12 March 2015
EMA/170755/2015
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 064

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

EXECUTIVE SUMMARY

This post-licensure study has been requested by the Korean Food and Drugs Administration (KFDA) to GSK, to provide additional local clinical data on immunogenicity, reactogenicity and safety of the HRV vaccine. The design is a placebo-controlled clinical trial in healthy infants in Korea to evaluate the immunogenicity, reactogenicity and safety of HRV. Two oral doses of HRV vaccine or placebo were administered starting at 6-12 weeks of age according to 0, 1-2 months schedule.

Study results show high immunogenicity results, which are in line with the seroconversion rates observed in studies conducted in the same region with similar setting. The safety profile was similar between the HRV vaccine and the placebo group, and the frequency of Grade 3 solicited and unsolicited AEs were low and in line with other studies.

This paediatric study does not influence the benefit risk for Rotarix.

No SmPC and PL changes are proposed.

1. RECOMMENDATION

No further action is required.

2. INTRODUCTION

On 15 April 2011, the MAH submitted a completed paediatric study for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

The MAH proposed no regulatory action.

3. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study(ies)
GSK Biologicals' lyophilised HRV vaccine contained not less than $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 Live Attenuated HRV strain lyophilised with active substance: 9 milligrams (mg) of sucrose, 18 mg of Dextran, 13.5 mg of sorbitol, 9 mg of amino acids, 2.25 mg of Dulbecco's Modified Eagle Medium (DMEM) reconstituted with liquid diluent containing 60 mg of calcium carbonate, 2.5 mg of xanthan and 1 mL of water for injection. Lot number of the HRV vaccine: DROTA024A, Lot numbers of the diluent: AD05A471C and AD05A598B.

Clinical aspects

1. Introduction

The MAH submitted a final report(s) for:

- Clinical Study Report for Study 112269 (Rota-068): Immunogenicity, reactogenicity and safety study to evaluate two doses of the lyophilised formulation of the human rotavirus (HRV) vaccine when administered to healthy Korean infants previously uninfected with HRV.

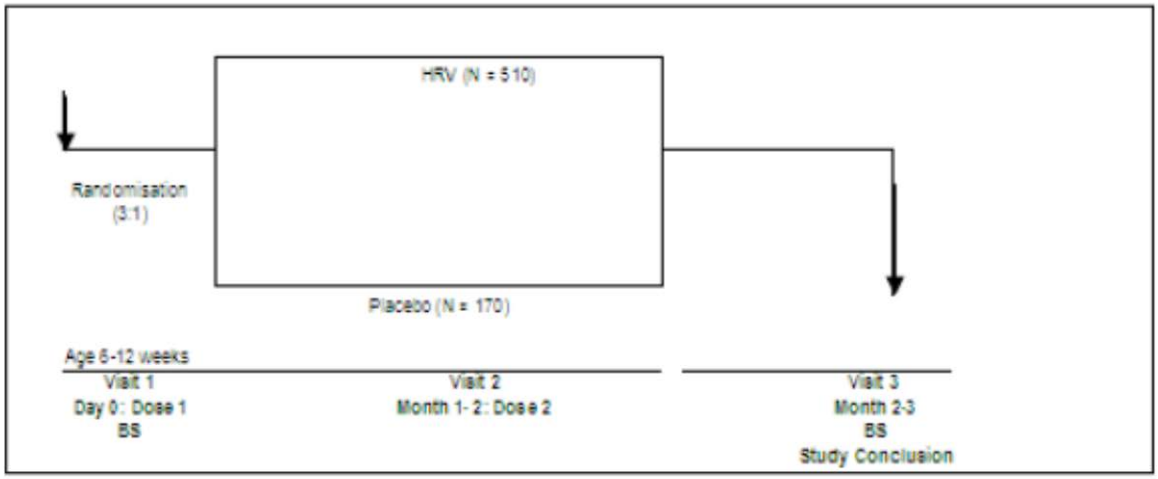
This post-licensure study has been requested by the Korean Food and Drugs Administration (KFDA) to provide additional local clinical data on immunogenicity, reactogenicity and safety of the HRV vaccine, as the data in the pre-licensure study Rota-041 was considered insufficient due to the small number of subjects in the ATP cohort (N=72).

