London, 15 November 2018
EMA/902091/2019
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

rotavirus vaccine, live

Procedure no: EMEA/H/C/000639/P46/093

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 2018, the MAH submitted a completed paediatric study, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The initial due date of this submission was 18 September 2016. A letter informing of delay of this submission was sent to EMA on 16 September 2016, informing the EMA of the delay in the availability of the Clinical Study Report within 6 months from the last subject last visit, and hence a delay in this submission.

Study Hib-MenCY-TT-016 (112931) is a phase IIIb, open, randomised, controlled, multicentre study conducted in the US to assess the co-administration of Rotarix with Hib-MenCY-TT (MenHibrix, GSK) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GSK) with Hib-MenCY-TT at 12 to 15 months of age.

No changes to the Product Information of Rotarix are proposed.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study Hib-MenCY-TT-016 (112931) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The formulation of Rotarix administered was the lyophilised formulation.

2.3. Clinical aspects

2.3.1. Introduction

Following the introduction of Hib-conjugate and S. pneumoniae conjugate vaccines in the routine infant immunization schedule in the US, there has been a dramatic reduction in the incidence of diseases caused by Hib and S. pneumoniae. Neisseria meningitidis has become a leading cause of bacterial meningitis in the US, with serogroups B, C and Y being responsible for the majority of cases.

In 2013, the Advisory Committee on Immunization Practices (ACIP) reviewed the burden of meningococcal disease among infants and children aged 0–59 months. The number of US infants at increased risk for meningococcal disease is small (estimated at 3,000–5,000), making a targeted high-risk vaccination policy feasible and reasonable given the potential increased risk in these infants. In infants, not at increased risk for meningococcal disease, rates of this disease have declined in all age groups since 2000 and in 2011. The overall rate of meningococcal disease was at a historic low of 0.21 per 100,000 population. In the US, during 1993–2011, average annual rates of meningococcal disease were higher among children aged 0 through 59 months (1.74 per 100,000 population) than in adolescents aged 11 through 19 years (0.57 per 100,000). The epidemiology of meningococcal disease is dynamic, and rates of disease could increase in the future, requiring a reassessment of immunization strategy.

The Hib-MenCY-TT conjugate vaccine (MenHibrix) using Tetanus Toxoid (TT) as the carrier protein for the Hib and the meningococcal components was developed to be administered as a 4-dose vaccination series at 2, 4, 6 and 12-15 months of age. On June 14th, 2012, MenHibrix was approved by the FDA for use in infants. This vaccine is anticipated to allow vaccination against serogroups C and Y meningococcal disease without increasing the number of injections required to fully vaccinate a child according to the routine childhood schedule in the US.

The MAH submitted a final report for Study Hib-MenCY-TT-016 (112931) which aims to demonstrate the acceptability of the co-administration of Rotarix, Prevnar 13 and Havrix with GSK's Hib-MenCY-TT vaccine. Rotarix was administered to both study groups at month 0 and 2.

The first primary objective was to demonstrate the non-inferiority in terms of anti-PRP concentration of a 4-dose vaccination course of Hib-MenCY-TT co-administered with Prevnar 13 and Havrix compared to a 3-dose vaccination course of PedvaxHIB co-administered with Prevnar 13 and Havrix. The other primary confirmatory objectives was to demonstrate the non-inferiority in terms of Rotarix IgA GMCs, S. pneumoniae GMCs and anti-HAV concentrations.

The study was initiated on 19-February-2014 and completed on 18-March-2016. The data lock point was on 16-March-2018.

2.3.2. Clinical study

Study Hib-MenCY-TT-016 (112931): A phase IIIb, open, randomized, controlled, multicenter study to assess the coadministration of Rotarix (GlaxoSmithKline Biologicals') with Hib-MenCY-TT (GlaxoSmithKline Biologicals' Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals') with Hib-MenCY-TT at 12 to 15 months of age.

Methods

Objectives

Before concluding on the primary objectives for Rotarix, Prevnar 13, and Havrix, the following objective was to be reached:

Co-primary objectives

- To demonstrate the non-inferiority of a four dose vaccination course of Hib-MenCY-TT coadministered with Prevnar 13 and Havrix compared to a three dose vaccination course of PedvaxHIB co-administered with Prevnar 13 and Havrix in terms of anti-PRP concentration.

  Criterion for non-inferiority (1 month post dose 4): Lower limit of the standardized asymptotic 95% CI for the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-PRP concentrations ≥1.0 µg/mL is ≥-10% (clinical limit for non-inferiority).

To conclude independently on the following primary objectives of Epoch 001 or Epoch 002, a Bonferroni correction was to be used to evaluate these objectives (2.5% two-sided for Epoch 001 and 2.5% two-sided for Epoch 002). As per the hierarchical procedure, the first primary objective would have to be reached to conclude on the second primary objective of that Epoch.

Epoch 001:

- To demonstrate the non-inferiority of a 2-dose primary vaccination course of Rotarix coadministered with Hib-MenCY-TT, Pediarix and Prevnar 13 compared to that of Rotarix coadministered with PedvaxHIB, Pediarix and Prevnar 13 in terms of Rotarix IgA GMCs.

  Criteria for non-inferiority (2 months post-dose 2): Lower limit of the two-sided standardized asymptotic 97.5% CI on the ratio of anti-rotavirus IgA GMC (HibCY group over PedHIB group) ≥0.5 (clinical limit for non-inferiority).

