Taiwan to conduct a post-licensure study to assess the potential impact of the HBIG dose received by subjects after birth on the HRV vaccine by evaluating the immunogenicity and safety of the HRV vaccine. Two doses of the HRV vaccine were immunogenic with the anti-rotavirus IgA antibody seroconversion of 100%. These results indicate that administering HBIG after birth does not seem to negatively impact the immune response to the HRV antigen. In addition, the seroconversion rate observed in this study was comparable to the results observed in a previous study conducted in the same geographic location.

V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

- Two doses of the HRV vaccine were immunogenic in healthy infants who received HBIG after birth as shown by the anti-rotavirus IgA antibody seroconversion rate of 100.0% [95% CI: 78.2%; 100.0%] two months post-Dose 2.
- Irritability was the most frequently reported solicited AE after each dose. None of the unsolicited symptoms reported were rated grade 3 in intensity and causally related to vaccination.
- There was one SAE (Bronchiolitis) reported during the study period that was not assessed to be related to vaccination.
- There were no fatal events reported in the study.
- RV was not identified in the one GE stool sample collected in the study.

➢ **Recommendation**

Fulfilled:

No further action required

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

None