Amsterdam, 19 August 2021
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Human Medicines Division

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

RotaTeq

rotavirus vaccine, live, oral

Procedure no: EMEA/H/C/000669/P46/046

Note

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

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1. Introduction

On June 4, 2021, the MAH submitted a completed paediatric study for Rotateq, 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 V114-027 "A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants study" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- V114-027 "A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants study"

2.3.2. Clinical study

V114-027 "A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants study"

Description

Methods

Objective(s)

Primary objectives

- To evaluate the safety and tolerability of complete V114 (Group 5) and mixed Prevnar13™/V114 dosing schedules (Groups 2, 3, and 4) compared with a complete dosing schedule of Prevnar13™ (Group 1) with respect to the proportion of participants with adverse events (AEs).

- To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days following Dose 4 for participants administered mixed dosing schedules of Prevnar 13™/V114 (Groups 2, 3, and 4) compared with participants administered a complete dosing schedule of Prevnar 13™ (Group 1)

Secondary objectives

- To compare the proportion of participants with anti-hepatitis B surface antigen (HBsAg) concentration ≥10 mIU/mL at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RECOMBIVAX HB™ versus participants administered a complete primary infant series dosing schedule of Prevnar 13™ (Groups 1 and 2) concomitantly with RECOMBIVAX HB™
- To compare the anti-rotavirus Immunoglobulin A (IgA) Geometric Mean Titer (GMT) at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RotaTeq™ versus participants administered a complete primary infant series dosing schedule of Prevnar 13™ (Groups 1 and 2) concomitantly with RotaTeq™
- To evaluate the anti-PnPs serotype-specific IgG GMCs and the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥ 0.35 μg/mL) at 30 days following Dose 3 separately for each vaccination group (Groups 1, 2, 3, 4, and 5)
- To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered a complete dosing schedule of V114 (Group 5) compared with participants administered a complete dosing schedule of Prevnar 13™ (Group 1)

Study design

This was a multicenter, randomized, active-controlled, parallel-group, double-blind interchangeability study to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age. In 2 intervention groups, infants received a 4-dose series of either Prevnar 13™ (Group 1) or V114(Group 5). In 3 other intervention groups, the immunization series was initiated with Prevnar13™ and changed to V114 at Dose 2, 3 or 4(Groups 4, 3, and 2, respectively). Infants also received other licensed paediatric vaccines administered concomitantly with the PCV, including RECOMBIVAXHB™ and RotaTeq™.

Study population /Sample size

The planned enrolment total was 900 participants. As no hypothesis testing was planned the study size is intended for descriptive data.

Eligible participants were healthy male or female infants approximately 2 months of age (42 to 90 days, inclusive) without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine.

Treatments

All participants received Rotateq concomitantly with study and comparator vaccines. The study participants were randomized to the following groups:

Intervention Group Name	Dose 1 (Visit 1, ~2 months of age) ≥42 days of age to ≤90 days of age	Dose 2 (Visit 2, ~4 months of age) 4 months of age to 1 day prior to 5 months of age	Dose 3 (Visit 3, ~6 months of age) 6 months of age to 1 day prior to 7 months of age	Dose 4 (Visit 5, ~12 to 15 months of age) 12 months of age to 1 day prior to 16 months of age
Group 1	Prevnar 13™	Prevnar 13™	Prevnar 13™	Prevnar 13™
Group 2	Prevnar 13™	Prevnar 13™	Prevnar 13™	V114
Group 3	Prevnar 13™	Prevnar 13™	V114	V114
Group 4	Prevnar 13™	V114	V114	V114
Group 5	V114	V114	V114	V114

Outcomes/endpoints

Primary endpoints:

Following any vaccination with V114 or Prevnar 13™:

- Solicited injection-site AEs from Day 1 through Day 14 postvaccination
- Solicited systemic AEs from Day 1 through Day 14 postvaccination
- Vaccine-related serious adverse events (SAEs) through completion of study participation

Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days postdose 4 (PD4)

Secondary endpoints:

Anti-HBsAg response at 30 days postdose 3 (PD3) of V114 or Prevnar 13™

Anti-rotavirus IgA response at 30 days PD3 of V114 or Prevnar 13™

Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3

Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13™at 30 days PD4

CHMP comment: This report will focus on endpoints relevant to Rotateq.