- To demonstrate the non-inferiority of a 3-dose primary vaccination course of Prevnar 13 co administered with Hib-MenCY-TT, Rotarix and Pediarix compared to that of Prevnar 13 coadministered with PedvaxHIB, Rotarix and Pediarix in terms of S. pneumoniae GMCs.

  Criteria for non-inferiority (1 month after the third dose): Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is ≥0.5 (clinical limit for non-inferiority).

Epoch 002:

- To demonstrate the non-inferiority of a 2-dose vaccination course of Havrix when the first dose is co-administered with Hib-MenCY-TT and Prevnar 13 at 12 to 15 months of age compared to that of Havrix when the first dose is co-administered with PedvaxHIB and Prevnar 13 at 12 to 15 months of age.

  Criteria for non-inferiority (1 month after the second Havrix vaccination): Lower limit of the two-sided standardized asymptotic 97.5% CI on the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-HAV concentrations ≥15 mIU/mL is ≥-10% (clinical limit for non-inferiority).

- To demonstrate the non-inferiority of a 4-dose vaccination course of Prevnar 13 co-administered with Hib-MenCY-TT and Havrix compared to that of Prevnar 13 co-administered with PedvaxHIB and Havrix in terms of S. pneumoniae GMCs.

  Criteria for non-inferiority (1 month after the fourth dose): Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is ≥0.5 (clinical limit for non-inferiority).

Secondary objectives

Immunogenicity:

- To evaluate the anti-PRP immune response 2 months post-dose 2 (PedHIB group only), 1 month post-dose 3 and 1 month post-dose 4 (HibCY group only) after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate hSBA-MenC and hSBA-MenY immune response 1 month post-dose 3 and 1 month post-dose 4 after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate anti-rotavirus IgA immune response 2 months after the 2nd dose of Rotarix vaccination.

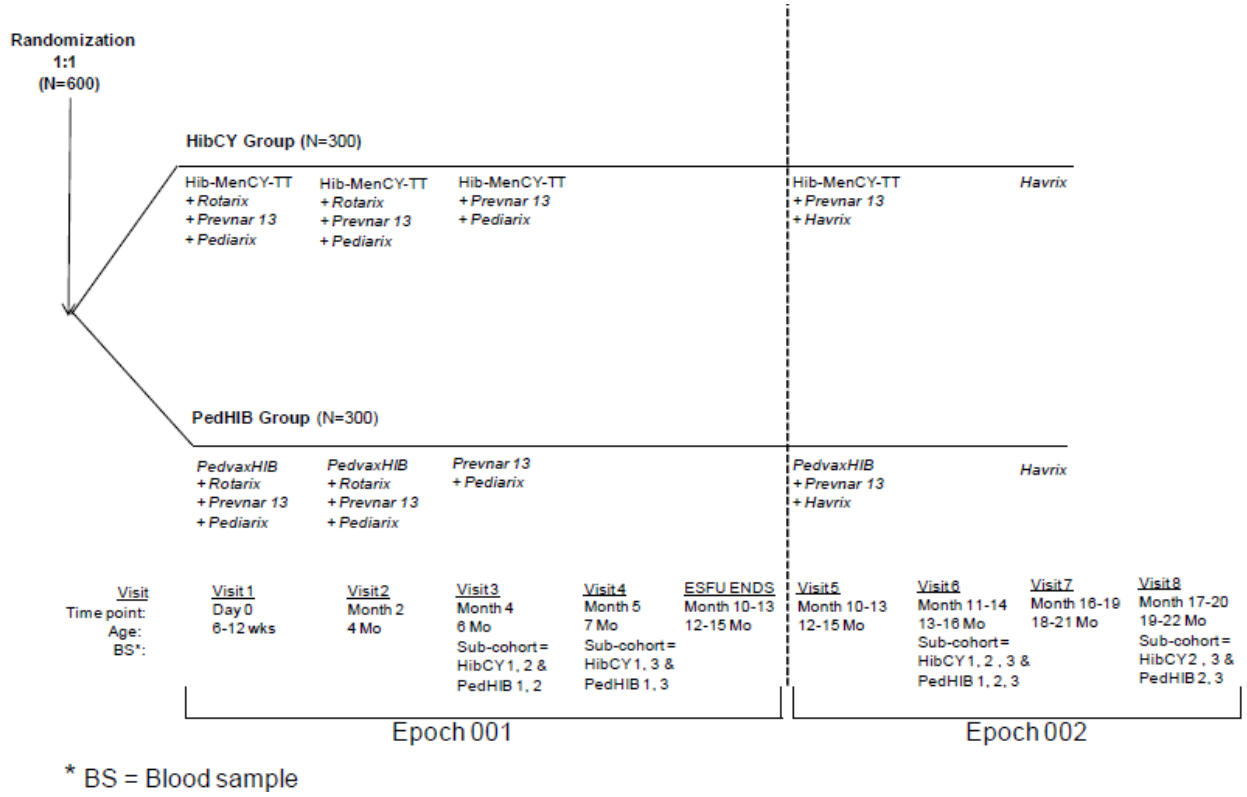
- To evaluate anti-S. pneumoniae immune response above thresholds 1 month post-dose 3 and 1 month post-dose 4 after Prevnar 13 vaccination.
- To evaluate anti-HAV immune response 1 month post-dose 1 and 1 month post-dose 2 after Havrix vaccination.