2. Clinical study

- **Description**

This Phase IV, double-blind randomised study involved two parallel treatment groups (HRV vaccine group and Placebo group) to evaluate the immunogenicity, reactogenicity and safety of

GlaxoSmithKline (GSK) Biologicals' oral live attenuated HRV vaccine in healthy infants previously uninfected with HRV (see figure).
The study was conducted in 19 centres in Korea, from 25 August 2009 to 23 July 2010.



N = number of subjects planned to be enrolled
BS: Blood Sample
HRV: Human Rotavirus Vaccine

➢ Methods

- *Objective(s)*

Primary:

- To demonstrate at least 40% increase in seroconversion rate, in the HRV vaccine group at Visit 3 (i.e. one month post-Dose 2) as compared to Placebo group.

Secondary:

- To assess the immunogenicity of the HRV vaccine in terms of serum anti Rotavirus (RV) Immunoglobulin A (IgA) antibody concentrations at Visit 3 (i.e. one month post-Dose 2).
- To assess the reactogenicity of HRV vaccine in terms of occurrence of solicited adverse events (AEs) within the 8-day follow-up period after each vaccine dose.
- To assess the safety of HRV vaccine in terms of occurrence of unsolicited AEs within a 31-day follow-up period after any vaccine dose.
- To assess the safety of HRV vaccine in terms of serious adverse events (SAEs) throughout the study period.
- To assess the presence of RV in gastroenteritis (GE) stools collected up to Visit 3.
- To evaluate non-inferiority in terms of seroconversion rate from the Rota-068 (112269/068) study as compared to that of the seroconversion rate observed in the Rota-023 (444563/023) study.

- *Study design*

The study was a Phase IV, double-blind, randomised (3:1), placebo controlled study with two parallel treatment groups (HRV vaccine group and Placebo group). Two oral doses of HRV vaccine or placebo were administered starting at 6-12 weeks of age according to 0, 1-2 months schedule. Subjects were allowed to receive routine infant vaccines concurrently with the study vaccine. All concomitant vaccines received were to be recorded in the electronic Case Report Forms (eCRF). Blood samples were to be collected from all the subjects at Visit 1 and Visit 3 and stool samples were to be collected from subjects with report of GE between Dose 1 of HRV vaccine or Placebo and Visit 3. Data collection was done by Remote Data Entry (RDE) using eCRFs.

- *Study population /Sample size*

Number of subjects	Total	HRV vaccine group	Placebo group
Planned	680	510	170

I.

- *Treatments*

Treatment was two oral doses of the HRV vaccine, starting at 6-12 weeks of age according to 0, 1-2 months schedule. Subjects were allowed to receive routine infant vaccines concurrently with the study vaccine.

The comparator was two oral doses of the placebo (1 ml containing 2.25 mg of DMEM, 9 mg of sucrose, 18 mg of dextran, 13.5 mg of sorbitol, 9 mg of amino acids reconstituted with GSK Biologicals' calcium carbonate buffer containing 60 mg calcium carbonate and 0.25% xanthane in 1 mL water for injection. Lot number of the placebo: PROTA004A.)

The same diluents which were used for the HRV vaccine were used for the placebo.

II.

- *Outcomes/endpoints*

Primary endpoint:

- Anti-RV IgA seroconversion at Visit 3, measured using Enzyme Linked Immunosorbent Assay (ELISA).

Secondary endpoints:

Immunogenicity:

- Serum anti-RV IgA antibody concentration at Visit 3, measured by Geometric Mean Concentrations (GMCs) using ELISA.
- Anti-RV IgA seroconversion rate observed in this study as compared to the seroconversion rate in the Rota-023 (444563/023) study.

Safety/reactogenicity:

- Occurrence of each type of solicited AE during the 8-day (Day 0-Day 7) follow-up period after each dose of the HRV vaccine or placebo.
- Occurrence of unsolicited AEs during the 31-day (Day 0-Day 30) follow-up after any dose of HRV vaccine or placebo.
- Occurrence of SAEs throughout the study period (i.e. from Dose 1 of HRV vaccine or placebo to study conclusion at Visit 3).
- Presence of RV in GE stool samples collected after administration of Dose 1 of HRV vaccine or placebo up to Visit 3.

III.

- *Statistical Methods*

IV. All statistical analyses were performed using SAS® version-9.11 on Windows XP Professional and StatXact-8.0 procedure on SAS®. The analyses were performed as planned in the protocol and reporting and analysis plan (RAP). The range was not calculated for height in cm and weight in kg per group and overall.

Analysis of demographics

V. The mean and standard deviation (SD) of height in centimetre (cm) and weight in kilograms (kg) were calculated per group and overall at Visit 1. The mean, range and SD of age in weeks were calculated per group and overall, at each dose. The racial and gender composition, per group and overall were also presented. The distribution of subjects enrolled among the study centres was tabulated as a whole and per group.

Analysis of immunogenicity

VI. The primary analysis was based on the ATP cohort for immunogenicity.

VII. For each treatment group, at each time point that a given antigen was measured:

- Seropositivity/ seroconversion rates, GMCs and their exact 95% CI were tabulated.

VIII. The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-RV IgA antibody concentrations at Visit 3 between the HRV vaccine group and the Placebo group were computed. The primary objective was reached if the LL of the two-sided asymptotic standardised 95% CI for the difference in seroconversion rate between two treatments (HRV vaccine minus placebo) was ≥ 40%. Non-inferiority in terms of seroconversion rate observed between the Rota-068 (112269/068) study and the Rota-023 (444563/023) study was reached if the LL of the two-sided 95% CI for the difference in seroconversion rate between the Rota-068 (112269/068) study and (minus) the Rota-023(444563/023) study was above -20%.

Analysis of safety

IX. The primary analysis was based on the TVC.

X. The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the 8-day (Day 0-Day 7) solicited follow-up period was tabulated by group, for each dose, for overall doses and per subject. The percentage of AEs reported by subjects within the 31-day (Day 0-Day 30) follow-up period after vaccination with its exact 95% CI was tabulated by group. The incidence, with exact 95% CI, of each individual solicited general AE, was calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The same calculations were done for each individual solicited general AE rated as Grade 3 and for each individual solicited general AE related to the vaccination. The incidence, with exact 95% CI, of any Grade 2 or Grade 3 fever, vomiting or diarrhoea was calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The verbatim reports of unsolicited AEs were 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 AEs occurring within the 31-day (Day 0-Day 30) follow-up period with its exact 95% CI was tabulated by PT. Similar tabulation was done for vaccination and for unsolicited AEs rated as Grade 3. The percentage of subjects with presence of RV in GE stool samples collected from Dose 1 of HRV vaccine or placebo up to Visit 3 was tabulated by group. The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine or placebo up to Visit 3 was tabulated by group. The percentages of subjects who received at least one concomitant medication during the 8-day (Day 0-Day 7) solicited follow-up period after vaccination and during the study period were tabulated by type of medication. SAEs reported during the study period were summarised by group.

➢ **Results**

- Recruitment/ Number analysed

Number of subjects	Total	HRV vaccine group	Placebo group
Planned	680	510	170
Enrolled	684	508	176
Completed	627	465	162
Total vaccinated cohort	684	508	176
ATP cohort for safety	526	386	140
ATP cohort for immunogenicity	432	318	114

- Baseline data

XI. The mean age of the subjects in the ATP cohort for immunogenicity was 8.8 weeks (range: 6 to 12 weeks) at the time of the first dose of HRV vaccine or placebo and 16.2 weeks (range: 10 to 24 weeks) at the time of the second dose of HRV vaccine or placebo. Majority of the subjects (98.8%) were of East Asian heritage; 47.7% of the subjects were female and 52.3% of the subjects were male. Demographic characteristics were similar in the two groups (Rotarix and placebo).

XII. The percentage of subjects who received at least one concomitant vaccination was 87.7% and 87.6% at Dose 1 of HRV vaccine or placebo respectively, and 64.6% and 66% at Dose 2 of HRV vaccine or placebo respectively. The proportion of subjects receiving each concomitant vaccine was relatively similar between the Rotarix and the placebo groups, but no statistical test was provided.

- Efficacy results

Immunogenicity results (ATP cohort for immunogenicity):

- The anti-RV IgA antibody seroconversion rate was 88.1% [95% CI: 84%; 91.4%] in the HRV vaccine group and 4.4% [95% CI: 1.4%; 9.9%] in the Placebo group at Visit 3.
- The anti-RV IgA GMC was 208.5 U/mL [95% CI: 174.2; 249.5] in the HRV vaccine group and <20 U/mL in the placebo group.

- The difference in the seroconversion rate observed in the HRV vaccine group and (minus) the Placebo group was 83.66%. The LL of the two sided asymptotic standardised 95% CI for the difference in the percentage of subjects who seroconverted for anti-RV IgA antibody at one month after Dose 2 between the HRV vaccine group and (minus) the Placebo group was 77.26%, which is above the pre-defined clinical limit of 40% (criteria specified for fulfilling the primary objective).
- The LL of the 95% CI for the difference in the seroconversion rate observed in the Rota-068 (112269/068) study and (minus) the Rota-023 (444563/023) study was 5.64% which is above the pre-defined clinical limit of-20% (criteria specified for fulfilling the secondary objective).

- Safety results (total vaccinated cohort):

XIII.

XIV. The incidence of the overall symptoms (solicited or unsolicited) was 72.6% [95% CI: 68.5%; 76.5%] in the HRV vaccine group and 76.7% [95% CI: 69.8%; 82.7%] in the Placebo group. There was no increase in the incidence of the symptoms (solicited or unsolicited) from Dose 1 to Dose 2 of HRV vaccine or placebo.

XV. *Solicited AEs during the 8-day follow-up period:*
- The percentage of subjects reporting Grade 2 or Grade 3 solicited symptoms (fever, vomiting or diarrhoea) was 14.8% [95% CI: 11.8%; 18.2%] in the HRV vaccine group and 12.5% [95% CI: 8%; 18.3%] in the Placebo group.
- Irritability was the most frequently reported solicited general symptom in both the HRV vaccine group and the Placebo group. It was reported for 47.4% [95% CI: 43%; 51.9%] of the subjects in the HRV vaccine group and 50.6% [95% CI: 42.9%; 58.2%] of the subjects in the Placebo group after Dose 1 and 33.5% [95% CI: 29.2%; 38%] of the subjects in the HRV vaccine group and 36.4% [95% CI: 29%; 44.3%] of the subjects in the Placebo group after Dose 2.
- Grade 3 solicited symptoms were reported for less than 2.8% of the subjects after each dose in both groups. Vomiting was the most frequently reported Grade 3 solicited symptom in both groups.
- Irritability was the most frequently reported solicited symptom as assessed by the investigator to be causally related to the vaccination reported after each dose in both groups.

XVI. *Unsolicited AEs during the 31-day follow-up period after any vaccination:*
- At least one unsolicited symptom was reported for 29.1% [95% CI: 25.2%; 33.3%] of the subjects in the HRV vaccine group and 33.5% [95% CI: 26.6%; 41%] of the subjects in the Placebo group. Nasopharyngitis was the most frequently reported unsolicited symptom in both groups.

XVII. *GE Episodes:*
- The percentage of subjects reporting GE episodes from Dose 1 of HRV vaccine or Placebo up to Visit 3 was 8.3% in the HRV vaccine group and 9.7% in the Placebo group.
- None of the stool samples tested were positive for RV either with the vaccine strain or the wild type strain.

XVIII. *SAEs:*
- There were no fatal events reported in this study.
- Non-fatal SAEs were reported for 3.3% of the subjects in the HRV vaccine group and 7.4% of the subjects in the Placebo group from Dose 1 of HRV vaccine or placebo up to Visit 3. Bronchitis was the most frequently reported non-fatal SAE in both groups. None of the SAEs were considered by the investigator to be causally related to study vaccination.
- One subject (subject no.672 in the HRV vaccine group) was withdrawn from the study due to an SAE-Malignant Lymphoma. The decision to withdraw this subject was taken by both investigator and parents.

3. Discussion on clinical aspects

The seroconversion rate observed for the HRV vaccine group in this study was 88.1% [95% CI: 84%; 91.4%] at Visit 3, and is in line with the seroconversion rates observed in the studies conducted in the same region with similar setting. The primary objective for this study was met, as the LL of the 95% CI

for the treatment difference (HRV vaccine and (minus) placebo) was above the pre-defined clinical limit of 40%.

One of the objectives in this study was to evaluate non-inferiority in terms of seroconversion rate observed in this study as compared to that of the seroconversion rate observed in the Rota-023 study. This objective was met since the LL of the 95% CI for the difference in the seroconversion rate between this study and (minus) the Rota-023 (444563/023) study was above the pre-defined clinical limit of-20%.

The reactogenicity profiles of the HRV vaccine and the placebo in terms of occurrence of any, Grade 3 or related AEs were similar. There was no clinically meaningful difference observed in the incidence of unsolicited AEs and SAEs between both the groups. The safety data observed in this study were also similar to that of the Rota-041 study with irritability being the most frequently reported solicited symptom after each dose and the frequency of the Grade 3 solicited and unsolicited AEs were low in both the studies. There were no fatal SAEs reported in both studies.

Among the subjects who reported GE; none of the stool samples tested positive for RV either with the vaccine strain or the wild type strain. These findings seem surprising since most pre-licensure studies of HRV using ELISA found that approximately 50% of infants shed vaccine strain after the first dose (range 35–80%, depending on the dose and study parameters).[1,2] The peak time of HRV shedding has not been well assessed but it begins to decrease between 7 and 15–21 days after vaccination. There might be two explanations for the absence of HRV strain in the stools of vaccinated subjects:

- Stools were only tested if gastro-enteritis (GE) was present; these GE episodes may have occurred after the first 7 days post-vaccination, when HRV shedding is less frequent. The MAH has provided no aggregate data on the GE timing, besides the time between doses and visits.
- Of all the GE episodes reported in the HRV vaccine group, stool results were not available for 31.4% of the GE episodes, as either the stool samples were not collected or the stool samples were collected but the results were not available. Results were thus available for only 35 stool samples in the HRV group.

However, no explanation is provided in the report since the MAH is not discussing this finding.

Overall, the results of this study provides evidence that GSK Biologicals' HRV vaccine is immunogenic, well tolerated and displays a good safety profile in a population of infants in Korea.

4. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATIONS

➢ Overall conclusion

This placebo-controlled clinical trial of HRV vaccine among infants in Korea showed high immunogenicity results, which are in line with the seroconversion rates observed in the studies conducted in the same region with similar setting. The safety profile was similar between the HRV vaccine and the placebo group, and the frequency of Grade 3 solicited and unsolicited AEs were low and in line with other studies.

This paediatric study does not influence the benefit risk for Rotarix. No SmPC and PL changes are proposed and there is no regulatory action.

➢ Recommendation

No further action is required.

5. REQUEST FOR SUPPLEMENTARY INFORMATION

None.

[1] Anderson EJ. Rotavirus vaccines: viral shedding and risk of transmission. Lancet Infect Dis. 2008 Oct;8(10):642-9.
[2] Rotarix EPAR