20 November 2014
EMA/174194/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Rotarix

International non-proprietary name: human rotavirus, live attenuated

Procedure No. EMEA/H/C/000639/P46 082

Note

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

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1. Introduction

On 29 August 2014, the MAH submitted a completed paediatric study for Rotarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study Malaria-063 is a standalone study. The main objective of the study was to compare immune responses to the hepatitis B component of an experimental hepatitis B+ malaria (RTS,S/AS01$_E$) vaccine, and compare the antibody levels to that of Engerix-B.

It should be noted that Engerix-B, Synflorix, Infanrix/Hib and Polio Sabin are also administered in the study. Article 46 applications for these concerned vaccines have been sent in parallel to relevant authorities.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation of Rotarix was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- MALARIA-063, Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01$_E$ candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa

2.3.2. Clinical study

MALARIA-063, Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01$_E$ candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa

Description

This was a phase III, multi-center, open, randomized, controlled trial with 11 study groups. Rotarix was one of the vaccines that were co-administered with the experimental vaccine RTS,S/AS01$_E$.

Methods

Objectives

Primary:

Immunogenicity

To demonstrate in terms of antibody response to the HBs antigen (HBsAg), the non-inferiority of RTS,S/AS01$_E$ to a primary vaccination regimen of a licensed hepatitis B vaccine (Engerix-B) integrated into an Expanded Program of Immunization (EPI) regimen.

Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the difference in percent seroprotection below 5% between recipients of licensed hepatitis B vaccine (Engerix-B) and recipients of RTS,S/AS01$_E$ vaccine.

Secondary:

Immunogenicity

- To demonstrate the non-inferiority of antibody responses to rotavirus vaccine when co-administered with *versus* without RTS,S/AS01$_E$ as part of an EPI regimen.

  Criteria for non-inferiority: one month post Dose 2, UL of the 2-sided 95%CI on the geometric mean titer (GMT) ratio (measured with an enzyme-linked immunosorbent assay [ELISA] test), is below a limit of 2 for the rotavirus vaccine when co-administered with versus without RTS,S/AS01E.

- To describe the antibody responses to the rotavirus vaccine (proportion of subjects with anti-RV antibody titers as determined by ELISA ≥ 20 U/ml), measured by ELISA, when the rotavirus vaccine is co-administered with and without RTS,S/AS01E as part of an EPI regimen.

- To describe the antibody responses to the RTS,S/AS01$_E$ vaccine (proportion of subjects with anti-CS antibody titers as determined by ELISA ≥ 0.5 EU/ml), measured by ELISA, when the RTS,S/AS01E vaccine is co-administered with and without rotavirus vaccine as part of an EPI regimen.

A number of other objectives were also included in the study, but as these were not related to Rotarix they will not be assessed within this procedure.

Safety

- Evaluation of the safety profile of the RTS,S/AS01$_E$ candidate malaria vaccine, when co-administered with a rotavirus vaccine or a pneumococcal conjugate vaccine integrated into an EPI regimen.

Study design

Subjects were randomized into 11 study groups in a 1:1:1 : 1:1:1 : 1:1:1 : 3 : 3 ratio (this means five treatment groups of which the three RTS,S/AS01$_E$ groups were randomized to receive three different lots).

Blood sampling:

- Groups RERo[P], RE[RoP] and HERo[P] will have a total of seven blood samples taken: at Visit 1 (screening) and Visit 8, 10, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01$_E$ or Engerix-B).

- Groups REP[Ro] and HEP[Ro] will have a total of 8 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 12, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01$_E$ or Engerix-B).

- Blood for safety evaluation was collected at screening (Visit 1) to ensure healthy children were recruited.

Study population /Sample size

Male or female infants between 8 and 12 weeks of age at the time of first vaccination free of obvious health problems as established by medical history and clinical examination before entering into the study, who were born to a mother seronegative for HBsAg and human immunodeficiency virus (HIV) and for whom the investigator believed that the parents/Legally acceptable representatives (LARs) would comply with the requirements of the protocol. Results of laboratory screening tests for alanine aminotransferase (ALT), creatinine, hemoglobin, platelets count and total white cell count had to be within pre-defined limits. Subjects should not have received previous vaccination with diphtheria tetanus, B. pertussis (whole-cell or acellular), *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, hepatitis B vaccine or rotavirus vaccine. Signed or thumb-printed informed consent was obtained from the parents/LARs of each subject.

A total of 705 subjects (141 per treatment group) were planned to be enrolled in order to have at least 600 evaluable subjects (approximately 120 subjects in each treatment group).

Treatments

Study vaccine: A candidate malaria vaccine RTS,S/AS01$_E$ containing, per 0.5 ml dose, 25 µg RTS,S antigen, 25 µg MPL, 25 µg QS21 with liposomes. Vaccination schedule /site: 0, 1, 2-month schedule; children 8-12 weeks of age at first vaccination received intramuscular (IM) vaccinations into the left anterolateral thigh.

Concomitant vaccines:

Hepatitis B vaccine: Engerix-B. 0, 1, 2-month schedule + booster at Month 50; infants 8-12 weeks of age at first vaccination received IM vaccinations into the left anterolateral thigh.

DTPaHib vaccine: Infanrix/Hib. 0, 1, 2-month schedule + booster at Month 16; infants 8-12 weeks of age at first vaccination received IM vaccinations into the right deltoid.

OPV: Polio Sabin. 0, 1, 2-month schedule; infants 8-12 weeks old at first vaccination received the OPV doses orally.

Pneumococcal conjugate vaccine: Synflorix. 0, 1, 2-month schedule + booster at Month 16; infants received IM vaccinations into the right anterolateral thigh.

Rotavirus vaccine: Rotarix. Two doses given one month apart; infants received the vaccinations orally.

Outcomes/endpoints

Only the endpoints related to the primary vaccination epoch (up to Month 3) and to the safety follow-up epoch (up to Month 8) are described here. Only primary endpoints and secondary endpoints relating to Rotarix are assessed within this procedure. Other endpoints are assessed within other P46 procedures for the other products.

Immunogenicity:

- Non-inferiority of the immune response to the hepatitis B antigen induced by RTS,S/AS01$_E$ vaccine versus a licensed hepatitis B vaccine.
    - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01$_E$ or Engerix-B.

Secondary Outcome/Efficacy Variables:

Immunogenicity:

- Non-inferiority of the immune response to the rotavirus antigen when the rotavirus vaccine is given as part of an EPI regimen with and without RTS,S/AS01$_E$ co-administration.

  Anti-rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.

- Immune response to the rotavirus antigen of the rotavirus vaccine, when given as part of an EPI regimen with and without RTS,S/AS01$_E$ co-administration.

  Anti-rotavirus antibody (IgA) titers one month post Dose 2 of rotavirus vaccine.

- Immune response to the CS antigen of the investigational vaccine RTS,S/AS01$_E$ when given as part of an EPI regimen with and without rotavirus co-administration.

  Anti-CS antibody titers one month post Dose 3 of RTS,S/AS01$_E$.

Safety:

For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro], RERo[P], RE[RoP], HEP[Ro] and HERo[P]), to describe the occurrence of solicited general and local adverse events (AEs) over a 7-day follow-up period (day of vaccination and 6 subsequent days) after the first, second and third doses of RTS,S/AS01$_E$ or a licensed hepatitis B vaccine.

For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro], RERo[P], RE[RoP], HEP[Ro] and HERo[P]), to describe the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after the first, second and third doses of RTS,S/AS01$_E$ or a licensed hepatitis B vaccine.

To describe the occurrence of serious adverse events (SAEs).

- SAEs from the time of first vaccination until 3 month post Dose 1 (Visit 8) of RTS,S/AS01$_E$ or a licensed hepatitis B vaccine.
- SAEs from the time of first vaccination until 8 month post Dose 1 (Visit 9) of RTS,S/AS01$_E$ or a licensed hepatitis B vaccine.
- Fatal SAEs from study start until study end*.
- Potential Immune-mediated disorders (pIMDs) from study start until study end*.

* The current report presents fatal SAEs and pIMDs reported between study start and Month 8. Longer follow-up will be reported in annex study reports.

Statistical Methods

Antibodies against rotavirus vaccine antigen: non-inferiority of rotavirus antigen response

The 95% CI of the anti-rotavirus antibody (IgA) geometric mean titers (GMT) ratio of rotavirus antigen response when co-administered without over co-administered with RTS,S/AS01$_E$ (HERo[P] over RERo[P]) (measured by an ELISA test), was calculated one month post Dose 2 of rotavirus vaccine. If the UL of this CI was below 2, non-inferiority was concluded.

Results

Recruitment / Number analysed

The participant flow is described in Figure 2. The number of subjects in the different groups is shown in Table 28 (TVC).

Figure 2 Consort, according to vaccination with RTS,S/AS01E or Engerix-B (pooled lot groups and pooled groups for primary vaccination) (Month 3)

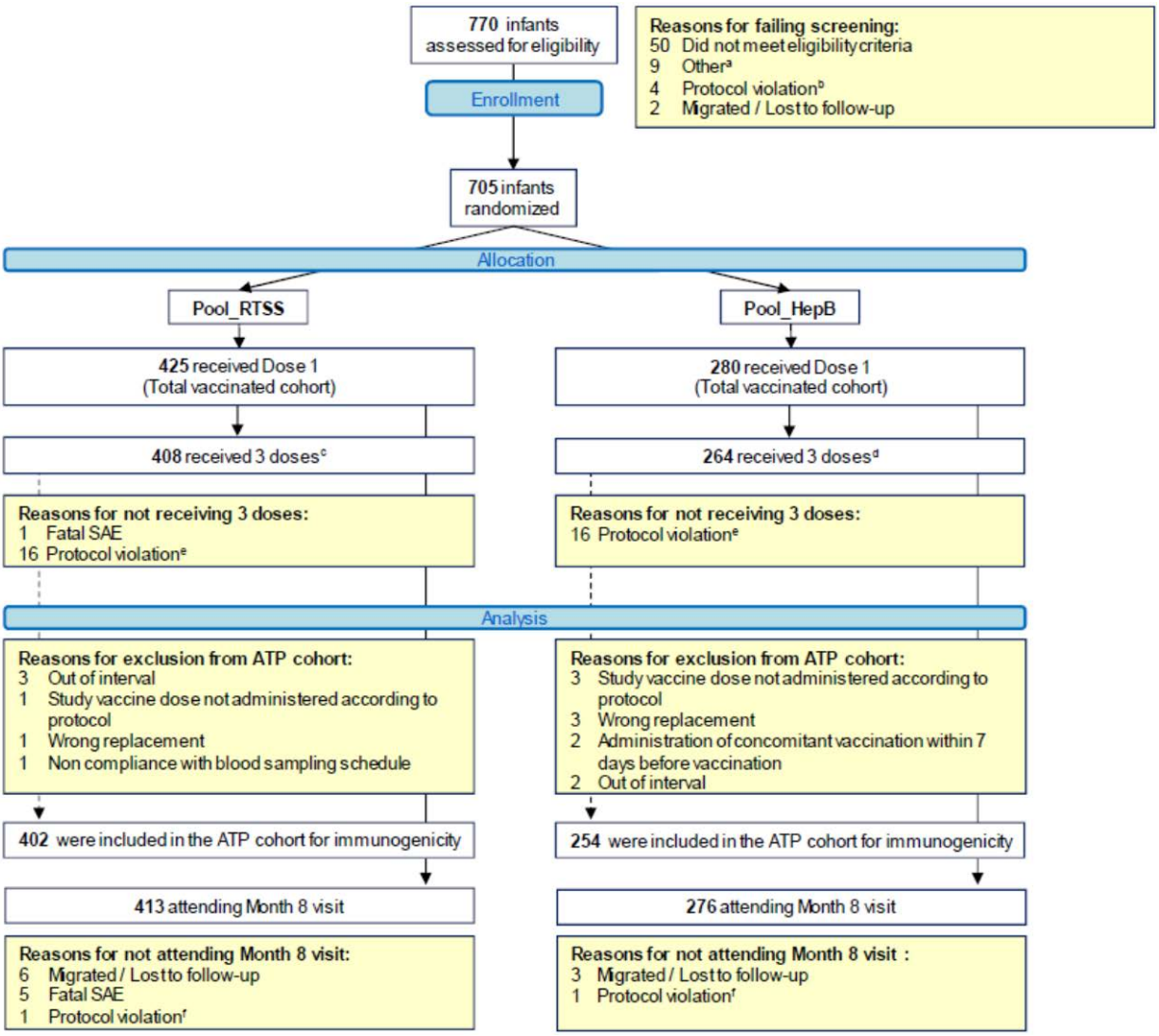

Table 28 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort)

	pool_RTSS *INFANRIX*/HIB VACCINE N = 425		pool_RTSS *POLIO SABIN* N = 425		pool_RTSS *ROTARIX* VACCINE N = 425		pool_RTSS RTS,S AS01E N = 425		pool_RTSS *SYNFLORIX* VACCINE N = 425		Pool_HepB *ENGERIX* N = 280		Pool_HepB *INFANRIX*/HIB VACCINE N = 280		Pool_HepB *POLIO SABIN* N = 280		Pool_HepB *ROTARIX* VACCINE N = 280		Pool_HepB RTS,S AS01E N = 280	
Total number of doses received	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	17	4.0	0	0.0	0	0.0	2	0.7	0	0.0	0	0.0	16	5.7	278	99.3
1	17	4.0	17	4.0	1	0.2	17	4.0	17	4.0	16	5.7	16	5.7	16	5.7	1	0.4	0	0.0
2	0	0.0	0	0.0	407	95.8	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	263	93.9	0	0.0
3	408	96.0	408	96.0	0	0.0	408	96.0	407	95.8	262	93.6	264	94.3	264	94.3	0	0.0	2	0.7
Any	425	100	425	100	408	96.0	425	100	425	100	278	99.3	280	100	280	100	264	94.3	2	0.7

	Pool_HepB *SYNFLORIX* VACCINE N = 280	
Total number of doses received	n	%
0	1	0.4
1	15	5.4
2	0	0.0
3	264	94.3
Any	279	99.6

pool_RTSS = All study groups with RTS,S/AS01E vaccine (REP[Ro]_1 + REP[Ro]_2 + REP[Ro]_3 + RERo[P]_1 + RERo[P]_2 + RERo[P]_3 + RE[RoP]_1 + RE[RoP]_2 + RE[RoP]_3)

Pool_HepB = All study groups with Engerix-B vaccine (HEP[Ro]+ HERo[P])

N = number of subjects in each group 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

Efficacy results

Only results relating to Rotarix will be summarised and assessed in this assessment report.

Immune response to rotavirus vaccine antigens (ELISA) according to co-administration vaccine regimen

ATP cohort for immunogenicity

1. Anti-rotavirus antibody **seropositivity rates and GMCs** assessed by ELISA, per co-administration vaccine regimen, are presented in table 90.

Table 90 Anti-RV seropositivity rates and GMCs following *Rotarix* vaccination in co-administration with RTS,S/AS01$_E$ or *Engerix*-B, Month 3 (ATP cohort for immunogenicity)

				≥ 20 U/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-rotavirus IgA antibody	RERo[P]	PII(M3)	120	44	36.7	28.1	45.9	24.9	19.3	32.0	<20.0	1499.0
	HERo[P]	PII(M3)	116	43	37.1	28.3	46.5	27.6	20.8	36.5	<20.0	3386.0

RERo[P] = RTS,S/AS01$_E$ + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
HERo[P] = *Engerix*-B + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PII(M3) = Post Dose 2, Month 3

2. Non-inferiority of the rotavirus vaccine antibody response assessed by ELISA, per co-administration vaccine regimen, is presented in table 91.

Table 91 **Non-inferiority assessment of rota antibody responses to *Rotarix* when co-administered with RTS,S/AS01$_E$ vs *Engerix*-B, GMC ratios, Month 3 (ATP cohort for immunogenicity)**

				GMC ratio (HERo[P] / RERo[P])		
HERo[P]		RERo[P]			95% CI	
N	GMC	N	GMC	Value	LL	UL
116	27.6	120	24.9	1.11	0.76	1.61

RERo[P] = RTS,S/AS01$_E$ + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
HERo[P] = *Engerix*-B + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Assessor's comment

The immunogenicity results relating to the rotavirus antigen are well in agreement with previously reported results.

Statistical non-inferiority was demonstrated since the UL of the 95% CI of the GMC ratios of rotavirus IgA titers (HERo[P] over RERo[P]) was 1.61, which was below the predefined limit of 2.

3. Immune response to the anti-CS antigen of RTS,S/AS01$_E$ when given with and without rotavirus vaccine

One month post Dose 3 of RTS,S/AS01$_E$, anti-CS GMT was 205.5 EU/ml when RTS,S/AS01E was co-administered with EPI vaccines (DTPa/Hib + OPV) alone (RE[RoP]) and 188.5 EU/ml when RTS,S/AS01$_E$ was co-administered with a rotavirus vaccine and EPI vaccines (DTPa/Hib + OPV) (RERo[P]) (ATP cohort for immunogenicity), as presented in Table 79.

Table 79 **Anti-CS seropositivity rates and GMTs per co-administration regimen, Month 3 (ATP cohort for immunogenicity)**

				≥ 0.5 EU/ml				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-CS antibody	REP[Ro]	SCREENING	141	91	64.5	56.0	72.4	0.7	0.6	0.9	<0.5	5.8
		PIII(M3)	141	141	100	97.4	100	142.2	116.4	173.7	0.9	1855.4
	RERo[P]	SCREENING	124	87	70.2	61.3	78.0	0.8	0.7	0.9	<0.5	15.2
		PIII(M3)	123	123	100	97.0	100	188.5	156.5	227.0	4.2	1443.7
	RE[RoP]	SCREENING	137	80	58.4	49.7	66.7	0.6	0.6	0.8	<0.5	14.9
		PIII(M3)	136	135	99.3	96.0	100	205.5	167.3	252.5	<0.5	1836.1
	HEP[Ro]	SCREENING	136	84	61.8	53.0	70.0	0.6	0.6	0.7	<0.5	6.5
		PIII(M3)	135	16	11.9	6.9	18.5	0.3	0.3	0.3	<0.5	263.5
	HERo[P]	SCREENING	118	75	63.6	54.2	72.2	0.7	0.6	0.8	<0.5	4.2
		PIII(M3)	118	12	10.2	5.4	17.1	0.3	0.3	0.4	<0.5	145.1

REP[Ro] = RTS,S/AS01$_E$ + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Synflorix*) + *Rotarix* staggered
RERo[P] = RTS,S/AS01$_E$ + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
RE[RoP] = RTS,S/AS01$_E$ + EPICoAd (*Infanrix*/Hib + *Polio Sabin*) + staggered (*Synflorix* + *Rotarix*)
HEP[Ro] = *Engerix*-B + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Synflorix*) + *Rotarix* staggered
HERo[P] = *Engerix*-B + EPICoAd (*Infanrix*/Hib + *Polio Sabin* + *Rotarix*) + *Synflorix* staggered
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
SCREENING = Pre-vaccination
PIII(M3) = Post Dose 3, Month 3

Assessor's comment

A formal statistical comparison of both groups (RE[RoP] versus RERo[P]) has not been performed. The anti-CS GMT CI are overlapping and therefore the lower mean value after co-administration of Rotarix is only suggestive of a potential interference of Rotarix on the anti-CS response of RTS,S/AS01$_E$.

Safety results

Summary

Safety

Summary of safety according to co-administration vaccine regimen

- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose the incidence overall doses of solicited local symptoms was as follows:
    - The incidence of **pain** at the site of any co-administered vaccine was **11.6%** when RTS,S/AS01$_E$ was administered with EPI vaccines alone (RE[RoP]), **13.2%** when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]) and **9.4%** when co-administered with a rotavirus vaccine and EPI vaccines (**RERo[P]**). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of pain was **10.5%** and when co-administered with a rotavirus vaccine and EPI vaccines (**HERo[P]**), the incidence of pain was **6.0%**. No Grade 3 pain was reported in all other groups.
    - The incidence of **redness** at the site of any co-administered vaccine was 0.7% when RTS,S/AS01$_E$ was administered with EPI vaccines alone (RE[RoP]) and 0.7% when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]). No redness was reported when RTS,S/AS01$_E$ was co-administered with a rotavirus vaccine and EPI vaccines (**RERo[P]**). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of redness was 1.0% and when co-administered with a rotavirus vaccine and EPI vaccines (**HERo[P]**), the incidence of redness was 0.3%. No Grade 3 redness was reported in all groups.
    - The incidence of **swelling** at the site of any co-administered vaccine was 2.1% when RTS,S/AS01$_E$ was administered with EPI vaccines alone (RE[RoP]), 2.1% when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]) and 1.0% when co-administered with a rotavirus vaccine and EPI vaccines (**RERo[P]**). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of swelling was 3.6% and when co-administered with a rotavirus vaccine and EPI vaccines (**HERo[P]**), the incidence of swelling was 0.8%. No Grade 3 swelling was reported in all groups.
- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose the solicited general symptoms with highest incidence overall doses were:
    - temperature (26.4%) and irritability/fussiness (7.8%) in REP[Ro] group.
    - temperature (13.7%) and irritability/fussiness (5.3%) in **RERo[P]** group.
    - temperature (14.2%) and irritability/fussiness (7.8%) in RE[RoP] group.
    - temperature (13.9%) and irritability/fussiness (5.9%) in HEP[Ro] group.

- temperature (7.8%) and irritability/fussiness (1.6%) in **HERo[P]** group.

All other solicited general symptoms (drowsiness and loss of appetite) were reported after ≤2.4% of vaccine dose.

- Grade 3 temperature (> 39.0°C) was reported after 1.2% of doses in the REP[Ro] group, 0.7% of doses in the RE[RoP] group, 0.2% of doses in the HEP[Ro] group and 1.0% of doses in the **HERo[P]** group. No other Grade 3 solicited general symptoms were reported.
- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose, the solicited general symptoms related to vaccination with highest incidence overall doses were:
  - temperature (20.0%) and irritability/fussiness (3.3%) in REP[Ro] group.
  - temperature (10.7%) and irritability/fussiness (2.8%) in **RERo[P]** group.
  - temperature (9.7%) and irritability/fussiness (2.6%) in RE[RoP] group.
  - temperature (9.7%) and irritability/fussiness (1.7%) in HEP[Ro] group.
  - temperature (5.5%) and irritability/fussiness (0.5%) in **HERo[P]** group.

  All other solicited general symptoms related to vaccination were reported after ≤0.5% of vaccine dose.
- Over a 30-day follow-up period (day of vaccination and 29 subsequent days), at least one unsolicited AE was reported by 85.2%, 81.0% and 85.1% in REP[Ro], RERo[P] and RE[RoP] groups and 85.1% and 75.5% in HEP[Ro] and HERo[P] groups. **Malaria, gastroenteritis, bronchitis, rhinitis,** and **pharyngitis** were the most frequently reported unsolicited AE in each groups.
- The percentage of subjects reporting at least one Grade 3 unsolicited AE within 30 days post vaccination was 0.7%, 1.4% and 1.4% in REP[Ro], RERo[P] and RE[RoP] groups and 0.7% and 1.4% in HEP[Ro] and HERo[P] groups. **Bronchopneumonia** and **gastroenteritis** and were the most frequently reported Grade 3 unsolicited AEs (3 and 2 subjects respectively).
- The percentage of subjects reporting at least one unsolicited AE related to vaccination within 30 days post vaccination was 0.7%, 0.7% and 3.5% in REP[Ro], RERo[P] and RE[RoP] groups and 2.1% and 4.3% in HEP[Ro] and HERo[P] groups. **Pyrexia** was the most frequently reported unsolicited AEs related to vaccination in each groups (1 subject in REP[Ro] and RERo[P] groups, 5 subjects in RE[RoP] group, 3 subjects in HEP[Ro] group and 6 subjects in HERo[P] group).
- From Dose 1 until 8 months post Dose 1 (Visit 9), the percentage of subjects reporting at least one SAE was 0.7%, 4.9% and 5.0% in REP[Ro], RERo[P] and RE[RoP] groups and 2.1% and 3.6% in HEP[Ro] and HERo[P] groups. **Bronchopneumonia** and **gastroenteritis** were the most frequently reported SAEs (6 and 5 subjects respectively). None of the SAEs were judged to be related to vaccination.
- Over a 30-day follow-up period (day of vaccination and 29 subsequent days), 4 fatal SAEs were reported in 2 subjects vaccinated with RTS,S/AS01$_E$ vaccine (1 subject in REP[Ro] and 1 subject in RE[RoP]). None of these fatal SAEs were judged to be related to vaccination.

- From the start of the study until Month 8 (Visit 9), there were 8 fatal SAEs reported in 5 subjects vaccinated with RTS,S/AS01$_E$ vaccine (1 subject in REP[Ro], 2 subjects in RERo[P] and 2 subjects in RE[RoP]). None of these fatal SAEs were judged to be related to vaccination.
- No potential immune mediated disorders were reported from the start of the study until Month 8 (Visit 9).

Assessor's comment

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

2.3.3. Discussion on clinical aspects

The current study was a study of an experimental malaria vaccine, and Rotarix was one of several vaccines included to study concomitant vaccination. A total of 425 subjects received at least one dose of Rotarix with the RTS,S vaccine and 280 subjects received at least one dose of Rotarix with Engerix-B. Thus, the addition of these results to the already presented extensive amount of data does not impact on the benefit/risk balance of Rotarix. The immune responses did not cause concern of lack of efficacy, and the safety dada did not give rise to new safety concerns. No further regulatory action is considered necessary.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The article 46 paediatric submission is considered fulfilled and no further regulatory action is needed. The provided data do not cause concern regarding efficacy or safety for Rotarix.

The benefit/risk balance of Rotarix therefore remains positive.