EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rotarix

rotavirus vaccine, live, attenuated

Procedure no: EMEA/H/C/000639/P46/092

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

A stand-alone submission of the final study report for the DTPa-HBV-IPV-135 study, in accordance with Article 46 of Regulation (EC) No 1901/2006. The DTPa-HBV-IPV-135 study is a Phase III, randomized, open-label, controlled, multicenter study to evaluate immunogenicity and safety of GSK Biologicals' Infanrix hexa vaccine when administered to healthy infants as primary vaccination at 2, 4 and 6 months of age, co-administered with Prevnar and Rotarix with a booster dose of GSK Biologicals' I*nfanrix* and *Hiberix* vaccines at 15-18 months of age. The study DTPa-HBV-IPV-135 was conducted in the United States of America. Rotarix was co-administered to all subjects at 2 & 4 months of age. This study evaluates the reactogenicity and safety of this co-administration.

1.1. Steps taken for the assessment

Submission date:	02/08/2018
Start of procedure:	20/08/2018
CHMP Rapporteur's preliminary assessment report circulated on:	24/09/2018
CHMP Rapporteur's updated assessment report circulated on:	11/10/2018
CHMP opinion:	18/10/2018

2. Assessment of the post-authorisation measure PAM

Objectives:

Primary: Epoch 001 (Primary vaccination):

- To demonstrate the non-inferiority of Infanrix hexa to Pediarix co-administered with ActHIB, in terms of antibody geometric mean concentrations (GMCs) for pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)] one month after the third dose of the primary vaccination.

  Criteria for non-inferiority: Non-inferiority in terms of immune response to pertussis antigens was to be demonstrated if, for each of the three antigens, the upper limit (UL) of the 95% confidence interval (CI) on the GMC ratio [Pedia divided by Hexa] was $\leq$ 1.5.

Secondary: Epoch 001 (Primary vaccination)

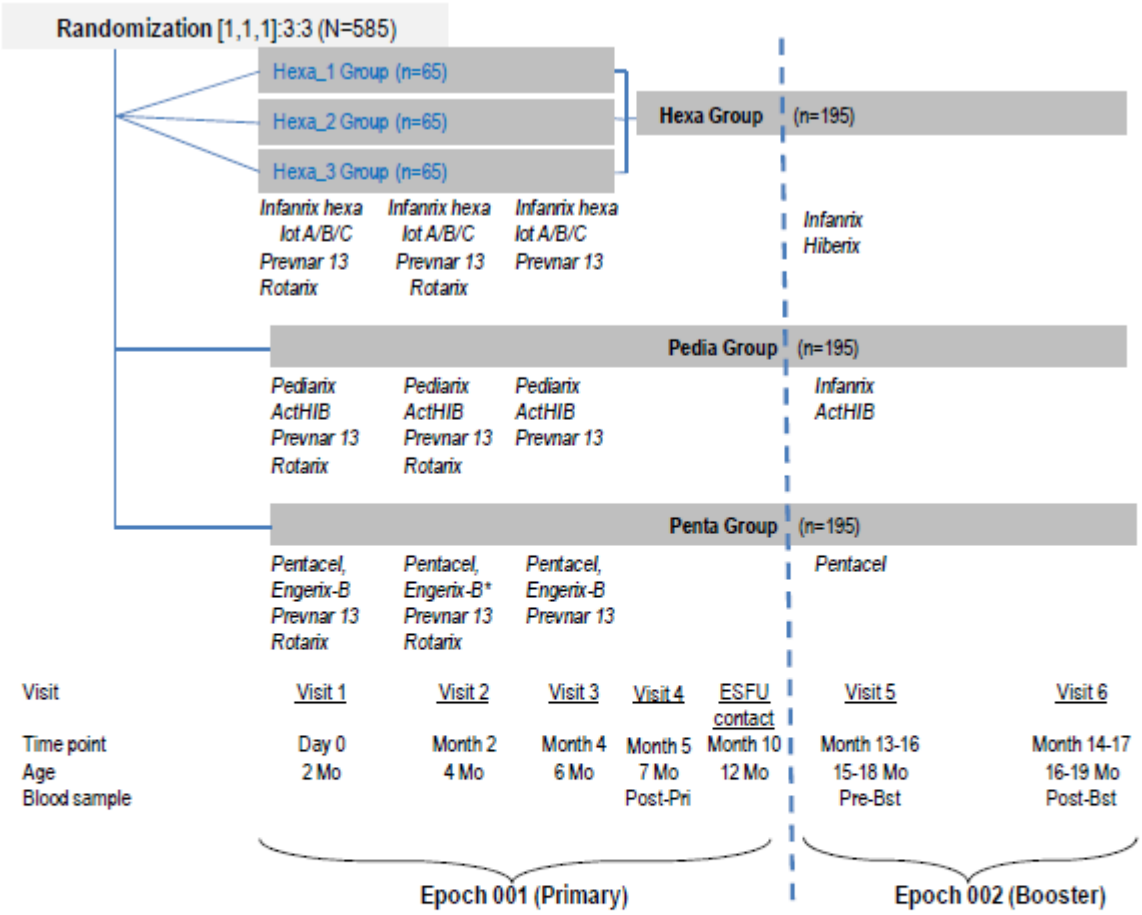
- To assess the immune response to Infanrix hexa, Pediarix, ActHIB, Pentacel and Engerix-B, in terms of seroprotection status, seropositivity status and concentrations or titers of antibodies to D (Diphtheria), T (Tetanus), HBs (Hepatitis B surface antigen), pertussis, poliovirus types 1, 2 and 3 and PRP (Polyribosyl-Ribitol- Phosphate) antigens, one month after the third dose of the primary vaccination.
- To assess the safety and reactogenicity of a 3-dose primary vaccination course of Infanrix hexa, of Pentacel coadministered with Engerix-B, and that of Pediarix co-administered with ActHIB, in terms of solicited local symptoms.