Safety:

- To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Rotarix, Pediarix and Prevnar 13 and of PedvaxHIB co-administered with Rotarix, Pediarix and Prevnar 13.
- To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Havrix and Prevnar 13 and of PedvaxHIB co-administered with Havrix and Prevnar 13.

Study design

Study Hib-MenCY-TT-016 (112931) is a Phase IIIB, open-label, randomized, controlled, multi-centric, single-country study with two parallel groups as presented in the figure below.



The duration of the study was 17-20 months:

- Epoch 001: starting at Visit 1 (Day 0) and ending at the day preceding Visit 5 (Month 10-13, fourth dose vaccination)
- Epoch 002: starting at Visit 5 (Month 10-13) and ending at Visit 8 (Month 17-20, 31 days after the 2nd Havrix vaccination).

Study population /Sample size

The study population involved healthy infants between, and including, 6 and 12 weeks years of age at the time of the first vaccination, born after a gestation period of 37 weeks, who had not received vaccination against Neisseria meningitidis, Haemophilus influenzae type b, diphtheria, tetanus, pertussis, rotavirus, pneumococcus, hepatitis A and/or poliovirus and who had not received more than one previous dose of hepatitis B vaccine which had to be administered at least 30 days prior to enrolment.

Subjects with history of intussusceptions or uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusceptions were excluded from enrolment.

Blinding

This study was conducted in an open manner, since the presentation and number of vaccines to be administered per visit differed for each group. The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Treatments

600 subjects were enrolled and randomized 1:1 to either HibCY or PedHIB groups:

- **HibCY group**: Hib-MenCY-TT, Prevnar 13 + Pediarix + **Rotarix at Months 0, 2**; Hib-MenCY-TT, Prevnar 13 + Pediarix at Month 4; Hib-MenCY-TT, Prevnar 13 + Havrix at Month 10-13; and Havrix at Month 16-19.
- **PedHIB group**: PedvaxHIB, Prevnar 13 + Pediarix + **Rotarix at Months 0, 2**; Prevnar 13 + Pediarix at Month 4; PedvaxHIB, Prevnar 13 + Havrix at Month 10-13; and Havrix at Month 16-19.

At enrolment, the subjects were associated to one of the three blood sampling schedules:

- The first 200 subjects were enrolled in the blood sample sub-cohort 3 with a blood draw one month post-third dose at Month 5 (Visit 4), one month post-fourth dose (Visit 6) and one month after the second Havrix vaccination (Visit 8).
- The next 200 subjects were enrolled in the blood sample sub-cohort 2 with a blood draw before the third vaccination dose at Month 4 (Visit 3), one month post-fourth dose (Visit 6) and one month after the second Havrix vaccination (Visit 8)
- The last 200 subjects were enrolled in the blood sample sub-cohort 1 with a blood draw before the third vaccination dose at Month 4 (Visit 3), one month post-third dose at Month 5 (Visit 4) and one month post-fourth dose (Visit 6).

Outcomes/endpoints

Primary endpoints

Immunogenicity with respect to the components of the co-administered vaccines

- Anti-PRP antibody concentrations ≥1.0 µg/mL (1 month post-dose 4 HibCY group, 1 month post-dose 3 PedHIB group).

- Anti-rotavirus serum IgA GMCs (2 months post-dose 2 of Rotarix)
- Anti-HAV antibody concentrations ≥15 mIU/mL (1 month post-dose 2 of Havrix)
- Anti-S. pneumoniae GMCs (1 month post-dose 3)
- Anti-S. pneumoniae GMCs (1 month post-dose 4)

Secondary endpoints

Immunogenicity

Immunogenicity with respect to the components of the investigational vaccine:

- Anti-PRP antibody concentrations ≥0.15 μg/mL and GMCs (2 months post-dose 2 [PedHIB group only], 1 month post-dose 3 and 1 month post-dose 4 [HibCY group only]).
- Anti-PRP antibody concentrations ≥1.0 μg/mL 2 months post-dose 2 (PedHIB group only) and 1 month post-dose 3 (HibCY group only).
- hSBA-MenC and hSBA-MenY antibody titres ≥1:8, ≥1:16, ≥1:32 and GMTs (1 month postdose 3 and 1 month post-dose 4).

Immunogenicity with respect to the components of the co-administered vaccines:

- Anti-rotavirus IgA antibody concentrations ≥20 U/mL (2 months post-dose 2 of Rotarix)
- Anti-HAV antibodies ≥15 mIU/mL and GMCs (1 month post-dose 1 of Havrix)
- Anti-HAV GMCs (1 month post-dose 2 of Havrix)
- S. pneumoniae antibody concentrations ≥0.15 µg/mL, ≥0.26 µg/mL and ≥0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in Prevnar 13 (1 month post-dose 3 and 1 month post-dose 4).

Safety and Reactogenicity

- Occurrence of each solicited adverse event 4 days (Day 0 to Day 3) after all vaccines post-primary and post-fourth dose.
    - Local symptoms
    - General symptoms
- Occurrence of unsolicited symptoms 31 days (Day 0 to Day 30) after all vaccines post-primary and post-fourth dose.
- Occurrence throughout the study of SAEs from Day 0 to study end.

