London, 13 October 2016
EMA/CHMP/631083/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Rotarix

International non-proprietary name: human rotavirus, live attenuated

Procedure No. EMEA/H/C/000639/P46/089

Note

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

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1. Introduction

On 28 June 2016, the MAH submitted the final report for an Infanrix-IPV study in which Rotarix lyophilised formulation is one of the coadministered vaccines, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study DTPA-IPV (INFANRIXIPV)-059 (114260) was a phase III, randomised, open-label, multicentre study to assess the immunogenicity, safety and reactogenicity of the combined DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-4-6 months of age in healthy subjects in South Korea.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study DTPA-IPV (INFANRIXIPV)-059 is a stand alone study.

The main objective of the study was to demonstrate that the immunogenicity of DTPa-IPV/Hib vaccine ("combo" registered as Infanrix-IPV/Hib in some countries) administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant but separate administration of DTPa-IPV (Infanrix-IPV) and Hib (Hiberix) vaccines, in terms of immune response to all vaccine antigens, one month after the third dose of the primary vaccination.

Rotarix and Synflorix were administered in the study as part of the local recommended immunization schedule, and in a staggered manner. Rotarix was administered orally at 6 weeks and 3.5 months of age. Synflorix (10Pn-PD-DiT) was administered at 6 weeks, 3.5 months and 5.5 months of age.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation of Rotarix was used in the study. Lot numbers for Rotarix and Diluent were AROTA217A and AD05A657A, resp.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study DTPA-IPV (INFANRIXIPV)-059 (114260) was a phase III, randomised, open-label, multicentre study to assess the immunogenicity, safety and reactogenicity of the combined DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-4-6 months of age in healthy subjects in South Korea.

This study did not generate immunogenicity data of Rotarix. The safety follow-up of these vaccinations was limited to the collection of serious adverse events.

2.3.2. Clinical study

DTPA-IPV (INFANRIXIPV)-059 (114260) was a phase III, randomised, open-label, multicentre study to assess the immunogenicity, safety and reactogenicity of the combined DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-4-6 months of age in healthy subjects in South Korea.

Description

This was a phase III, multi-center, open-label, randomized, controlled trial with 2 study groups. Rotarix was one of the vaccines that were co-administered during this study.

The first subject was enrolled on 04 March 2011 and the last study visit was on 24 February 2012.

Methods

Objectives

Primary:

Immunogenicity

To demonstrate that the immunogenicity of DTPa-IPV/Hib vaccine administered at 2, 4 and 6 months of age was non-inferior to that of the concomitant administration of DTPa-IPV and Hib vaccines, in terms of immune response to all vaccine antigens, one month after the third dose of the primary vaccination.

Non-inferiority was to be demonstrated if:

- the upper limits of the standardized asymptotic 95% confidence interval (CI) on the group differences [Control Group minus Combo Group] in percentages of subjects seroprotected against diphtheria, tetanus, poliovirus type 1, poliovirus type 2, poliovirus type 3 and Hib were all ≤ 10%, and,

- the upper limits of the 95% CI on the group ratios [Control Group divided by Combo Group] of geometric mean concentrations (GMCs) of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) were all ≤ 1.5.

Secondary:

Immunogenicity

- The immune response to the DTPa-IPV/Hib vaccine versus the DTPa-IPV and Hib vaccines administered separately was to be assessed, in terms of seroprotection/ seropositivity and antibody geometric mean concentrations/titres (GMCs/GMTs) to all antigens and in terms of vaccine response to pertussis antigens one month after the third dose of primary vaccination.

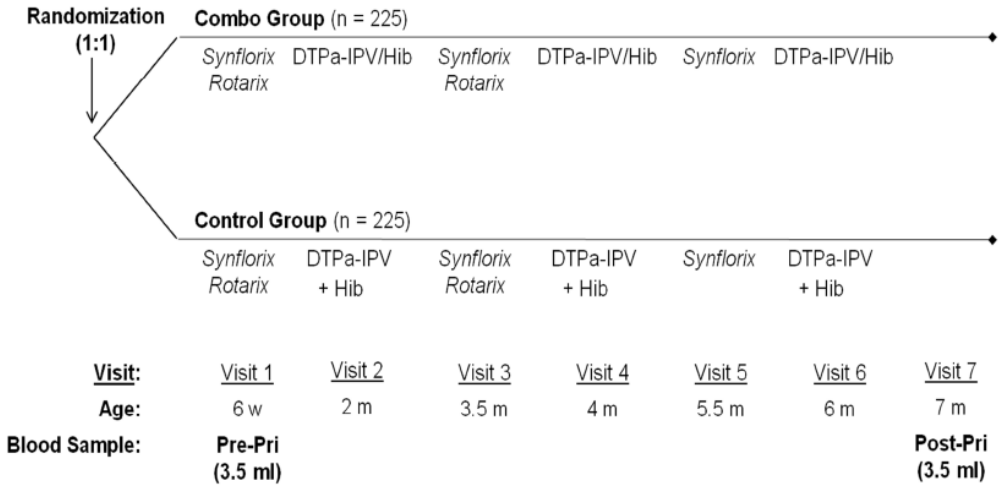
Safety

- The safety and reactogenicity of the DTPa-IPV/Hib, DTPa-IPV and Hib vaccines were to be assessed, in terms of solicited local and general symptoms.
- The **safety of all study vaccines** was to be assessed in terms of **unsolicited** adverse events (**AEs**) and serious adverse events (**SAEs**).

Study design

Subjects were randomized 1:1 into 2 study groups. This study was conducted in an open manner as the number of injections differed between groups.

Approximately 3.5 ml whole blood sample was taken from all subjects before the first dose and one month after the third dose of the DTPa-IPV/Hib vaccine or the DTPa-IPV and Hib vaccines.



n = number of subjects; w = weeks; m = months
Pre-pri = before the first vaccine dose of the DTPa-IPV/Hib vaccine or DTPa-IPV and Hib vaccines
Post-pri = one month after the third vaccine dose of the DTPa-IPV/Hib vaccine or DTPa-IPV and Hib vaccines

Study population /Sample size

A total of **451 subjects** (224 subjects in the Combo group and 227 subjects in the Control group) were randomised and completed in the study. Healthy males or females between, and including, 42 and 69 days of age at the time of the first vaccination, were included in the study. Written informed consent was obtained from the parents/ Legally Acceptable Representatives (LARs) of the subjects.

Evidence of previous or intercurrent diphtheria, tetanus, pertussis, poliomyelitis and Hib vaccination or disease led to exclusion of the subject from the study.

Treatments

Study vaccine: DTPa-IPV/Hib consisting of two components and combined prior to use ("combo")

(1) the **liquid DTPa-IPV component** presented in a prefilled syringe; and
(2) the **lyophilized Hib component** which was reconstituted with the liquid DTPa-IPV component.

Control vaccine: DTPa-IPV/Hib consisting of the same components but given separately ("control")

(1) the **liquid DTPa-IPV component** presented in a prefilled syringe; and
(2) the **lyophilized Hib component** which was reconstituted with the provided diluent.

The primary study vaccines were given at 2, 4, and 6 months of age.

Co-administered vaccines:

Pneumococcal conjugate vaccine: Synflorix given at 6 weeks, 3.5 months and 5.5 months of age. Infants received IM vaccinations into the right anterolateral thigh.

Rotavirus vaccine: Rotarix. Two doses given two months apart orally.

Study procedures

Rotarix was administered at Visit 1 and Visit 3.

