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

Procedure no: EMEA/H/C/000639/P46/090

Note

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

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Table of contents

1. Introduction

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

ROTARIX final report for study Hib-097 in accordance with Article 46 of Regulation (EC) No 1901/2006, in which Rotarix is coadministered.

Study Hib-097 is a Phase III, randomized, multicenter study performed in the US, double-blind for the immunogenicity and consistency evaluation of 3 lots of GSK Biologicals' Haemophilus influenzae type b (Hib) conjugate vaccine Hiberix (PRP-T, GSK) and single blind and controlled for the evaluation of safety and immunogenicity of Hiberix compared to the monovalent Hib vaccine ActHIB (PRP-T, Sanofi Pasteur) and open for comparison with Pentacel (DTaP-IPV/Hib, Sanofi Pasteur) when administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended co-administrations at separate sites.

Following the letter of notification of delay, dated 28 February 2014, the final study report for the study Hib-097 was submitted on 1 December 2016.

1.1. Steps taken for the assessment

Submission date:	01/12/2016
Start of procedure:	26/12/2016
CHMP Rapporteur's preliminary assessment report circulated on:	30/01/2017
CHMP Rapporteur's updated assessment report circulated on:	n/a
CHMP opinion:	23/02/2017

2. Assessment of the post-authorisation measure PAM P46 090

Study Hib-097 (112957) is a confirmatory study performed to support licensure of Hiberix in the US to evaluate consistency and immunogenicity of 3 lots of Hiberix versus ActHIB and Pentacel in a priming epoch at 2, 4, 6, and in a boosting epoch at 15-18 months of age in healthy infants.

The study was initiated on June 18, 2010 and completed on July 17, 2013 and was conducted at 67 sites in the US.

Hiberix is a Haemophilus influenzae type b (Hib) conjugate vaccine composed of H. influenzae type b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) conjugated to inactivated tetanus toxoid (PRP-T).

Rotarix is administered as a 2 dose primary vaccination schedule during the primary epoch of the study.

Methods

Primary objectives (Primary vaccination epoch)

Immunogenicity

Seven co-primary immunogenicity objectives were defined and assessed sequentially. A co-primary objective was only met if the statistical criteria for a particular objective, as well as those for all previous objectives were met. The first co-primary objective was:

- To demonstrate the lot-to-lot consistency of 3 manufacturing lots of Hiberix co-administered with Pediarix, Prevnar13 and Rotarix following 3 primary vaccine doses in terms of immune response to polyribosylribitol phosphate (PRP).

Secondary objectives (Primary vaccination epoch)

Immunogenicity

Seven secondary immunogenicity objectives were defined, and summarised as follows:

- To assess the immune responses to PRP antigen after administration of Hiberix, ActHib or Pentacel;
- To assess the immune responses to other vaccine antigens of the co-adminstered vaccines Pediarix, Prevnar 13 and Engerix-B.

Safety

- To evaluate the safety and reactogenicity of a 3-dose primary vaccination course of Hiberix coadministered with Pediarix, Rotarix and Prevnar13 , that of ActHIB co-administered with Pediarix, Rotarix and Prevnar13 and that of Pentacel co-administered with Prevnar13, Rotarix and Engerix-B.

CHMP comment

The immunogenicity objectives did not include the assessment of immune responses to Rotarix. Hence, no immunogenicity data were generated for Rotarix.

Since Rotarix was co-administrated with other vaccines in the study, the safety data do not relate to Rotarix alone, but to the combination of co-administered vaccines.

Study population

Healthy males or females between, and including, 6 and 12 weeks of age at the time of the first vaccination and born after a gestation period of minimum 36 weeks. Subjects with previous Haemophilus influenza type b, dipthteria, tetanus, pertussis, pneumococcal, rotavirus, poliovirus and hepatitis B diseasesor previous vaccination with Haemophilus influenzae type b, diphtheria, tetanus, pertussis, pneumococcus, rotavirus and/or poliovirus and/or more than one previous dose of hepatitis B vaccine were excluded from the study.

CHMP comment

The study protocol was correct in defining the main contra-indications of Rotarix as exclusion criteria (history of intussusception, history of uncorrected congenital malformation of the gastrointestinal tract that would have predisposed the infant to intussusception,hstory of Severe Combined Immunodeficiency Disease (SCID), acute disease at time of enrolment meaning a rectal temperature of ≥ 38°C.)

Sample size

A total of 4009 subjects were enrolled and received at least one dose of Rotarix.

Study population (Primary Total Vaccinated cohort):			
Number of subjects	***Hiberix***	***ActHIB***	***Pentacel***
Planned, N	3000	500	500
Randomized, N (Total Vaccinated Cohort)	2963	520	520
Completed to Visit 4, n (%)	2625 (88.6)	470 (90.4)	457 (87.9)
Completed to, ESFU CONTACT for primary epoch n (%)	2706 (91.3)	487 (93.7)	472 (90.8)
Demographics	***Hiberix***	***ActHIB***	***Pentacel***
N (Total Vaccinated Cohort)	2963	520	520
Females: Males	1424:1539	271:249	258:262
Mean Age, weeks (SD)	8.6 (1.08)	8.6 (1.13)	8.7 (1.12)
White - Caucasian / European heritage, n (%)	1757 (59.3)	324 (62.3)	314 (60.4)

Number of subjects entered, completed and withdrawn at visit 6 with reason for withdrawal (Booster Total Vaccinated cohort)

	Hiberix	***ActHIB***	***Pentacel***	**Total**
Number of subjects vaccinated	2337	435	400	3172
Number of subjects completed	2270	423	386	3079
Number of subjects withdrawn	67	12	14	93

Study design

The study design was a Phase III, randomized, multicenter and partially double-blind study (double-blind for the 3 Hiberix lots, single blind vs. the comparator ActHIB and open label vs. the comparator Pentacel).

The study groups were as follows:

Investigational Groups: 3 lots of Hiberix

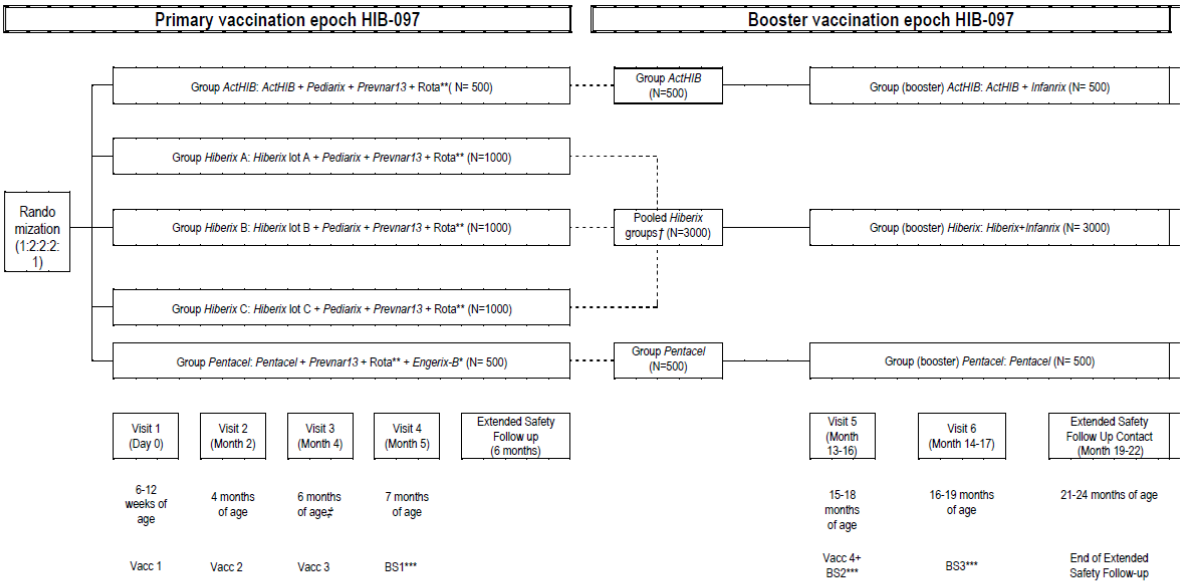
- Group Hiberix A (subjects received 3 doses of Hiberix lot A co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix)
- Group Hiberix B (subjects received 3 doses of Hiberix lot B co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix)
- Group Hiberix C (subjects received 3 doses of Hiberix lot C co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix)

The 3 groups received the same Hiberix lot co administered with Infanrix as booster vaccines.

Control Groups: Active controls

- Group ActHIB (subjects received 3 doses of ActHIB co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix). The group received the same lot of ActHIB co administered with Infanrix as booster vaccines.
- Group Pentacel (subjects received 3 doses of Pentacel co-administered with 3 doses of Prevnar13, 2 or 3 doses of Engerix-B* and 2 doses of Rotarix). The group received the same lot of Pentacel as a booster vaccine.

*If subjects had received a birth dose of Hepatitis B vaccine, then they received 2 doses of Engerix-B and if not they received 3 doses of Engerix-B concomitantly with the other vaccinations.



* *Engerix-B* was not to be given at Month 2 (4 months of age) if a birth dose of Hepatitis B vaccine was administered to the subject
** Rota stands for *Rotarix*. *Rotarix* was administered only at Day 0 and Month 2; The dotted line refers to the period between the primary vaccination epoch and the booster vaccination epoch
† Group *Hiberix* A + Group *Hiberix* B + Group *Hiberix* C (primary vaccination epoch)
‡ Visit 3 was to 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
***A blood sample was to be taken at Visit 4 from all subjects included in the Sub-cohorts *Hiberix* A-PRP, B-PRP and C-PRP, Sub-cohorts *ActHIB* and *Pentacel*. At Visit 5 and Visit 6, a blood sample was to be taken from all subjects included in the Sub-cohorts (booster) *ActHIB* and (booster) *Pentacel* and from subjects included in the Sub-cohort (booster) *Hiberix*.
BS: blood sample; Vacc: vaccination

Study vaccines

Groups	Visit	Vaccine [1]	Route [2]	Site [3]	Side [4]
Primary vaccination epoch					
Groups *Hiberix* A, *Hiberix* B and *Hiberix* C	1,2,3	*Hiberix*	IM	T	R
	1,2,3	*Pediarix*	IM	T	L
	1,2,3	*Prevnar13*	IM	T or D	L
	1,2	*Rotarix*	O		
Group *ActHIB*	1,2,3	*ActHIB*	IM	T	R
	1,2,3	*Pediarix*	IM	T	L
	1,2,3	*Prevnar13*	IM	T or D	L
	1,2	*Rotarix*	O		
Group *Pentacel*	1,2,3	*Pentacel*	IM	T	R
	1,2,3	*Engerix B*	IM	T	L
	1,2,3	*Prevnar13*	IM	T or D	L
	1,2	*Rotarix*	O		
Booster vaccination epoch					
Group (booster) *Hiberix*	5	*Hiberix*	IM	T	R
	5	*Infanrix*	IM	T	L
Group (booster) *ActHIB*	5	*ActHIB*	IM	T	R
	5	*Infanrix*	IM	T	L
Group (booster) *Pentacel*	5	*Pentacel*	IM	T	R

[1]Vaccine/ Control/Co-administered vaccine
[2]Oral (O)/ Intramuscular (IM)
[3]Deltoid (D)/Thigh (T)
[4]Left (L)/ Right (R)

Endpoints

Primary endpoint

Immunogenicity

- none specific for Rotarix

Secondary endpoints

Immunogenicity

- none specific for Rotarix

Safety

- Solicited local and general symptoms
    - Occurrence of specifically solicited local symptoms (pain, redness, and swelling at the injection site) during a 4-day follow-up period (i.e., day of vaccination and 3 subsequent days) following each dose of vaccine
    - Occurrence of specifically solicited general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite) during a 4-day follow-up period (i.e., day of vaccination and 3 subsequent days) following each dose of vaccine
- Unsolicited adverse events
    - Occurrence of all unsolicited symptoms within 31 days following each vaccination.
- Serious adverse events
    - Occurrence of all serious adverse events (SAEs) from Day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever came first.
- Specific adverse events
    - Occurrence of specific adverse events, i.e., new onset chronic diseases (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting ER visits from Day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever came first.

CHMP comment

Diarrhoea and irritability are common adverse reactions associated with Rotarix administration.

Irritability was included in the study protocol as a solicited general adverse event. Diarrhoea was reported as an unsolicited event.

Results

Immunogenicity results

Lot-to-lot consistency:

- The first primary objective regarding the lot-to-lot consistency of anti-PRP GMCs was not met since the two-sided 95% CI of the GMC ratio between Hiberix Lot A and Hiberix Lot B was [0.641, 0.974] and the GMC ratio between Hiberix Lot B and Hiberix Lot C was [1.161, 1.765], and thus were not within the pre-defined [0.67, 1.5] interval.
- For subsequent objectives in the hierarchy, no conclusion can be drawn.

After review of the lot-to-lot consistency clinical data, an in depth review of the quality data pertaining to the Hiberix consistency lots was performed. However, the release and stability results for the three Hiberix lots do not explain the failure to meet the consistency criterion for two pair-wise comparisons.

Additional post-hoc analyses of immunogenicity and safety were performed.

There were no observed differences in terms of lot-to-lot comparisons of fever and injection site reactions between the 3 Hiberix groups, indicating comparability of the safety profiles between the 3 lots and between groups.

All lot-to-lot consistency comparisons evaluated in this study fell within the [0.5; 2.0] interval, reflecting that the anti-PRP GMCs for each clinical lot were within a two-fold difference. Finally, no differences in the safety profiles were observed between the three lots. Therefore, the pre-specified limit to conclude equivalence for anti-PRP might have been too stringent, and the three lots can be considered to be clinically consistent enough to pool data for additional evaluation.

CHMP comment

No immune interferences with co-administered antigens (excluding Rotarix) were observed.

No immunogenicity results were generated for Rotarix in this study.

Safety results

Safety analysis was performed separately for primary vaccination epoch and booster vaccination epoch, using Prim-TVC and Booster-TVC respectively. Since more than 5% of the enrolled and vaccinated subjects were eliminated from the ATP cohort for analysis of safety, a second analysis was performed on the ATP cohort for analysis of safety in the primary and booster vaccination epochs. In addition, the safety analysis for booster epoch was performed on Hiberix group by inclusion status of primary immunogenicity subcohort to evaluate a potential bias due to unblinding part of the primary immunogenicity sub-cohorts in the Hiberix group.

At least one unsolicited AE was observed in 63.4%, 67.3% and 62.3% of subjects in Hiberix, ActHIB and Pentacel groups, respectively, during the 31 day (Day 0-30) post-vaccination period in the primary vaccination epoch. Of these, 10.7%, 12.5% and 9.6% of subjects in Hiberix, ActHIB and Pentacel groups, respectively, reported Grade 3 unsolicited symptoms. Unsolicited AEs that were assessed by the investigator to be causally related to vaccination were reported in 6.5%, 7.9% and 5.8% of subjects in Hiberix, ActHIB and Pentacel groups, respectively.

AEs of specific interest were observed in 108 (3.6%), 22 (4.2%) and 15 (2.9%) of subjects in Hiberix, ActHIB and Pentacel groups, respectively, from Day 0 of primary vaccination to the end of ESFU.

SAEs were reported for 107 (3.6%) subjects in the Hiberix group, 24 (4.6%) subjects in the ActHIB group and 21 (4.0%) subjects in the Pentacel group. Of these, five subjects (four in Hiberix group and one in ActHIB group) had SAEs that were considered by the investigator as related to the study vaccination (Normal sleep myoclonus, Kawasaki, seizure, involuntary muscle contraction in the Hiberix group and possible seizure in the ActHIB group). These SAEs resolved at the end of the primary vaccination epoch.

No fatal SAEs were reported.

The incidence of solicited general symptoms reported during the 4-day (Days 0-3) postvaccination period following each dose and overall for the Primary Total Vaccinated was documented.

Irritability

Irritability was the most frequently reported solicited general symptom in all the groups, reported in 87.0% of subjects in the Hiberix group, in 89.3% of subjects in the ActHIB group and in 87.5% of subjects in the Pentacel group.

Irritability was also the most commonly reported solicited general symptom graded 3 in intensity; reported for 12.3% of subjects in the Hiberix group, 15.9% of subjects in the ActHIB group and 10.7% of subjects in the Pentacel group.

Diarrhoea

Diarrhoea was reported in 1.7 to 2.1 % of doses which seems to suggest a frequency in agreement with the Rotarix SmPC (common: (≥1/100, <1/10).

Intussusception

Two cases of intussusception were reported: 5 months after the second dose of Rotarix in a female in the Pentacel group, and 15 months after the second dose of Rotarix in a male in the Hiberix group. Both subjects were hospitalised and the intussusception resolved 7 days later on treatment with water-soluble therapeutic enema and by surgical intervention, resp. In both cases, the investigator considered that there was no reasonable possibility that the intussusception may have been caused by Rotarix.

CHMP comment

Since Rotarix was co-administered with other vaccines, the reported adverse events cannot be attributed to a single vaccine. The 5 SAE that were considered by the investigator as related to the study vaccination (Normal sleep myoclonus, Kawasaki, seizure, involuntary muscle contraction in the Hiberix group and possible seizure in the ActHIB group) are not reported in the PI of Rotarix but could be attributed to the co-administrated vaccines.

Intussusception is a known adverse reaction of Rotarix but it is agreed with the investigator that the causality of both reported cases is unlikely, notably because of the time delay between vaccine administration and adverse event.

Conclusions

Although the criterion for anti-PRP concentrations ≥1.0 μg/mL was not met post-dose 3, for each consistency lot of Hiberix investigated in this clinical study, at least 95.6% of children achieved post-dose 3 anti-PRP concentrations ≥0.15 μg/mL, indicating that these children attained antibodies associated with short-term protection.

Accordingly, the post-hoc analyses demonstrating that the non-inferiority criterion for post-dose 3 anti-PRP concentrations ≥1.0 μg/mL compared to a vaccine that is current standard of care, such as Pentacel, should be considered as clinically relevant. The relevance of not meeting the non-inferiority criteria for anti-PRP concentrations ≥1.0 μg/ml is unclear since subjects were equally protected at the pre-booster time point.

Most importantly, after a full vaccination schedule >99.0% of subjects in the Hiberix group had achieved long-term protection anti-PRP concentrations of ≥1.0 μg/mL one month after the fourth dose vaccination with a non-inferior response compared to ActHIB and exploratory analyses to Pentacel. Hiberix has consistently demonstrated an acceptable anti-PRP immune response which is similar to other US licensed Hib vaccines (e.g. Pentacel) as evidenced both in this study, as well as in previous clinical trials and confirm the similarity of the anti-PRP responses to Hiberix to both US-licensed control vaccines after the full Hib vaccination schedule has been completed.

With regards to co-administered antigens, the pre-specified statistical criteria for the immunogenicity of co-administered diphtheria, tetanus, pertussis, polio and 13 serotypes of Streptococcal pneumoniae (S. pneumoniae) were met for the primary phase. The co-primary objectives for the primary

vaccination epoch were assessed sequentially. Since the statistical criteria for a particular objective, as well as those for all previous objectives were to be met in order to conclude on them, a formal conclusion on these objectives could not be drawn as the statistical criteria for the first co-primary objective, the lot-to-lot consistency for the Hib lots, could not be established.

The MAH concluded that no changes are needed to the PI of Rotarix since the data are aligned with the known safety profile, are aligned with the information already present in the PI related to concomitant administration of Rotarix with Hib monovalent or combination vaccines, and do not impact the B/R profile of the vaccine.

3. Rapporteur's overall conclusion

In study Hib-097 (112957), immune responses to Rotarix were not assessed, and as Rotarix was co-administered with other vaccines, the safety profile of Rotarix alone could not be investigated.

The study did not meet the predefined statistical criteria for Hiberix lot-to-lot consistency and non-inferiority of Hiberix to ActHIB, and several post-hoc analyses were performed to investigate the root cause thereof.

No immune interferences with co-administered antigens (excluding Rotarix antigens) were observed, and the safety profile appears acceptable and similar to two US-licensed Hib vaccines.

No new safety concerns that could be related to Rotarix were observed in this study.

In conclusion, the results of this study do not alter the B/R profile of Rotarix.

The B/R profile of Rotarix therefore remains positive.

The Rapporteur endorses the conclusions of the MAH.

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