- To assess the safety and reactogenicity of all study vaccines in terms of solicited general events, unsolicited adverse events, new-onset chronic illnesses (NOCIs; referred to as new-onset chronic diseases (NOCDs) in the protocol) and serious adverse events.

Methodology:

- Experimental design: Phase III, open-label, randomized, controlled, multi-centric, single-country study with five parallel groups.
    - Epoch 001: Primary, starting at Visit 1 (Day 0) and ending at safety follow up contact (i.e. six months following the third dose, Month 10);
    - Epoch 002: Booster, starting at Visit 5 (Month 13-16) and ending at Visit 6 (Month 14-17).
- Control: active controls.
    - Epoch 001: Pediarix + ActHIB and Pentacel + Engerix-B;
    - Epoch 002: Infanrix + ActHIB and Pentacel.

A total of 585 subjetcts (6-12 weeks old at the time of first vaccine) were randomised [1:1:1]:3:3 to 5 parallel groups and received vaccinations as follows :



N = number of subjects in the study; n = number of subjects in each group; Mo = months
Visit 3 should be conducted at least 8 weeks after Visit 2, with subjects at least 24 weeks of age, in order to comply with US recommendations on hepatitis B dosing
Post-Pri = blood sample collected from subjects, one month after the administration of the third dose in the Epoch 001
Pre-Bst = blood sample collected from subjects, before the administration of the booster dose in the Epoch 002
Post-Bst = blood sample collected from subjects, one month after the administration of booster dose in the Epoch 002
* *Engerix-B* should not be given at Month 2 (4 months of age) if a dose of hepatitis B vaccine was given at birth up to 30 days prior to study dose 1 to the subject in the Penta Group
ESFU = Extended safety follow-up

Vaccination schedules:

Epoch 001

- Hexa Group: Subjects in this group were to receive three doses of Infanrix hexa (lot A, lot B or lot C as per the group allocation) co-administered with Prevnar13 at 2, 4 and 6 months of age and Rotarix at 2 and 4 months of age.
    - Hexa_1 Group: Subjects were to receive lot A of Infanrix hexa;
    - Hexa_2 Group: Subjects were to receive lot B of Infanrix hexa;
    - Hexa_3 Group: Subjects were to receive lot C of Infanrix hexa.

- Pedia Group: Subjects in this group were to receive three doses of Pediarix and ActHIB co-administered with Prevnar13 at 2, 4 and 6 months of age and Rotarix at 2 and 4 months of age.
- Penta Group: Subjects in this group were to receive three doses of Pentacel and Engerix-B* co-administered with Prevnar13 at 2, 4 and 6 months of age and Rotarix at 2 and 4 months of age.

*Subjects in the Penta Group who received a dose of hepatitis B vaccine from birth up to 30 days prior to study vaccination were not to receive Engerix-B at 4 months of age (Visit 2).

Epoch 002

- Hexa Group: Subjects were to receive a booster dose of Infanrix and Hiberix vaccines at 15-18 months of age.
- Pedia Group: Subjects were to receive a booster dose of Infanrix and ActHIB vaccines at 15-18 months of age.
- Penta Group: Subjects were to receive a booster dose of Pentacel vaccine at 15-18 months of age.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max) at Visit 1	Epochs	
			Epoch 001	Epoch 002
Hexa_1	65	6 weeks -12 weeks	x	x
Hexa_2	65	6 weeks -12 weeks	x	x
Hexa_3	65	6 weeks -12 weeks	x	x
Pedia	195	6 weeks -12 weeks	x	x
Penta	195	6 weeks -12 weeks	x	x

The study groups and treatment foreseen in the study are presented in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups				
		Hexa_1	Hexa_2	Hexa_3	Pedia	Penta
Epoch 001						
Infanrix hexa		x	x	x		
	Hib					
Pediarix					x	
ActHIB	ActHIB				x	
	NaCl					
Pentacel	DTaP-IPV (Sanofi Pasteur)					x
	ActHIB					
Engerix-B *	HBV					x
Prevnar13	Prevenar 13	x	x	x	x	x
Rotarix	HRV	x	x	x	x	x
	$CaCO_3$					
Epoch 002						
Infanrix	DTPa	x	x	x	x	
Hiberix	Hib	x	x	x		
	NaCl					
ActHIB	ActHIB				x	
	NaCl					
Pentacel	DTaP-IPV (Sanofi Pasteur)					x
	ActHIB					

* *Engerix-B* should not be given at Month 2 (4 months of age) if a dose of hepatitis B vaccine was given at birth up to 30 days prior to study dose 1 to the subject in the Penta Group.

RESULTS Summary:

Safety results : Primary Total vaccinated cohort - Safety summary

Since Rotarix was co-administered with other vaccines, the safety analysis does not relate to the administration of Rotarix alone.

Any Symptom: In all three groups (Hexa, Pedia and Penta) over the primary doses, symptoms (solicited and/or unsolicited, local and/or general) were reported for 93.4-96.4% of subjects.

Solicited local symptoms: Pain was the most frequently reported solicited local symptom reported in 67.9% of subjects in the Hexa group, in 82.0% of subjects in the Pedia group and in 79.8% of subjects in the Penta group.

Pain was also the most frequently reported Grade 3 solicited local symptom reported in 4.3% of subjects in the Hexa group, 18.0% of subjects in the Pedia group and 11.7% of subjects in the Penta group.

Solicited general symptoms: Irritability / Fussiness was the most frequently reported solicited general symptom in all groups, reported in 87.7% of subjects in the Hexa group, in 96.3% of subjects in the Pedia group and in 94.1% of subjects in the Penta group overall. Irritability / fussiness was also the most commonly reported grade 3 solicited general symptom, reported for 9.6% of subjects in the Hexa group, 18.5% of subjects in the Pedia group and 16.0% of subjects in the Penta group overall.

Unsolicited adverse events: At least one unsolicited symptom within the 31-day post-vaccination period after each vaccination was reported for 57.9%, 55.7% and 49.0% of subjects in the Hexa, Pedia and Penta groups, respectively. The most commonly reported unsolicited symptom in the three groups was Upper Respiratory Tract Infection (URTI): Hexa group: 15.4%; Pedia group: 11.9%; Penta group: 13.3%. Grade 3 unsolicited symptoms were reported for 6.7%, 6.2% and 3.6% of subjects in Hexa, Pedia and Penta groups, respectively. The most commonly reported grade 3 unsolicited symptoms were: Hexa group: URTI and Otitis media (1.5%); Pedia group: URTI, Conjunctivitis and Irritability (1.0%); Penta group: URTI (1.0%).

Adverse events of interest: New Onset of Chronic Illness (NOCI) symptoms were reported for 7 subjects (3.6%) in the Hexa group, 11 subjects (5.7%) in the Pedia group and 10 subjects (5.1%) in the Penta group. The two reported symptoms in the Hexa group were Dermatitis atopic (2.6%) followed by Bronchial hyperreactivity (1.0%). In the Pedia group, the symptom reported by more than one subject was Dermatitis atopic (3.6%). In the Penta group, the symptoms reported by more than one subject were Dermatitis atopic (3.6%) and Asthma (1.0%).

Serious adverse events: Non-fatal SAEs from Dose 1 up to 6 months following priming doses were reported for 7 (3.6%) subjects in the Hexa group and Penta group, and 1 (0.5%) subject in the Pedia group. All SAE were considered recovered/resolved without sequelae at the end of the study except one non-causally related event of Choking in a 47-week-old female in the Hexa group which was considered recovered/resolved with sequelae.

Three SAEs occurring in two subjects were considered causally related to primary vaccination by the investigator: An SAE of Lethargy in an 8-week-old female subject in the Hexa group which recovered/resolved after one day without sequelae; 2 SAEs in the same subject: one "Apparent lifethreatening event" and one event of Leukocytosis were observed in a 10-week-old female subject in the Hexa group which recovered/resolved over 1-2 days without sequelae.

No fatal SAEs were reported during the primary vaccination Epoch of the study.

Withdrawals due to AEs /SAEs: Two subjects had adverse events leading to premature discontinuation during the primary vaccination period: one Hexa group subject with an SAE of Lethargy reported after the first vaccination; one Penta group subject with a Non-Serious Adverse Event of Seizure reported after the Month 2 dose.

Overall conclusions that relate to safety : Clinically acceptable safety and reactogenicity profile in the different vaccination groups, aligned with the very well-known profiles of the study vaccines.

3. Rapporteur's overall conclusion

The Rapporteur agrees with the conclusions of the Applicant. The safety results of this study are in line with the approved SmPC for Rotarix. No updates are considered necessary.

PAM fulfilled (all commitments fulfilled) - No further action required