Statistical Methods

Demographic characteristics (age at each dose in weeks, gender, geographical ancestry, ethnicity, height [cm], weight [kg], body mass index [BMI in kg/m²] at first dose, subcohort, vaccination history, center), timing between Hib-MenCY-TT vaccine constitution and vaccination at each dose, cohort description and withdrawal status were summarised by group using descriptive statistics:

- Frequency tables were generated for categorical variables such as geographical ancestry or timing between Hib-MenCY-TT vaccine constitution and vaccination;

- Mean, median and standard error were provided for continuous data such as age.
- The distribution of subjects enrolled among the study sites was tabulated as a whole and per group.

Analysis of immunogenicity:

The primary analysis of immunogenicity was based on the ATP cohorts for immunogenicity. If, for any vaccine group, the percentage of enrolled subjects with serological results excluded from this ATP cohort was more than 5%, a second analysis based on the Total Vaccinated Cohort was performed to support the ATP analysis.

Within groups assessment

For each treatment group and for each antibody assessed at the corresponding timepoint:

- Percentage of subjects with antibody concentration or titre ≥ endpoint specific threshold value with exact 95% confidence intervals (CIs) were calculated.
- Geometric Mean antibody Concentrations or Titres (GMCs or GMTs) with 95% CIs were tabulated.

The above analyses were performed by gender and geographical ancestry. In addition, antibody concentrations or titres were evaluated using reverse cumulative curves (RCC) for each antibody assessed.

Between groups assessment

Non-inferiority of Hib-MenCY-TT post-dose 4 when co-administered with Prevnar 13 and Havrix compared to PedvaxHIB post-dose 3 co-administered with Prevnar 13 and Havrix with respect to anti-PRP was evaluated through:

- Computation of the asymptotic standardized 95.0% CIs for the difference in the percentage of subjects with anti-PRP ≥ 1.0 µg/ml (HibCY group minus the PedHIB group) 1 month after the 4th dose of Hib-MenCY-TT vaccination and 1 month after the 3rd dose of PedvaxHIB vaccination. Indication of non-inferiority of Hib-MenCY-TT co-administered with Prevnar 13 and Havrix versus PedvaxHIB co-administered with Prevnar 13 and Havrix was to be a lower limit of the 95.0% CI greater than or equal to the pre-defined clinical limit of -10%.

Non-inferiority of Rotarix when co-administered with Hib-MenCY-TT compared to Rotarix coadministered with PedvaxHIB with respect to anti-Rota IgA was evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti-Rota IgA (HibCY group over the PedHIB group) 2 months after the 2nd dose of Rotarix vaccination. Indication of non-inferiority of Rotarix co-administered with Hib-MenCY-TT versus Rotarix coadministered with PedvaxHIB was to be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

Non-inferiority of Prevnar 13 when co-administered with Hib-MenCY-TT compared to Prevnar 13 coadministered with PedvaxHIB with respect to anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F was evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (HibCY group

over the PedHIB group) 1 month after the 3rd dose of Prevnar 13 vaccination. Indication of noninferiority of Prevnar 13 co-administered with Hib-MenCY-TT versus Prevnar 13 co-administered with PedvaxHIB was to be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

Non-inferiority of Havrix when co-administered with Hib-MenCY-TT compared to Havrix coadministered with PedvaxHIB with respect to anti-HAV was evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the difference in the percentage of subjects with anti-HAV ≥15 mIU/mL (HibCY group rate minus PedHIB group rate) one month after primary vaccination. Indication of non-inferiority of Hib-MenCY-TT was to be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of -10%.

Non-inferiority of Prevnar 13 when co-administered with Hib-MenCY-TT compared to Prevnar 13 coadministered with PedvaxHIB with respect to anti- S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F were to be evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (HibCY group over the PedHIB group) 1 month after the 4th dose of Prevnar 13 vaccination. Indication of non-inferiority of Prevnar 13 co-administered with Hib-MenCY-TT versus Prevnar 13 coadministered with PedvaxHIB was to be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

Results

Recruitment/ Number analysed

Of the 600 subjects who were vaccinated in the 27 study centers in the US, 462 completed the study (232 in HibCY group and 230 in group PedHIB group). A total of 138 subjects (65 in HibCY group and 73 in group PedHIB group) were withdrawn from the study. The main reasons for withdrawal were: consent withdrawal (not due to an adverse event), migrated/moved from study area, and lost to follow-up (subjects with incomplete vaccination course).

Table: Study population (Total vaccinated cohort)

Number of subjects	HibCY group	PedHIB group	Total
Planned, N	300	300	600
Randomised, N (Total Vaccinated Cohort)	297	303	600
Completed to visit 8 (Month 17 to 20), n (%)	232 (78.1)	230 (75.9)	462 (77.0)
Demographics	HibCY group	PedHIB group	Total
N (Total Vaccinated Cohort)	297	303	600
Females: Males	148:149	140:163	288:312
Mean Age, weeks (SD)	8.6 (1.1)	8.6 (1.1)	8.6 (1.1)
Median Age, weeks (minimum, maximum)	8 (6, 12)	8 (6, 12)	8 (6, 12)
White - Caucasian / European Heritage, n (%)	201 (67.7)	218 (71.9)	419 (69.8)

The first subject was enrolled in the study on 19-February-2014 and the last study visit was on 18-March-2016.

Baseline data

Epoch 001

The demographic profile for the two groups for the Rota ATP cohort for analysis of immunogenicity with respect to mean age, gender, ethnicity and geographical ancestry was comparable:

- The mean age for the HibCY and PedHIB groups at dose 1, dose 2 and dose 3 was 8.5 weeks, 17.3 weeks and 26.7 weeks, respectively.
- The overall distribution of females and males was 42.7% and 57.3%, respectively.
- The predominant geographic ancestry was White-Caucasian/European Heritage (75.7%).
- The percentage of subjects who received hepatitis B vaccination at birth was 96.3%.