Statistical Methods

The primary immunogenicity objective was descriptive without formal hypothesis testing. The serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days PD4 were compared between groups through the estimation of serotype-specific IgG GMC ratios for each serotype. Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) were calculated using an analysis of covariance (ANCOVA) model with vaccination group and stratification factor (hepatitis B vaccination status before enrolment = Yes, No) as covariates. The pairwise comparisons included Group 2 vs Group 1; Group 3 vs Group 1; and Group 4 vs Group 1.For the secondary objective of the noninferiority evaluation of immunogenicity of RECOMBIVAX HB™ when given concomitantly with V114 or Prevnar 13™, the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3 of V114 or Prevnar 13™ were compared between groups. The between-treatment difference based on the proportions of participants with anti-

HBsAg concentration ≥10 mIU/mL [V114 (Group 5) minus Prevnar 13™ (Group 1 + Group 2)] and its 95% CI were calculated using stratified Miettinen and Nurminen method. For the secondary objective of the noninferiority evaluation of immunogenicity of RotaTeq™ when given concomitantly with V114 or Prevnar 13™, the anti-rotavirus IgA GMT at 30 days PD3 of V114 or Prevnar 13™ was compared between groups through the estimation of anti-rotavirus IgAGMT ratios. Estimation of the anti-rotavirus IgA GMT ratio [V114 (Group 5)/Prevnar 13™ (Group 1 + Group 2)] and the corresponding 95% CIs were calculated using ANCOVA with vaccination group and stratification factor (hepatitis B vaccination status before enrolment = Yes, No) as covariates. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. P-values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) were provided for between-vaccination group differences in the percentage of participants with prespecified events.

Results

Recruitment/ Number analysed

Number of Participants Randomized/Treated/Completed/Discontinued:

Group 1: 179 randomized/ 179 vaccinated[a]/ 164 completed/ 15 discontinued

Group 2:181 randomized /181 vaccinated[a] / 167 completed / 14 discontinued

Group 3:180 randomized / 178 vaccinated[a] / 147 completed / 33 discontinued

Group 4:180 randomized / 179 vaccinated[a] / 160 completed / 20 discontinued

Group 5:180 randomized / 179 vaccinated[a] / 167 completed / 13 discontinued

TOTAL:900 randomized / 896 vaccinated[a] / 805 completed / 95 discontinued

[a]Vaccinated with at least 1 dose of PCV

Baseline data

Among the vaccinated participants(n=896):

Overall Median Age (range):9.0 weeks(6 to 12 weeks)

Sex: 473 (52.8%) male, 423 (47.2%) female

Ethnicity:683 (76.2%) not Hispanic or Latino, 212 (23.7%) Hispanic or Latino, 1 (0.1%) unknown

Gestational Age: 91 (10.2%) <37 weeks, 805 (89.8%) ≥37 weeks

Hepatitis B Vaccination Status Before Enrollment: 876 (97.8%) yes, 20 (2.2%) no

Efficacy results

Anti-rotavirus IgA Response at 30 Days Postdose 3

Following 3 doses of either V114 (Group 5) or Prevnar 13™ (Groups 1 and 2)in the infant primary series, RotaTeq™ administered concomitantly with V114elicited an immune response that was generally comparable to that elicited by RotaTeq™ administered concomitantly with Prevnar 13™.