Age	6 weeks	2 m	3.5 m	4 m	5.5 m	6 m	7 m
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Sampling time points	Pre-Pri						Post-Pri
Informed consent	●						
Check inclusion/exclusion criteria	●						
Medical history	●						
Physical examination including height and weight measurement	●						
Randomization	●						
Pre-vaccination body temperature	●	●	●	●	●	●	
Blood sampling for antibody determination	●						●
Check warnings and precautions	○	○	○	○	○	○	
Vaccination	●	●	●	●	●	●	
Check contraindications to subsequent vaccinations		●	●	●	●	●	
Daily post-vaccination recording of solicited adverse events (Days 0–3) by subjects' parent(s)/LAR(s)		●		●		●	
Recording of non-serious adverse events within 30 days post-vaccination		●		●		●	
Return of diary cards and transcription by investigator			●		●		●
Record any concomitant medication/ vaccination	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●
Reporting of serious adverse events	●	●	●	●	●	●	●
Study Conclusion							●

m = months
● was used to indicate a study procedure that requires documentation in the individual eCRF
○ was used to indicate a study procedure that does not require documentation in the individual eCRF

Outcomes/endpoints

Immunogenicity:

Immunogenicity outcomes are not discussed here as no immunogenicity data were collected for Rotarix.

Safety:

- The safety of Rotarix was assessed in terms of unsolicited adverse events (AEs) and serious adverse events (SAEs).
- All AEs starting within 30 days following administration of each dose of the primary study vaccines (DTPa-IPV/Hib or DTPa-IPV and Hib vaccines) were recorded onto the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they were considered vaccination-related.

- The standard time period for collecting and recording SAEs began at the first receipt of study vaccine and ended 30 days following administration of the last dose of study vaccine for each subject.
- In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that were related to study participation (e.g. protocol-mandated procedures, invasive tests) or were related to a concurrent GSK medication/vaccine or any fatal SAE was collected and recorded from the time the subject consents to participate in the study until she/he was discharged.
- A post-study AE/SAE was defined as any event that occurred outside of the AE/SAE reporting period. Investigators were not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learned of any SAE, including a death, at any time after a subject had been discharged from the study, and he/she considered the event reasonably related to the investigational product, the investigator promptly notified the Study Contact for Reporting SAEs.

Statistical Methods

Safety

Solicited local and general symptoms

- Occurrence of solicited local and general symptoms during the 4-day (Day 0-3) follow-up period after each dose of the DTPa-IPV/Hib or DTPa-IPV + Hib vaccines.

Unsolicited AEs

- Occurrence of unsolicited AEs during the 31-day (Day 0-30) follow-up period after each dose of the DTPa-IPV/Hib or DTPa-IPV + Hib vaccines, according to the MedDRA classification.

SAEs

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

Results

Recruitment / Number analysed

Table 1. Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion.

	Total			Combo group		Control group	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	454			226		228	
Study vaccine dose not administrated but subject number allocated (code 1030)	3	3		2	2	1	1
Total vaccinated cohort	451		100	224		227	
Administration of vaccine(s) forbidden in the protocol (code 1040)	5	5		1	1	4	4
Study vaccine dose not administered according to protocol (code 1070)	1	1		0	0	1	1
ATP cohort for safety	445		98.7	223		222	
Protocol violation (inclusion/exclusion criteria) (code 2010)	3	3		3	3	0	0
Administration of any medication forbidden by the protocol (code 2040)	2	2		2	2	0	0
Non-compliancewith vaccination schedule (including wrong and unknown dates) (code 2080)	9	9		5	5	4	4
Non-compliancewith blood sampling schedule (including wrong and unknown dates (code 2090)	1	1		0	0	1	1
ATP cohort for immunogenicity	430		95.3	213		217	

Combo group = Subjects received DTPa-IPV/Hib vaccine as a single injection at 2, 4 and 6 months of age
Control group = Subjects received DTPa-IPV and Hib vaccines at different injection sites at 2, 4 and 6 months of age
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Codes are listed based on a ranking order

Efficacy results

One month after the third dose of primary vaccination:

- All subjects in both the groups were seroprotected against **diphtheria** antigen. The anti-diphtheria GMCs were 8.096 IU/mL in the Combo group and 8.692 IU/mL in the Control group.
- All subjects in both the groups were seroprotected against **tetanus** antigen. The antitetanus GMCs were 10.259 IU/mL in the Combo group and 12.421 IU/mL in the Control group.
- All subjects in both the groups were seroprotected against **poliovirus** type 1 and type 2. The anti- poliovirus type 1 GMTs were 328.8 ED_{50} in the Combo group and 372.7 ED_{50} in the Control group. The anti - poliovirus type 2 GMTs were 340.6 ED_{50} in the Combo group and 400.2 ED_{50} in the Control group.
- All except one subject (99.5 %) in the Combo group and 99% of subjects in the Control group were seroprotected against poliovirus type 3 antigen. The anti - poliovirus type 3 GMTs were 377.7 ED_{50} in the Combo group and 465.3 ED_{50} in the Control group.
- All subjects in both groups were seropositive against **pertussis** PT, FHA and PRN antigens. The anti-PT, anti-FHA and anti-PRN GMCs were 54.2 EU/mL, 125 EU/mL and 125.8 EU/mL respectively in the Combo group and 56 EU/mL, 134.2 EU/mL and 133.4 EU/mL respectively in the Control group.
- Vaccine response rates to PT antigen were observed in 99.5% of subjects in both the groups. Vaccine response rates to FHA antigen were observed in 98.1% of subjects in Combo group

and in 96.7% of subjects in Control group. Vaccine response rates to PRN antigen were observed in 100% of subjects in Combo group and 99.5% of subjects in Control group.

- All subjects in both the groups were seroprotected against **Hib** PRP antigen. The anti- PRP GMCs were 8.456 μg/ml in the Combo group and 18.700 μg/ml in the Control Group.

Assessor's comment

No immunogenicity data were collected for Rotarix.

Immunogenicity data of the primary study vaccines (DTPa-IPV/Hib or DTPa-IPV and Hib vaccines) show very high seroprotection rates in both Combo and Control group.

Safety results

All 224 enrolled subjects in the Combo group and 227 subjects in the Control group received at least one dose of their allocated vaccines.

As Rotarix was administered at Visit 1 (6 weeks) and Visit 3 (3,5 months), the recording of non-serious AE within 30 days post-vaccination at Month 2 and Month 4 reflects also the safety profile of Rotarix.

Summary of safety according to co-administration vaccine regimen

- *Any solicited symptom/unsolicited AE:* During the 4-day post-vaccination follow-up period, any solicited symptom and unsolicited AE were reported for 96.9% of subjects in the Combo group and Control group. Grade 3 symptoms were more frequently reported in the Combo group (26.8%) compared to the Control group (20.7%).
- *Solicited local symptoms:* During the 4-day post-vaccination period, redness was the most frequently reported solicited local symptom, reported for 79.0% of subjects in the Combo group and 73.6% of subjects in the Control group. Redness was also the most frequently reported Grade 3 solicited local symptom, reported for 12.9% of subjects in Combo group and 11.5% of subjects in the Control group.
- *Solicited general symptoms:* During the 4-day post-vaccination period, **irritability** was the most frequently reported solicited general symptom, reported for **80.8%** of subjects in the Combo group and 80.2% of subjects in the Control group. Irritability was also the most frequently reported Grade 3 solicited general symptom, reported for 6.7% of subjects in the Combo group and 4.0% of subjects in the Control group.
- *Unsolicited AEs*: During the 31-day post-vaccination period, at least one unsolicited AE was reported for 58% of subjects in the Combo group and 54.2% of subjects in the Control group. **Nasopharyngitis** reported for 37 subjects (16.5%) was the most frequently reported unsolicited AE in the Combo group while nasopharyngitis and upper respiratory tract infection reported for 29 subjects (12.8%) were the most frequently reported unsolicited AEs in the Control group. At least one Grade 3 unsolicited AE was reported for four subjects (1.8%) in the Combo group and five subjects (2.2%) in the Control group. **Urinary tract infection**, reported for two subjects (0.9%) was the most frequently reported Grade 3 unsolicited AE in the Control group. At least one unsolicited AE possibly related to vaccination was reported for 6.7% subjects in the Combo group and 3.5% of subjects in the Control group. **Diarrhoea** and injection site mass, reported for four subjects (**1.8%**) were the most frequently reported unsolicited AEs possibly related to vaccination in the Combo group while diarrhoea and

nasopharyngitis, reported for two subjects (**0.9%**) were the most frequently reported unsolicited AEs possibly related to vaccination in the Control group.

