16 March 2015
EMA/178804/2015
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 061

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

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1. INTRODUCTION

This AR concerns a study which was submitted by the MAH in compliance with Article 46 of the regulation 1901/2006.

Following the request from The Cosmetics, Devices and Drugs Authority in Sri Lanka, this study was undertaken to evaluate the safety and reactogenicity of GSK Biologicals' oral live attenuated HRV vaccine, Rotarix when administered to healthy infants aged from 6 weeks (first dose) to not more than 24 weeks (second dose). The interval between doses was to be not less than 4 weeks.

The MAH's experts stated that the submitted paediatric study does not influence the benefit risk for Rotarix and that subsequently there are neither consequential regulatory actions nor changes to the product information necessary.

2. STUDY SUMMARIES

Study 111664

- **General**

Study 111664 was conceptualized as an open, multi-centric post-marketing surveillance (PMS) with the intent to evaluate reactogenicity and safety of two doses of the oral live attenuated human rotavirus (HRV) vaccine, known under the trade-name Rotarix™, when administered according to a 0, 2 month schedule to Sri Lankan infants aged at least 6 weeks at the time of first vaccination.

- **Objective(s)**

In order to attain the goal of the study as stated, the following objectives and matching endpoints were defined:

Primary:

- To assess the reactogenicity of Rotarix in terms of occurrence of at least one grade "2" or grade "3" fever, vomiting or diarrhoea within a 8-day follow-up period after each vaccine dose.

  Endpoint: Occurrence of at least one grade "2" or grade "3" fever, vomiting or diarrhoea during the 8-day (Day 0 – Day 7) follow-up period after each vaccine dose.

Secondary:

- To assess the reactogenicity of Rotarix in terms of occurrence of solicited adverse events (AEs) within a 8-day follow-up period after each vaccine dose.

  Endpoint: For each type of solicited symptom, occurrence of the symptom within the 8-day (Day 0 – Day 7) follow-up period after each vaccine dose.

- To assess the safety of Rotarix in terms of occurrence of unsolicited AEs within a 31-day follow-up period after each vaccine dose.

  Endpoint: Occurrence of unsolicited symptoms during the 31-day (Day 0 – Day 30) follow-up period after each vaccine dose, according to Medical Dictionary for Regulatory Activities (MedDRA) classification.

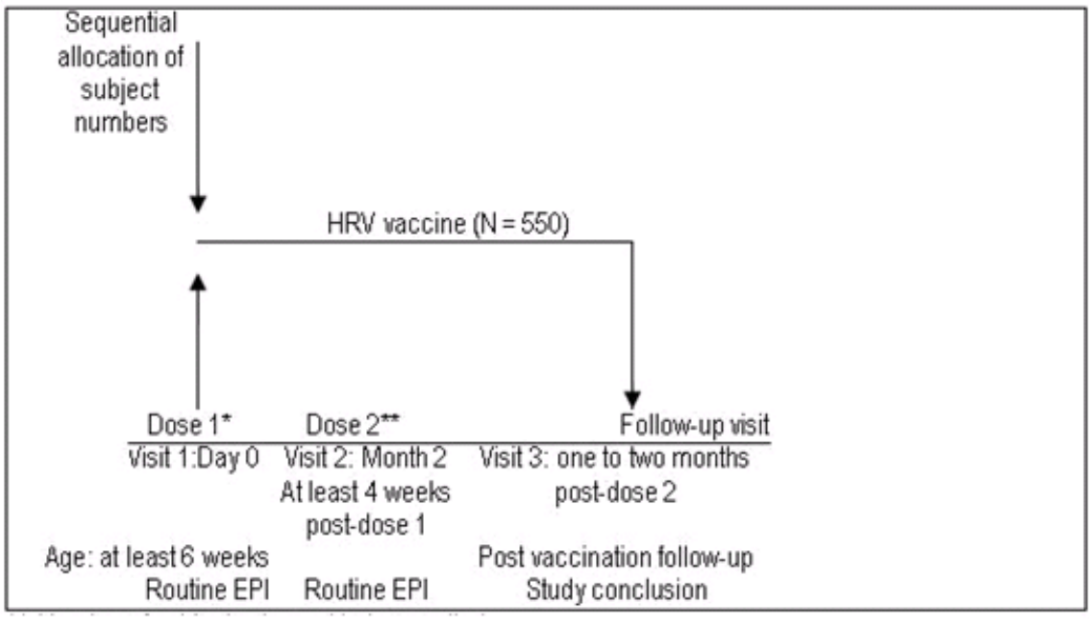
- To assess the safety of Rotarix in terms of serious adverse events (SAEs) throughout the study period after Dose 1 of Rotarix.