The demographic profile of the first three doses ATP cohort for analysis of immunogenicity was comparable to the Rota ATP cohort.

The demographic profile of the first three doses TVC cohort for analysis of immunogenicity was comparable to the Rota ATP cohort and first three doses ATP cohort.

Epoch 2

The demographic profile for the two groups for the fourth dose TVC with respect to mean age, gender, ethnicity and geographical ancestry was comparable.

- The mean age for the HibCY and PedHIB groups at dose 4 and dose 5 was 12.6 months and 18.8 months, respectively.
- The overall distribution of females and males was 48.0% and 52.0%, respectively.
- The predominant geographic ancestry was White-Caucasian/European Heritage (71.7%).
- The percentage of subjects who received hepatitis B vaccination at birth was 95.6%

The demographic profile of the Havrix ATP cohort for analysis of immunogenicity was comparable to the fourth dose TVC.

Efficacy results

Immunogenicity

Non-inferiority of Rotarix co-administration post-dose 2 (Epoch 001)

The non-inferiority of a 2-dose primary vaccination course of Rotarix co-administered with Hib-MenCY-TT, Pediarix and Prevnar13 compared to that of Rotarix coadministered with PedvaxHIB, Pediarix and Prevnar13 in terms of Rotarix IgA GMCs was met, as two months after the second dose, the lower limit of the two-sided standardized asymptotic 97.5% CI on the ratio of anti-rotavirus IgA GMC (HibCY group over PedHIB group) was 0.77 which was more than 0.5 (clinical limit for non-inferiority).

Table: GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose (Rota ATP cohort for analysis of immunogenicity)

				Adjusted GMC ratio (HibCY group / PedHIB group)		
HibCY group		PedHIB group			97.5% CI	
N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
155	139.0	161	114.9	1.21	0.77	1.90

HibCY group = Hib-MenCY-TT, *Prevnar 13* + *Rotarix* at Months 0, 2 Hib-MenCY-TT, *Prevnar 13* at Month 4 Hib-MenCY-TT, *Prevnar 13* + *Havrix* at Month 10-13 and *Havrix* at Month 16-19
PedHIB group = *PedvaxHIB*, *Prevnar 13* + *Rotarix* at Months 0, 2 *Prevnar 13* + *Pediarix* at Month 4 *PedvaxHIB*, *Prevnar 13* + *Havrix* at Month 10-13 and *Havrix* at Month 16-19
Adjusted GMC = geometric mean antibody concentration adjusted for the blood sample subcohorts
N = Number of subjects with post-vaccination results available
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for the blood sample subcohorts - pooled variance); LL = lower limit, UL = upper limit

Anti-rotavirus antibodies

The percentage of subjects with anti-rotavirus IgA concentrations ≥ 20 U/mL and GMCs after the second dose was:

- Anti-rotavirus IgA concentrations ≥ 20 U/mL was observed in at least 81.3% of subjects in the HibCY group and 80.1% of subjects in the PedHIB group.
- The anti-rotavirus IgA GMC was 138.9 U/mL in the HibCY group and 115.0 U/mL in the PedHIB group

Table: Percentage of subjects with anti-rotavirus IgA concentrations equal to or above the cut-off values of 20 U/mL and GMCs after the second dose (Rota ATP cohort for analysis of immunogenicity)

				≥ 20 U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-rotavirus IgA antibody	HibCY group	PII(M4)	155	126	81.3	74.2	87.1	138.9	104.0	185.5
	PedHIB group	PII(M4)	161	129	80.1	73.1	86.0	115.0	87.5	151.0

HibCY group = Hib-MenCY-TT, *Prevnar 13* + *Rotarix* at Months 0, 2 Hib-MenCY-TT, *Prevnar 13* at Month 4 Hib-MenCY-TT, *Prevnar 13* + *Havrix* at Month 10-13 and *Havrix* at Month 16-19
PedHIB group = *PedvaxHIB*, *Prevnar 13* + *Rotarix* at Months 0, 2 *Prevnar 13* + *Pediarix* at Month 4 *PedvaxHIB*, *Prevnar 13* + *Havrix* at Month 10-13 and *Havrix* at Month 16-19
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
PII(M4) = Post-vaccination Dose 2 at Month 4

Anti-rotavirus antibodies by gender

GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for males and females (Rota ATP cohort) are presented in the following Tables.

Table: GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for males (Rota ATP cohort for analysis of immunogenicity)

			Adjusted GMC ratio (HibCY group / PedHIB group)			
HibCY group		PedHIB group			97.5% CI	
N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
84	114.2	97	113.6	1.01	0.55	1.83

HibCY group = Hib-MenCY-TT, Prevnar 13 + Rotarix at Months 0, 2 Hib-MenCY-TT, Prevnar 13 at Month 4 Hib-MenCY-TT, Prevnar 13 + Havrix at Month 10-13 and Havrix at Month 16-19
PedHIB group = PedvaxHib, Prevnar 13 + Rotarix at Months 0, 2 Prevnar 13 + Pediarix at Month 4 PedvaxHib, Prevnar 13 + Havrix at Month 10-13 and Havrix at Month 16-19
Adjusted GMC = geometric mean antibody concentration adjusted for the blood sample subcohorts
N = Number of subjects with post-vaccination results available
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for the blood sample subcohorts - pooled variance); LL = lower limit, UL = upper limit

Table : GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for females (Rota ATP cohort for analysis of immunogenicity)

				Adjusted GMC ratio (HibCY group / PedHIB group)		
HibCY group		PedHIB group			97.5% CI	
N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
71	173.8	64	118.0	1.47	0.73	2.98

Anti-rotavirus antibodies by geographical ancestry

GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for subjects with White - Caucasian / European Heritage (Rota ATP cohort) are presented in the following Table.

Table : GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for subjects with White - Caucasian / European Heritage (Rota ATP cohort for analysis of immunogenicity).

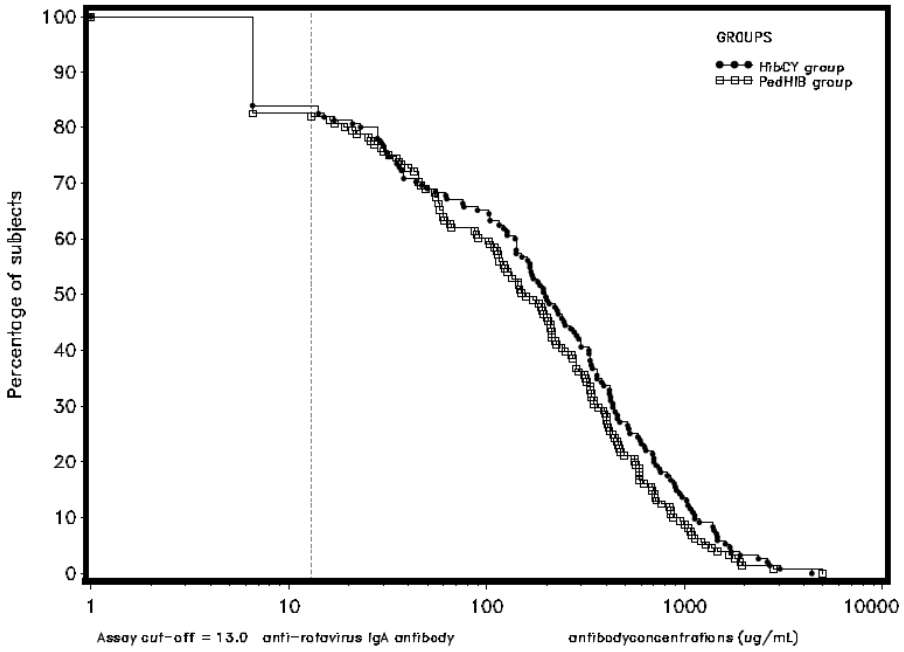
				Adjusted GMC ratio (HibCY group / PedHIB group)		
HibCY group		PedHIB group			97.5% CI	
N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
117	142.9	123	110.7	1.29	0.76	2.20

GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for subjects with other geographical ancestries (Rota ATP cohort) are presented in the following Table.

Table : GMC ratios between HibCY and PedHIB groups for anti-Rota IgA concentrations two months after the second dose for subjects with other geographical ancestries (Rota ATP cohort for analysis of immunogenicity).

				Adjusted GMC ratio (HibCY group / PedHIB group)		
HibCY group		PedHIB group			97.5% CI	
N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
38	132.3	38	125.0	1.06	0.43	2.60

The reverse cumulative curves for anti-rotavirus IgA antibody concentrations one month after the second dose (Rota ATP cohort for analysis of immunogenicity) are presented below:



Assessor's comment

The immunogenicity profile of Rotarix is consistent with earlier data.

Safety results

Solicited adverse events

Irritability was the most frequently reported solicited general symptom in both groups (in 90.9% of the subjects in HibCY group and 94.9% of the subjects in PedHIB group [after 69.1% and 78.4% of doses,

respectively]). Grade 3 irritability was reported in 14.0% of the subjects of HibCY and 22.4% of the subjects of PedHIB group [after 5.9% and 10.4% of doses, respectively]. All other grade 3 solicited general symptoms were reported in 10.8% or fewer subjects (5.4% or fewer doses). Most of the reported grade 3 solicited general symptoms were considered by the investigator to be related to vaccination.

Table : Incidence of irritability reported during the 4-day (Days 0-3) postvaccination period following each dose and overall (First three doses Total Vaccinated Cohort)

		HibCY group					PedHIB group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Irritability / Fussiness	All	285	203	71.2	65.6	76.4	291	238	81.8	76.9	86.0
	Grade 2 or 3	285	83	29.1	23.9	34.8	291	121	41.6	35.9	47.5
	Grade 3	285	10	3.5	1.7	6.4	291	34	11.7	8.2	15.9
	Related	285	196	68.8	63.0	74.1	291	231	79.4	74.3	83.9
	Grade 3 Related	285	9	3.2	1.5	5.9	291	32	11.0	7.6	15.2
	Medical advice	285	2	0.7	0.1	2.5	291	1	0.3	0.0	1.9
Dose 2											
Irritability / Fussiness	All	273	191	70.0	64.1	75.3	278	232	83.5	78.6	87.6
	Grade 2 or 3	273	87	31.9	26.4	37.8	278	124	44.6	38.7	50.7
	Grade 3	273	22	8.1	5.1	11.9	278	33	11.9	8.3	16.3
	Related	273	183	67.0	61.1	72.6	278	225	80.9	75.8	85.4
	Grade 3 Related	273	22	8.1	5.1	11.9	278	31	11.2	7.7	15.5
	Medical advice	273	1	0.4	0.0	2.0	278	2	0.7	0.1	2.6
Dose 3											
Irritability / Fussiness	All	262	173	66.0	59.9	71.7	265	184	69.4	63.5	74.9
	Grade 2 or 3	262	77	29.4	23.9	35.3	265	77	29.1	23.7	34.9
	Grade 3	262	16	6.1	3.5	9.7	265	20	7.5	4.7	11.4
	Related	262	166	63.4	57.2	69.2	265	181	68.3	62.3	73.9
	Grade 3 Related	262	16	6.1	3.5	9.7	265	18	6.8	4.1	10.5
	Medical advice	262	0	0.0	0.0	1.4	265	0	0.0	0.0	1.4
Overall/dose											
Irritability / Fussiness	All	820	567	69.1	65.9	72.3	834	654	78.4	75.5	81.2
	Grade 2 or 3	820	247	30.1	27.0	33.4	834	322	38.6	35.3	42.0
	Grade 3	820	48	5.9	4.3	7.7	834	87	10.4	8.4	12.7
	Related	820	545	66.5	63.1	69.7	834	637	76.4	73.3	79.2
	Grade 3 Related	820	47	5.7	4.2	7.5	834	81	9.7	7.8	11.9
	Medical advice	820	3	0.4	0.1	1.1	834	3	0.4	0.1	1.0
Overall/subject											
Irritability / Fussiness	All	286	260	90.9	87.0	94.0	295	280	94.9	91.8	97.1
	Grade 2 or 3	286	158	55.2	49.3	61.1	295	192	65.1	59.3	70.5
	Grade 3	286	40	14.0	10.2	18.6	295	66	22.4	17.7	27.6
	Related	286	253	88.5	84.2	91.9	295	275	93.2	89.7	95.8
	Grade 3 Related	286	39	13.6	9.9	18.2	295	63	21.4	16.8	26.5
	Medical advice	286	3	1.0	0.2	3.0	295	3	1.0	0.2	2.9

One subject in HibCY group and two subjects in PedHIB group had fever > 40 °C.

Table : Incidence of fever reported during the 4-day (Days 0-3) postvaccination period following each dose and overall (First three doses Total Vaccinated Cohort)

		HibCY group					PedHIB group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Temperature (°C)	All	285	32	11.2	7.8	15.5	291	60	20.6	16.1	25.7
	>38.5	285	11	3.9	1.9	6.8	291	17	5.8	3.4	9.2
	>39.0	285	1	0.4	0.0	1.9	291	3	1.0	0.2	3.0
	>39.5	285	0	0.0	0.0	1.3	291	0	0.0	0.0	1.3
	>40.0	285	0	0.0	0.0	1.3	291	0	0.0	0.0	1.3
	Related	285	32	11.2	7.8	15.5	291	57	19.6	15.2	24.6
	>38.5 Related	285	11	3.9	1.9	6.8	291	16	5.5	3.2	8.8
	>39.0 Related	285	1	0.4	0.0	1.9	291	3	1.0	0.2	3.0
	>39.5 Related	285	0	0.0	0.0	1.3	291	0	0.0	0.0	1.3
	>40.0 Related	285	0	0.0	0.0	1.3	291	0	0.0	0.0	1.3
	Medical advice	285	0	0.0	0.0	1.3	291	2	0.7	0.1	2.5
Dose 2											
Temperature (°C)	All	273	53	19.4	14.9	24.6	279	81	29.0	23.8	34.7
	>38.5	273	13	4.8	2.6	8.0	279	27	9.7	6.5	13.8
	>39.0	273	3	1.1	0.2	3.2	279	9	3.2	1.5	6.0
	>39.5	273	0	0.0	0.0	1.3	279	2	0.7	0.1	2.6
	>40.0	273	0	0.0	0.0	1.3	279	1	0.4	0.0	2.0
	Related	273	52	19.0	14.6	24.2	279	79	28.3	23.1	34.0
	>38.5 Related	273	12	4.4	2.3	7.6	279	27	9.7	6.5	13.8
	>39.0 Related	273	3	1.1	0.2	3.2	279	9	3.2	1.5	6.0
	>39.5 Related	273	0	0.0	0.0	1.3	279	2	0.7	0.1	2.6
	>40.0 Related	273	0	0.0	0.0	1.3	279	1	0.4	0.0	2.0
	Medical advice	273	1	0.4	0.0	2.0	279	2	0.7	0.1	2.6
Dose 3											
Temperature (°C)	All	262	43	16.4	12.1	21.5	265	45	17.0	12.7	22.1
	>38.5	262	11	4.2	2.1	7.4	265	20	7.5	4.7	11.4
	>39.0	262	6	2.3	0.8	4.9	265	7	2.6	1.1	5.4
	>39.5	262	2	0.8	0.1	2.7	265	2	0.8	0.1	2.7
	>40.0	262	1	0.4	0.0	2.1	265	1	0.4	0.0	2.1
	Related	262	43	16.4	12.1	21.5	265	44	16.6	12.3	21.6
	>38.5 Related	262	11	4.2	2.1	7.4	265	20	7.5	4.7	11.4
	>39.0 Related	262	6	2.3	0.8	4.9	265	7	2.6	1.1	5.4
	>39.5 Related	262	2	0.8	0.1	2.7	265	2	0.8	0.1	2.7
	>40.0 Related	262	1	0.4	0.0	2.1	265	1	0.4	0.0	2.1
	Medical advice	262	0	0.0	0.0	1.4	265	3	1.1	0.2	3.3

		HibCY group					PedHIB group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
Temperature (°C)	All	820	128	15.6	13.2	18.3	835	186	22.3	19.5	25.3
	>38.5	820	35	4.3	3.0	5.9	835	64	7.7	6.0	9.7
	>39.0	820	10	1.2	0.6	2.2	835	19	2.3	1.4	3.5
	>39.5	820	2	0.2	0.0	0.9	835	4	0.5	0.1	1.2
	>40.0	820	1	0.1	0.0	0.7	835	2	0.2	0.0	0.9
	Related	820	127	15.5	13.1	18.1	835	180	21.6	18.8	24.5
	>38.5 Related	820	34	4.1	2.9	5.7	835	63	7.5	5.8	9.6
	>39.0 Related	820	10	1.2	0.6	2.2	835	19	2.3	1.4	3.5
	>39.5 Related	820	2	0.2	0.0	0.9	835	4	0.5	0.1	1.2
	>40.0 Related	820	1	0.1	0.0	0.7	835	2	0.2	0.0	0.9
	Medical advice	820	1	0.1	0.0	0.7	835	7	0.8	0.3	1.7
Overall/subject											
Temperature (°C)	All	286	95	33.2	27.8	39.0	295	130	44.1	38.3	49.9
	>38.5	286	30	10.5	7.2	14.6	295	53	18.0	13.8	22.8
	>39.0	286	10	3.5	1.7	6.3	295	18	6.1	3.7	9.5
	>39.5	286	2	0.7	0.1	2.5	295	4	1.4	0.4	3.4
	>40.0	286	1	0.3	0.0	1.9	295	2	0.7	0.1	2.4
	Related	286	94	32.9	27.5	38.6	295	126	42.7	37.0	48.6
	>38.5 Related	286	29	10.1	6.9	14.2	295	52	17.6	13.5	22.5
	>39.0 Related	286	10	3.5	1.7	6.3	295	18	6.1	3.7	9.5
	>39.5 Related	286	2	0.7	0.1	2.5	295	4	1.4	0.4	3.4
	>40.0 Related	286	1	0.3	0.0	1.9	295	2	0.7	0.1	2.4
	Medical advice	286	1	0.3	0.0	1.9	295	6	2.0	0.7	4.4

Serious adverse events (SAEs)

Overall, 19 subjects reported SAEs from dose 1 up to study end: 8 (2.7%) in HibCY group, and 11 (3.6%) in PedHIB group. All SAEs were considered by the investigator as not causally related to the vaccination.

One death (sudden infant death syndrome) was reported in the HibCY group (158 days after post-dose 3). This event was considered by the investigator as not causally related to the vaccination.

Adverse events led to premature discontinuation/withdrawal from the study in 6 subjects (1 death [sudden infant death syndrome] in the HibCY group and 5 nonfatal SAEs in PedHIB group).

Assessor's comment

Rotarix was administered to both study groups and co-administered with other study vaccines. The safety and reactogenicity profile of Rotarix could therefore not be assessed independently.

No new safety events were reported.

The safety and reactogenicity results were consistent with the known safety profile of Hib-MenCY-TT vaccine.

2.3.3. Discussion on clinical aspects

The current study evaluated the immunogenicity of Rotarix when administered according to a 2-dose schedule in 6-12 weeks old subjects in 27 study centres in the US. Rotarix was co-administered with DTPa-HBV-IPV, pneumococcal conjugate vaccine, and either Hib-MenCY-TT or Hib vaccine.

All the co-primary objectives of the study were met as the pre-defined criteria have been reached. Since the first primary objective for Hib-MenCY-TT vaccine with respect to the percentage of subjects with anti-PRP concentration was met, the rest of the co-primary objectives for Rotarix, Prevnar 13, and Havrix were also assessed and these were equally met.

Anti-rotavirus IgA concentrations ≥ 20 U/mL was observed in at least 81.3% of subjects in the HibCY group and 80.1% of subjects in the PedHIB group.

The immunogenicity profile of Rotarix is consistent with earlier data.

Rotarix was administered to both study groups and co-administered with other study vaccines. The safety and reactogenicity profile of Rotarix could therefore not be assessed independently, but no new safety events were reported.

3. Rapporteur's overall conclusion and recommendation

This study investigated the acceptability of the co-administration of Rotarix, Prevnar 13 and Havrix with the candidate Hib-MenCY-TT vaccine.

The non-inferiority of the immunogenicity of Rotarix and Prevnar 13 when co-administered with Hib-MenCY-TT as compared to the immunogenicity of Rotarix and Prevnar 13 co-administered with US-licensed PedvaxHIB and the non-inferiority of the immunogenicity of Havrix and Prevnar 13 when co-administered with Hib-MenCY-TT as compared to the immunogenicity of Havrix and Prevnar 13 co-administered with PedvaxHIB, were demonstrated.

Rotarix was administered to both study groups and co-administered with other study vaccines. The safety and reactogenicity profile of Rotarix could therefore not be assessed independently, but no new safety events were reported.

Based on the presented immunogenicity and safety results the benefit risk balance for Rotarix remains positive. The presented data support the previously presented data. No regulatory action is considered necessary based on the current study results.

☒ **Fulfilled**