- Responses to RotaTeq™ administered concomitantly with V114 met noninferiority criteria as assessed by anti-rotavirus IgA GMTs at 30 days PD3.The lower bound of the 2-sided 95% CI of

the anti-rotavirus IgA GMT ratio (Group5/[Group 1 + Group 2]) was greater than 0.50 (Table 11)

- Anti-rotavirus IgA GMTs at 30 days PD3 were generally comparable across intervention groups (Table 12)
- Anti-rotavirus IgA responses as assessed by GMTs at 30 days PD3 in the FAS population were consistent with those observed in the PP population (Table 13)

Table: 11 Analysis of Anti-rotavirus IgA GMTs at 30 Days Postdose 3 (Per-Protocol Population) (Group 5 versus Group 1+Group 2)

Antigen	Group 5 (N=179)		Group 1+Group 2 (N=360)		GMT Ratio[a] (Group 5 / Group 1+Group 2)	
	n	GMT[a]	n	GMT[a]	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Rotavirus	152	283.1	290	291.4	0.97 (0.70, 1.34)	<0.001

[a] GMTs, GMT ratio, CI, and p-value are calculated using an ANCOVA model utilizing the natural log-transformed antibody titers as the response with vaccination group and hepatitis B vaccination status before enrollment as covariates.

[b] A conclusion of non-inferiority of RotaTeq™ administered concomitantly with V114 to RotaTeq™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the GMT ratio (Group 5/Group 1+Group 2) being >0.5 (1-sided p-value <0.025).

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.

Note: Per protocol, dose 3 was administered at ~6 months of age.

Group 1: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → Prevnar 13™

Group 2: Prevnar 13™ → Prevnar 13™ → Prevnar 13™ → V114

Group 5: V114 → V114 → V114 → V114

ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean titer (U/mL); IgA=immunoglobulin A; U=units.

Table 12. Summary of Anti-rotavirus IgA GMTs at 30 Days Postdose 3 (Per-Protocol Population)

Antigen	Group 1 (N = 179)			Group 2 (N = 181)			Group 3 (N = 178)			Group 4 (N = 179)			Group 5 (N = 179)		
	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]	n	Observed Response	95% CI[a]
Rotavirus	147	286.5	(218.1, 376.2)	143	329.5	(254.9, 426.1)	136	258.5	(195.3, 342.2)	143	322.4	(247.0, 420.8)	152	298.3	(228.2, 390.0)

[a] The within-group CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis..

Table 13 Analysis of Anti-rotavirus IgA GMTs at 30 Days Postdose 3 (Full Analysis Set Population) (Group 5 versus Group 1+Group 2)

Antigen	Group 5 (N=179)		Group 1+Group 2 (N=360)		GMT Ratio[a] (Group 5 / Group 1+Group 2)	
	n	GMT[a]	n	GMT[a]	Estimate (95% CI)[ab]	p-value[ab] (1-sided)
Rotavirus	157	286.4	306	286.4	1.00 (0.73, 1.37)	<0.001

[a] GMTs, GMT ratio, CI, and p-value are calculated using an ANCOVA model utilizing the natural log-transformed antibody titers as the response with vaccination group and hepatitis B vaccination status before enrollment as

covariates.

[b] A conclusion of non-inferiority of RotaTeq™ administered concomitantly with V114 to RotaTeq™ administered concomitantly with Prevnar 13™ is based on the lower bound of the 2-sided 95% CI for the GMT ratio (Group 5/Group 1+Group 2) being >0.5 (1-sided p-value <0.025).

Safety results

- When administered concomitantly with RECOMBIVAX HB™ and RotaTeq™, complete V114 and mixed Prevnar 13™ and V114 dosing regimens were generally well-tolerated with safety profiles generally comparable to a complete dosing regimen of Prevnar 13™.
- When an investigator assessed a systemic AE as related to PCV, it was usually assessed as related to all concomitantly administered vaccines.
- The proportions of participants with systemic AEs related to PCV, RECOMBIVAX HB™, or RotaTeq™ were generally comparable across intervention groups and in general, the vaccine-related systemic AEs for the concomitant vaccines were consistent with those reported for PCV.
- No new safety issues for RECOMBIVAX HB™ or RotaTeq™ were identified.

2.3.3. Discussion on clinical aspects

The immune responses in terms of IgA against Rotateq when administered together with the investigational vaccine compared administration together with Prevenar 13. No concern regarding immunogenicity of RotaTeq was raised based on this study. Likewise, no new safety signal for RotaTeq was raised in this study. Immune responses to other antigens are not assessed within this procedure. Thus, further regulatory action concerning RotaTeq is not considered necessary based on these results.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

None