  Endpoint: Occurrence of SAEs throughout the study period following Dose 1.

- **Study design**

The study design is summarized in figure 1 as follows:

Figure 1: Study design scheme



HRV vaccine: GSK Biologicals' *Rotarix*
N = number of subjects planned to be enrolled.
*Dose 1 was to be administered not later than 19 weeks of age
**Dose 2 to be administered before 24 weeks of age

The duration of the whole of the study was planned as approximately 3-4 months, on a per subject basis. A number of specific solicited AEs, knowing fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting, were to be recorded in the 8-day window following administration (including the day of vaccination itself). Unsolicited AEs were to be recorded until Day 30 after each dose. SAEs were to be recorded at all times.

Planned between visit intervals are shown in table 1:

Table 1: Between-visit intervals

Interval	Length of interval
1 (Visit 1→Visit 2)	Not less than 4 weeks
2 (Visit 2→Visit 3)	One to two months

Note: The date of the previous visit served as the reference date for intervals between study visits.

- **Study population / Sample size**

The number of subjects to be included in the study was determined to be 550 subjects as per the regulatory authority requirements. Evaluation took place on the Total vaccinated Cohort (TVC), in other words on all vaccinated subjects for whom data was available.

Any male or female infant of at least 6 weeks of age at the time of the first vaccination was eligible to participate, unless it had a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine, if it was suffering from an acute disease at time of enrolment, if it had a history of uncorrected congenital malformation of the gastrointestinal tract that would predispose for IS or if any other contraindication in the approved SPC was applicable to the subject in question.

- **Demography Results**

Five hundred twenty two subjects were enrolled, with 96% of these receiving two doses of vaccine. There were no unexpected outliers on the demographic profiles of the participants.

Table 3: Number and percentage of subjects who received study vaccine doses (Total Vaccinated cohort)

	HRV Group N = 522	
Total number of doses received	**n**	**%**
1	21	4.0
2	501	96.0
Any	522	100

HRV: GSK Biologicals' *Rotarix*
N = number of subjects included in the considered cohort
n (%) = number (percentage) of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

- **Safety results**

Table 4 provides a summary on the number of subjects presenting with grade 2 or 3 AEs.

Table 4: Percentage of doses and of subjects reporting grade 2 or 3 symptoms (fever, vomiting, diarrhoea) during the 8-day (Day 0 – Day 7) solicited follow-up period (Total Vaccinated cohort)

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	522	46	8.8	6.5	11.6
Dose 2	HRV	501	50	10.0	7.5	12.9
Overall/dose	HRV	1023	96	9.4	7.7	11.3
Overall/subject	HRV	522	78	14.9	12.0	18.3

HRV: GSK Biologicals' *Rotarix*
For each dose and overall/subject:
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects presenting at least one type of symptom
For overall/dose:
N = number of administered doses
n (%) = number (percentage) of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

The overall most frequently occurring solicited AE was fever, being reported for 18.0% and 20.2% of subjects following Dose 1 and Dose 2, respectively. The most reported grade 3 AE turned out to be vomiting, which was observed in 1.7% and 1.0% of subjects following Dose 1 and Dose 2 of the vaccination respectively.