- *SAEs*: A total of 57 SAEs were reported in 46 subjects (25 subjects in the Combo group and 21 subjects in the Control group). Among the SAEs, bronchiolitis, urinary tract infections and gastro-enterititis were the most frequently reported SAEs in both the groups. All SAEs led to hospitalisation and were resolved by the end of study.
- *Withdrawals due to AEs/SAEs:* None of the subjects were withdrawn due to an AE or SAE, during the study period.
- No fatal events were reported during the study period.
- One case of intussusception was reported.

Intussusception case

This female subject was enrolled in the prophylactic open study 114260 (DTPa-IPV-059). On 15 March 2011 and 16 May 2011, she received the 1st and 2nd dose of 10-valent pneumococcal-protein D conjugate vaccine (Synflorix, IM, left thigh) and rotavirus vaccine (Rotarix, oral). On 29 March 2011 and 30 May 2011, she received the 1st and 2nd dose of combined diphtheria, tetanus, acellular pertussis, inactivated polio, haemophilus influenzae type b vaccine (Infanrix-IPV/Hib, IM R thigh). On 19 July 2011, she received a 3rd dose of Synflorix. On 02 August 2011, she received a 3rd dose of Infanrix-IPV/Hib.

On 09 August 2011, 85 days after the 2nd dose of Rotarix, 21 days after the 3rd dose of Synflorix, seven days after the 3rd dose of Infanrix-IPV/Hib, this six-month-old subject developed acute gastroenteritis and intussusception. The subject was hospitalised.

The subject was treated with cefpiramide, Medilac-S, sulphamethoxazole, sodium chloride and Dextrose + sodium chloride. Intussusception resolved on 11 August 2011. Acute gastroenteritis resolved on 25 August 2011.

The investigator considered that there was no reasonable possibility that the acute gastroenteritis and intussusception may have been caused by Rotarix, Synflorix and Infanrix-IPV/Hib.

Assessor's comment

There were no new safety issues for Rotarix based on the results of this study.

AE related to Rotarix were treated as unsolicited AE as per study protocol. The most common AE reported within 30 days of Rotarix administration are diarrhea and irritability (SmPC Rotarix, 2016). As these AE are also part of the expected safety profile post-DTaP and Hib vaccination (SmPC Infanrix-IPV, 2014; SmPC Hiberix, 2016), it is surprising that diarrhea was treated as an unsolicited AE and therefore not included as a predefined safety endpoint. The frequency of diarrhea observed in this study (0.9 – 1.8%) is at the lower limit of being classified as "common" AE (>1% - <10%), which might be attributed to underreporting in case of an unsolicited AE.

2.3.3. Discussion on clinical aspects

A limitation of the current study is the potential bias due to the open-label design.

Another limitation is the lack of specific endpoints for assessing the clinical aspects of Rotarix. The study was also not designed nor powered to detect rare AE. All study subjects (n=451) received two doses of Rotarix.

The immune responses against rotavirus antigens were not determined, but immune responses to the primary study vaccines were acceptable. The safety data did not give rise to new safety concerns.

Thus, the addition of these results to the already presented clinical data does not impact on the benefit/risk balance of Rotarix. No further regulatory action is considered necessary.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

No data on the immunogenicity of *Rotarix* were provided in this report.

Study DTPA-IPV (INFANRIXIPV)-059 was not designed to exclude an effect of Rotarix on the immunogenicity and safety of the primary study vaccines (containing DTPa-IPV and Hib antigens) in health infants. Nevertheless, the provided data do not cause concern regarding safety of Rotarix.

The Article 46 paediatric submission is considered fulfilled, and no further regulatory action is needed.

The benefit/risk balance of Rotarix remains positive.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.