Fever was also the most frequently reported solicited AE with a causal relationship to vaccination; reported for 18.0% and 20.2% of subjects following Dose 1 and Dose 2, respectively.

Table 5 provides an overview of the unsolicited AEs reported during the study.

<u>Table 5:</u> Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Day 0 – Day 30) post-vaccination period (Total Vaccinated cohort)

		HRV Group N = 522			
				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
At least one symptom		25	4.8	3.1	7.0
Gastrointestinal disorders (10017947)	Constipation (10010774)	8	1.5	0.7	3.0
	Diarrhoea (10012735)	1	0.2	0.0	1.1
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	3	0.6	0.1	1.7
Infections and infestations (10021881)	Foot and mouth disease (10016961)	1	0.2	0.0	1.1
	Urinary tract infection (10046571)	2	0.4	0.0	1.4
Metabolism and nutrition disorders (10027433)	Decreased appetite (10061428)	1	0.2	0.0	1.1
Nervous system disorders (10029205)	Crying (10011469)	1	0.2	0.0	1.1
	Somnolence (10041349)	5	1.0	0.3	2.2
Psychiatric disorders (10037175)	Insomnia (10022437)	1	0.2	0.0	1.1
Renal and urinary disorders (10038359)	Dysuria (10013990)	1	0.2	0.0	1.1
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	2	0.4	0.0	1.4
	Rhinorrhoea (10039101)	2	0.4	0.0	1.4
	Upper airway obstruction (10067775)	1	0.2	0.0	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.2	0.0	1.1
	Rash macular (10037867)	2	0.4	0.0	1.4

HRV: GSK Biologicals' *Rotarix*
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

The percentage of subjects reporting at least one unsolicited AE during the 31-day (Day 0 – Day 30) follow-up period was 4.8%, with constipation being the most commonly reported one at 1.5% of the subjects. The percentage of subjects reporting at least one grade "3" unsolicited AE stood at 0.6%, while unsolicited AEs with causal relationship to vaccination were reported for 1.0% of subjects (table 6).

Table 16: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Day 0 – Day 30) post-vaccination period (Total Vaccinated cohort)

		HRV Group N = 522			
				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
At least one symptom		5	1.0	0.3	2.2
Nervous system disorders (10029205)	Somnolence (10041349)	3	0.6	0.1	1.7
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.2	0.0	1.1
	Rash macular (10037867)	1	0.2	0.0	1.1

HRV: GSK Biologicals' *Rotarix*
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

During the study no fatal events occurred, and there was but one SAE reported, albeit leading to study discontinuation, which was considered as unlikely to be related to the vaccination.

In total 8.8% of participants started taking concomitant medication during the study, of which the majority (5.7%) took anti-pyretics.

➢ **Conclusions:**

- No safety concerns were raised on the available data.
- No fatal events and IS cases were reported in the study.
- One subject reported a SAE that was not considered by the investigator to have a causal relationship to vaccination.
- No cases of IS (bowel intussusception), Kawasaki disease or Pneumonia have been reported in this study.
- Two doses of GSK Biologicals' Rotarix vaccine was well tolerated and had a good safety profile in the local paediatric population

3. ASSESSOR'S CONCLUSIONS ON CLINICAL ASPECTS

- The open study 111664 aimed to investigate the tolerability and safety of the HRV vaccine in young children in the Sri Lankan community, when administered according to the local vaccination schedule.
- During the course of the investigation no unexpected safety results were encountered, and the number and types of AEs (including SAEs), whether solicited or not, reported were entirely within the range of expected issues of this vaccine.

No new issues that would warrant regulatory actions were found to exist in any of the study results provided, and results were in agreement with the already established knowledge on Rotarix safety and immunogenicity.

This submission is thus hereby considered to be fulfilled.

4. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

This submission is considered fulfilled, and no further regulatory action is required.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

5. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable