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Procedure Management and Committees Support 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/P46/045

Note

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

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1. Introduction

On 19 February 2016, the MAH submitted a completed paediatric study Prot. No. 024, 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 programme

The MAH stated that the study, entitled:

- A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Immunogenicity of V260/ROTATEQ® (Rotavirus Vaccine, Live, Oral, Pentavalent) in Healthy Chinese Infants is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the studies

The pharmaceutical formulation used in the studies consisted of a 2 mL, oral solution of 5 live human bovine reassortant rotavirus strains (G1, G2, G3, G4, and P1A[8]), which contained a minimum of 2.0 to 2.8 × 106 infectious units (IU) per reassortant dose, depending on the serotype, and not greater than 116 × 106 IU per dose in the aggregate. The reassortants were suspended in a buffered stabilizer solution which contained sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, culture media (containing inorganic salts, amino acids and vitamins), and also purified water.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Immunogenicity of V260/ROTATEQ® (Rotavirus Vaccine, Live, Oral, Pentavalent) in Healthy Chinese Infants

The applicant has provided data published in the literature that China has experienced significant morbidity and economic burden associated with rotavirus infection. In 2007, there were an estimated 12.1 million annual rotavirus diarrhoea episodes, which resulted in 3.5 million rotavirus-related outpatient visits and 220,000 paediatric hospital admissions. Rotavirus accounts for approximately 31 to 50% of hospitalized children with diarrhoea and 25% of acute gastroenteritis (AGE) in outpatient visits in China. Among the estimated 11,420 deaths due to diarrhea in children less than 5 years of age in 2008, 41.3% were attributable to rotavirus.

In accordance with the China Regulatory Requirements for licensure of new vaccines, a Phase I study (V260 PN028) was completed in 2010 and demonstrated that RotaTeq™ was generally well tolerated in Chinese adults, children, and infants.

In order to support the NDA for RotaTeq™ in China, Protocol 024, a Phase III study, was designed as a randomized, double-blinded, placebo-controlled, multi-centered trial to evaluate the efficacy, safety, and immunogenicity of RotaTeq™ among infants in China.

The primary objective was to evaluate the efficacy of RotaTeq™ against RVGE caused by naturally-occurring rotavirus (regardless of serotype or disease severity) in Chinese infants. This study also assessed the immunogenicity and safety of the China Expanded program in Immunisation (EPI) vaccines, oral poliovirus vaccine (OPV) and diphtheria, tetanus, acellular pertussis vaccine (DTaP) when given concomitantly with RotaTeq™/placebo in subjects participating in the Concomitant Use Cohort.

2.3.2. Clinical studies

Clinical study number and title

- NCT02062385 A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Immunogenicity of V260/ROTATEQ® (Rotavirus Vaccine, Live, Oral, Pentavalent) in Healthy Chinese Infants

Description

Methods

Objectives

Primary Objective:

To evaluate the efficacy of 3 doses of V260 against rotavirus gastroenteritis caused by naturally-occurring rotavirus (regardless of serotype or disease severity), occurring at least 14 days following the third dose.

Secondary Objectives:

(1) To assess the safety of V260 with respect to all adverse experiences (AEs) within 30 days after each dose of V260/placebo. [Note: Safety assessment in the context of V260 concomitant-use with OPV and DTaP are also to be summarized for the Concomitant Use Cohort (both the Immunogenicity and Non-Immunogenicity Subgroups].

(2) To evaluate the efficacy of 3 doses of V260 against severe rotavirus gastroenteritis caused by naturally occurring rotavirus (regardless of serotype) occurring at least 14 days following the third dose.

(3) To evaluate the efficacy of V260 against any rotavirus gastroenteritis that occurs at least 14 days after the first dose in all subjects receiving at least one dose of V260.

(4) To evaluate the efficacy of 3 doses of V260 against i) severe and ii) any severity rotavirus gastroenteritis caused by rotavirus serotypes G1, G2, G3, G4, and G-serotypes that contain P1A[8] (e.g., G9) that occurs at least 14 days following the third dose.

(5) To evaluate the impact of V260 on occurrence of any and severe all cause gastroenteritis.

(6) To characterize the antibody responses against OPV antigens.

(7) To characterize the antibody responses against DTaP antigens.

(8) To characterize the immune response to V260 as measured by anti-rotavirus IgA.

(9) To characterize the immune response to V260 as measured by serum neutralizing antibody (SNA).

Study design

This is a randomized, double-blind, placebo-controlled, multi-centered study conducted in conformance with Good Clinical Practices. The purpose was to investigate clinical efficacy, immunogenicity, and safety/tolerability of a 3-dose regimen of V260 (ROTATEQ®) in healthy Chinese infants. Approximately 4040 eligible infants, at least 6 weeks (42 days) and up to 12 weeks (84 days) of age at time of the first vaccination of ROTATEQ®/placebo, were randomly assigned in a 1:1 ratio to receive either ROTATEQ® or placebo. In this study, administration of oral poliovirus vaccine (OPV) and diphtheria, tetanus, acellular pertussis vaccine (DTaP) were allowed according to China Expanded Program on Immunization (EPI). OPV and DTaP were administered either in a concomitant-use or in a staggered-use dosing schedule with ROTATEQ®/placebo. All subjects were followed for efficacy and safety. Antibody responses to OPV, DTaP, and ROTATEQ® were evaluated in a subset of subjects.

Study population /Sample size

Approximately 4040 eligible infants, at least 6 weeks (42 days) and up to 12 weeks (84 days) of age at time of the first vaccination of ROTATEQ®/placebo, were randomly assigned in a 1:1 ratio to receive either ROTATEQ® or placebo.

Treatments

Eligible subjects were randomly assigned in a 1:1 ratio to 2 vaccination groups to receive either RotaTeq™ or placebo. Each subject received 3 doses of RotaTeq™/placebo administered approximately 4 weeks apart and was followed for a minimum of 30 days following the final vaccination of RotaTeq™/placebo for safety follow-up.

Both OPV and DTaP, the routine China Expanded Program on Immunization (EPI) vaccines, were allowed as standard of care and administered either in a concomitant-use or in a staggered use dosing schedule with RotaTeq™/placebo. The subjects were allocated to 1 of 2 Cohorts:

<u>The Staggered Use Cohort</u>

ROTATEQ®/placebo was given in a staggered fashion with OPV + DTaP (includes non-immunogenicity subgroup and immunogenicity subgroup). A total of 3240 subjects received 3 doses of ROTATEQ®/placebo in a 1:1 ratio, administered approximately 4 weeks apart.

<u>Concomitant Use Cohort</u>

ROTATEQ®/placebo given concomitantly with OPV + DTaP (includes non-immunogenicity subgroup and immunogenicity subgroup). A total of 800 subjects received 3 doses of ROTATEQ®/placebo in a 1:1 ratio, administered approximately 4 weeks apart.

Outcomes/endpoints

Endpoints

Primary efficacy endpoint

Efficacy against any severity of RVGE regardless of serotype that occurs ≥ 14 days Postdose 3

Secondary immunogenicity endpoints

- Postdose 3 antibody seroconversion rates for poliovirus types 1, 2, and 3 in Concomitant Use Immunogenicity Subgroup
- In Concomitant Use ImmunogenicitySubgroup, Summary of Postdose 3 antibody responses by GMTs and seroconversion rates of OPV and DTaP.
- In Concomitant Use Immunogenicity Subgroup, Summary of Postdose 3 IgA Response: GMT and percent ≥ 3- fold rise from baseline
- In Staggered Use Immunogenicity Subgroup, Summary of Postdose 3 IgA, SNA for G1, G2,G3, G4, P1A[8] Response: GMT and percent ≥ 3-fold rise from Baseline

Safety Endpoints

Safety endpoints include incidence of adverse events [AEs] collected for 30 days following each dose (Days 1 to 14 via Vaccine Report Card [VRC]). In addition, any serious AEs (SAEs), any deaths, and reports of intussusception, were to be reported from the time of written consent until the end of the entire study (defined as last subject's last study visit).

Statistical Methods

Efficacy:

Primary Analysis

Statistical methodology: For the primary hypothesis, ROTATEQ® was considered efficacious if the lower bound of the 2-sided CI for efficacy was > 0% at the final analysis. To calculate the CI and associated p-value, an exact conditional method based on a Poisson distribution was used, which evaluates the number of subjects with RVGE in the group that received ROTATEQ® conditional on the total number of subjects with RVGE, accounting for any potential differential follow-up between the 2 vaccination groups. The Clopper-Pearson method was used for the CI.

Key Secondary Analysis

The statistical methodology was the same as the primary analysis.

The Per-Protocol for efficacy (PPE) population served as the primary population for the analysis of efficacy in this study. The PPE population was defined as subjects who received the 3 scheduled doses of study vaccine, adhered to guidelines for the administration of the study vaccine, and did not have important deviations from the protocol that may substantially affect the results of the primary efficacy endpoint.

Immunogenicity:

For the OPV components, the statistical criterion was that the difference in the percentage with seroconversion between subjects receiving ROTATEQ® concomitantly with OPV/ DTaP versus subjects receiving placebo concomitantly with OPV/ DTaP (ROTATEQ® minus placebo) excluded a decrease of 10 percentage points or more. One-sided tests of H0: PV260-PPlacebo ≤ -0.10 versus H1: PV260-PPlacebo > -0.10 was performed at the 0.025 Confidential significance level for each of the poliovirus components. The statistical criterion for non-inferiority corresponded to the 2-sided 95% CI for the difference in the seroprotection rates (ROTATEQ® minus placebo) excluding a decrease of 10%. The 95% CI was calculated using the method proposed by Miettinen and Nurminen.

The Per-Protocol for Immunogenicity (PPI) population served as the primary population for the analysis of immunogenicity in this study. The PPI population was antigen specific. Evaluable subjects were those who received their scheduled doses without intervening laboratory-confirmed disease specific to the antigen earlier than the blood sample collection Postdose 3, adhered to the guidelines for administration of vaccine, and had valid values available for analysis within specified day ranges.

Safety:

The analysis of safety results followed a tiered approach. The tiers differed with respect to the analyses that were performed. Safety parameters or adverse experiences of special interest that were identified a priori constitute “Tier 1” safety endpoints that were subjected to inferential testing for statistical significance with p values and 95% CIs provided for between-group comparisons. Other safety parameters were considered Tier 2 or Tier 3.Tier 2 parameters were assessed via point estimates with 95% CIs provided for between group comparisons; only point estimates by vaccination group were provided for Tier 3 safety parameters.

The All-Subjects-as-Treated (ASaT) population was used for the analysis of safety data in this study. The ASaT population consisted of all randomized subjects who received at least 1 dose of ROTATEQ or placebo.

Results

Recruitment / Number analysed

The disposition of subjects is provided by vaccination group for all randomized subjects in Table 1. Of the 4173 subjects screened, a total of 133 subjects were screened for the study but never randomized.

The most common reason for subjects not randomized was screen failure (98.5%).

Of the 4040 subjects randomized, 4037 (99.9%) subjects received at least 1 dose of study vaccine. Overall, 96.0% of the subjects completed the 3-dose series of study vaccination and 95.9% of the subjects completed the study. The number (%) of subjects that discontinued from the study was low and similar in the 2 vaccination groups (4.5% in the group that received ROTATEQ® vs. 3.7% in the placebo group). The most common reason for study discontinuation was withdrawal by parent/guardian.

Overall, 3 subjects were randomized but not vaccinated and 158 (3.9%) subjects discontinued from study vaccination prior to receiving 3 doses. The number (%) of subjects discontinued from the study vaccination was low and similar in the 2 vaccination groups (4.2% in the group that received

ROTATEQ® vs. 3.6% in the placebo group). The most common reason for vaccination discontinuation was withdrawal by subject (parent/guardian).

Enrolment was conducted at 5 study sites in Guangxi of China.

Table 1 Disposition of Subjects
(All Randomized Subjects)

	ROTATEQ®		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					133	
Subjects in population	2,020		2,020		4,040	
Vaccinated at						
Vaccination 1	2,018	(99.9)	2,019	(100.0)	4,037	(99.9)
Vaccination 2	1,946	(96.3)	1,959	(97.0)	3,905	(96.7)
Vaccination 3	1,932	(95.6)	1,946	(96.3)	3,878	(96.0)
Trial Disposition						
Completed	1,930	(95.5)	1,946	(96.3)	3,876	(95.9)
Discontinued	90	(4.5)	74	(3.7)	164	(4.1)
Adverse Event	20	(1.0)	13	(0.6)	33	(0.8)
Death	0	(0.0)	1	(0.0)	1	(0.0)
Lost To Follow-Up	1	(0.0)	0	(0.0)	1	(0.0)
Protocol Violation	1	(0.0)	0	(0.0)	1	(0.0)
Study Terminated By Sponsor†	2	(0.1)	0	(0.0)	2	(0.0)
Subject Moved	11	(0.5)	11	(0.5)	22	(0.5)
Withdrawal By Parent/Guardian	55	(2.7)	49	(2.4)	104	(2.6)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
† Subjects did not complete the vaccination of OPV/DTaP prior to database lock

Efficacy results

Primary Analysis of Efficacy Against RVGE Caused by Naturally Occurring Rotavirus (regardless of serotype or disease severity)

A summary of the primary PPE analysis is given in Table 2. This includes an accounting of the subjects included in the primary analysis of efficacy in the per-protocol population using the per-protocol case definition , as well as a point estimate, confidence interval (CI), and p-value for efficacy. As shown in Table 2, the point estimate of primary vaccine efficacy against RVGE caused by naturally-occurring rotavirus (regardless of serotype and disease severity), occurring at least 14 days following the third dose was 69.3% in the PPE population. The lower bound of the corresponding two-sided 95% CI was 54.5%, with a p value of <0.0001. Of the 143 subjects classified as RVGE cases according to the per-protocol case definition, 49 cases were G1 serotype, 5 were G2 serotype, 4 were G3 serotype, 2 were G4 serotype, and a total of 132 were G serotypes containing P1A[8].

Table 2
Primary Efficacy Analysis of Naturally Occurring Rotavirus Gastroenteritis Cases at Least 14 Days Postdose 3 Through the Entire Efficacy Follow-up Period in the Per-Protocol Population Using Per-Protocol Case Definition

	ROTATEQ®	Placebo
Subjects vaccinated	2018	2019
Protocol violators[†]	87	73
Subjects with no follow-up	0	0
Subjects classified as unevaluable per per-protocol case definition[‡]	4	9
Subjects contributing to efficacy analysis	1927	1937
Days of efficacy follow-up	428477	422252
Subjects classified as rotavirus gastroenteritis cases per protocol case definition	34	109
Efficacy estimate(%) and 95% CI	69.3 (54.5 ,79.7)	
P-value for efficacy > 0%	<.0001	
Conclusion[§]	Efficacious	

[†] Subjects identified in Protocol Violator Memo, including subjects with less than 3 doses; subjects with medical history of temporary immunoglobuline decreased; subjects who did not give the appropriate Informed Consent.

[‡] Subjects where classified as unevaluable due to rotavirus gastroenteritis occurred prior to 14 days Postdose 3, incomplete clinical and/or laboratory results, or stool samples collected out of day range.

[§] A conclusion of "efficacious" indicates that the criterion for efficacy was met (i.e., the lower bound of the 95%CI was > 0%)

NOTE: Rotavirus gastroenteritis cases consist of all subjects with at least 1 episode classified as positive for specific serotype. Multiple positive episodes for 1 subject are counted as a single case, and the first positive episode is used as the date of the case.

CI = Confidence Interval

Secondary Efficacy Analyses

Analysis of Efficacy Against Severe RVGE Caused by Naturally Occurring Rotavirus (regardless of serotype) Occurring at Least 14 Days Following the Third Vaccination:

Table 3 shows the results of the secondary endpoint evaluation; the vaccine efficacy was 78.9% (95% CI: 59.1%, 90.1%) against naturally occurring severe RVGE (score >11 on the Vesikari Scoring System) at least 14 days Postdose 3 in the per-protocol for efficacy (PPE) population.

Table 3

Efficacy Analysis of Naturally Occurring Severe Rotavirus Gastroenteritis Cases (Severity Score ≥11 on the Vesikari Scoring System) at Least 14 Days Postdose 3 Through the Entire Efficacy Follow-up Period in the Per-Protocol Population Using Per-Protocol Case Definition

	ROTATEQ®	Placebo
Subjects vaccinated	2018	2019
Protocol violators†	87	73
Subjects with no follow-up	0	0
Subjects classified as unevaluable per per-protocol case definition‡	5	9
Subjects contributing to efficacy analysis	1926	1937
Days of efficacy follow-up	431061	429345
Subjects classified as rotavirus gastroenteritis cases per protocol case definition with severity score ≥11	11	52
Efficacy estimate(%) and 95% CI	78.9 (59.1 ,90.1)	
P-value for efficacy > 0%	<.0001	
Conclusion§	Efficacious	

† Subjects identified in Protocol Violator Memo, including subjects with less than 3 doses; subjects with medical history of temporary immunoglobuline decreased; subjects who did not give the appropriate Informed Consent.

‡ Subjects where classified as unevaluable due to rotavirus gastroenteritis occurred prior to 14 days Postdose 3, incomplete clinical and/or laboratory results, or stool samples collected out of day range, or due to missing severity scoring items

§ A conclusion of "efficacious" indicates that the criterion for efficacy was met (i.e., the lower bound of the 95%CI was > 0%)

NOTE: Rotavirus gastroenteritis cases consist of all subjects with at least 1 episode classified as positive and having a severity score ≥11 on the Vesikari grading scale. Multiple positive episodes for 1 subject are counted as a single case, and the first positive episode is used as the date of the case.

CI = Confidence Interval

Analysis of Efficacy Against Any RVGE Occurring at least 14 Days after the First Vaccination:

A total of 147 RVGE cases were included in the ITT analysis. In addition to 143 RVGE cases which were included in the PPE analysis, there were 4 RVGE cases identified in the interval from 14 days after the first dose to 13 days after the third dose. The efficacy estimate of RotaTeq™ against RVGE caused by any rotavirus serotype that occurred at least 14 days after the first dose was 69.0% with a 95% CI (54.4, 79.4).

Analysis of Efficacy Against RVGE Caused by G1, G2, G3, G4, and G serotypes that Contained P1A[8]:

Nearly all of the cases of RVGE that occurred in PN024 were due to serotypes contained in the vaccine. Thus, the efficacy against any-severity and severe RVGE caused by serotypes contained in the vaccine (G1, G2, G3, G4, and G-serotypes that contain P1A[8] (i.e. G9)) that occurred at least 14 days following the third vaccination was 69.9% with a 95% CI (55.2, 80.3) and 78.9% with a 95% CI (59.1, 90.1), respectively.

Analysis of Efficacy Against Gastroenteritis by Any Cause:

A secondary efficacy objective was to evaluate the efficacy of RotaTeq™ against gastroenteritis of any cause when compared with placebo. Data showed the efficacy of RotaTeq™ against gastroenteritis of

any cause occurring at least 14 days Postdose 3 was 14.1% with a 95% CI (1.9, 24.8) in the PPE population, and the efficacy of RotaTeq™ against severe gastroenteritis of any cause occurring at least 14 days Postdose 3 was 49.9% with a 95% CI (29.0, 65.1) in PPE population.

Secondary Outcomes

Immunogenicity Analyses

A secondary objective of this study was to characterize the antibody responses against oral poliovirus vaccine (OPV) and diphtheria, tetanus, acellular pertussis vaccine (DTaP) antigens in the populations that include any subject who received OPV and DTaP concomitantly (on the same day) with each of the 3 doses of RotaTeq™/placebo. This was conducted on subjects enrolled in Cohort 2 Immunogenicity Subgroup A (Concomitant Use) which included 400 subjects. For antibody responses to OPV, 187 subjects who received RotaTeq™ and 192 subjects who received placebo were included in the per-protocol immunogenicity (PPI) analysis. The hypothesis tested was the proportion of subjects who achieve the OPV seroprotection criteria: neutralizing antibody titers ([NA] ⩾1:8) for poliovirus types 1, 2, and 3, measured at Postdose 3 of OPV, in subjects receiving OPV concomitantly with V260 is non - inferior to that in subjects receiving OPV concomitantly with placebo. [Noninferiority criterion corresponds to the lower bound of the two -sided 95% confidenceinterval on the difference in proportions, excluding a decrease of ⩾10 percentage points]. The statistical criterion for non-inferiority was met; see Table 4.

In addition, antibody responses to DTaP antigens were characterized; 187 subjects who received RotaTeq™ and 194 subjects who received placebo were included in the PPI analysis (Table 5). The geometric mean titer (GMTs) and seroprotection rate/seropositivity rate (SPRs) of these antibodies were generally comparable between the RotaTeq + OPV + DTaP group and the placebo + OPV + DTaP group.

Table 4
Statistical Analysis of Non-inferiority of Poliovirus Type 1, 2 and 3 Seroprotection Rates Postdose 3 (Per-Protocol Immunogenicity for OPV Population, Concomitant Use Group)

Antigen	ROTATEQ® (N=187)		Placebo (N=192)		Estimated Difference[†][§] (Percentage Points) (95% CI)[‡]	P-value[‡]	Non-inferiority Conclusion
	n	Observed Response	n	Observed Response			
Poliovirus Type 1	187	98.93%	192	100.00%	-1.07% (-3.82%, 0.91%)	<.0001	Non-inferior[‡]
Poliovirus Type 2	187	100.00%	192	100.00%	0.00% (-2.02%, 1.97%)	<.0001	Non-inferior[‡]
Poliovirus Type 3	187	98.93%	192	98.96%	-0.03% (-2.89%, 2.77%)	<.0001	Non-inferior[‡]

PPI: Evaluable subjects are those who receive their scheduled doses without intervening laboratory-confirmed disease specific to the antigen earlier than the blood sample collection Postdose 3, adhere to the guidelines for administration of vaccine, and have valid values available for analysis within specified day ranges.
[†] Based on Miettinen & Nurminen method.
[‡] A 95% CI on the difference excluding a decrease of 10 percentage points or more and associated one sided p-value < 0.025 implies that the difference is statistically significantly less than the pre-specified clinically relevant decrease of 10 percentage points and allows for a conclusion of non-inferiority.
[§] [ROTATEQ® + OPV] - [Placebo + OPV].
N = Number of subjects in Per-Protocol Immunogenicity for OPV population.
n = Number of subjects contributing to the per-protocol analyses.
CI = Confidence interval.
Seroprotection Rate = Proportion of subjects who achieve the seroprotection criteria: neutralizing antibody titers [NA] ≥ 1:8.

Table 5
Immunogenicity Summary of Response to Diphtheria, Tetanus, Pertussis Toxin, Pertussis Filamentous Hemagglutinin (Per-Protocol Immunogenicity for DTaP Population, Concomitant Use Group)

			ROTATEQ® (N=187)			Placebo (N=194)		
Antigen	Parameter	Time Point	n	Observed Response	95% CI	n	Observed Response	95% CI
Diphtheria	GMT	Predose 1	178	0.027	(0.024, 0.030)	184	0.027	(0.024, 0.030)
		Postdose 3	187	0.949	(0.864, 1.043)	194	0.980	(0.900, 1.067)
	SPR ≥ 0.1 IU/mL	Predose 1	181	3.31%	(1.23%, 7.08%)	186	2.69%	(0.88%, 6.16%)
		Postdose 3	187	99.47%	(97.06%, 99.99%)	194	99.48%	(97.16%, 99.99%)
Pertussis FHA	GMT	Predose 1	181	2.965	(2.715, 3.237)	186	2.902	(2.647, 3.181)
		Postdose 3	187	18.060	(16.801, 19.414)	194	17.135	(15.828, 18.550)
	SPR ≥ 20 EU/mL	Predose 1	181	0.00%	(0.00%, 2.02%)	186	0.00%	(0.00%, 1.96%)
		Postdose 3	187	44.92%	(37.65%, 52.35%)	194	43.81%	(36.72%, 51.10%)
Pertussis Toxin	GMT	Predose 1	181	5.319	(4.800, 5.894)	186	5.064	(4.565, 5.618)
		Postdose 3	187	46.086	(43.347, 48.998)	194	45.770	(42.974, 48.747)
	SPR ≥ 20 EU/mL	Predose 1	181	1.66%	(0.34%, 4.77%)	186	1.08%	(0.13%, 3.83%)
		Postdose 3	187	95.19%	(91.06%, 97.78%)	194	94.33%	(90.08%, 97.14%)
Tetanus	GMT	Predose 1	179	0.041	(0.036, 0.046)	183	0.040	(0.035, 0.044)
		Postdose 3	187	4.354	(4.034, 4.700)	194	4.724	(4.365, 5.112)
	SPR ≥ 0.1 IU/mL	Predose 1	181	12.15%	(7.78%, 17.82%)	186	12.37%	(8.00%, 17.97%)
		Postdose 3	187	100.00%	(98.05%, 100.00%)	194	100.00%	(98.12%, 100.00%)

PPI: Evaluable subjects are those who receive their scheduled doses without intervening laboratory-confirmed disease specific to the antigen earlier than the blood sample collection Postdose 3, adhere to the guidelines for administration of vaccine, and have valid values available for analysis within specified day ranges.

N = Number of subjects in Per-Protocol Immunogenicity for DTaP population.

n = Number of subjects contributing to the per-protocol analysis.

GMT = Geometric mean titer.

CI = Confidence interval.The two-sided 95% CI for the GMTs is based on the natural log-transformed titers and t-distribution.The two-sided 95% CI for binomial responses is provided using the exact method by Clopper-Pearson

SPR = Seroprotection/seropositivity rate for proportion of subjects who achieve the seroprotection or seropositivity criteria. The seroprotection criteria for diphtheria and tetanus are defined as: (1) anti-diphtheria: antibody titers ≥0 .1 IU/mL; (2) anti-tetanus: antibody titers ≥0.1 IU/mL; The seropositivity criteria for pertussis are defined as: (3) anti-pertussis toxin: antibody titers ≥20EU/mL; (4) anti-pertussis filamentous hemagglutinin(FHA): antibody titers ≥20EU/mL. All of these seroprotection/seropositivity criteria are based on NIFDC laboratory criteria.

Other secondary objectives included characterizing the immunogenicity of RotaTeq™ as measured by 1) serum anti-rotavirus total immunoglobulin A (IgA) and 2) serum neutralizing antibody (SNA) responses to the human rotavirus serotypes G1, G2, G3, G4, and P1A[8].

Analysis on anti-rotavirus total IgA was conducted on subjects enrolled in Cohort 1 Immunogenicity Subgroup A (Concomitant Use) and Cohort 2 Immunogenicity Subgroup B (Staggered Use), while type-specific SNA was performed in subjects of Cohort 2 Immunogenicity Subgroup B (Staggered Use). A total of 361 subjects who received RotaTeq™ and 372 subjects who received placebo were included in the PPI analysis for anti-rotavirus total IgA (Table 6). A total of 175 subjects who received RotaTeq™

and 180 subjects who received placebo were included in the PPI analysis for type-specific SNA (Table 7).

A 3-fold rise in titer from baseline was used as the criteria for seroconversion. A 3-fold rise in titer and GMTs were summarized by vaccination group in the PPI population.

Table 6
Immunogenicity Summary for Serum Anti-Rotavirus Total IgA (Per-Protocol Immunogenicity for ROTATEQ® Population)

Antigen (Assay)	Parameter	ROTATEQ® (N=361)			Placebo (N=372)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
Serum Anti-rotavirus Total IgA	Predose 1 GMT	349	0.15	(0.13, 0.18)	356	0.17	(0.14, 0.21)
	Postdose 3 GMT	361	82.42	(66.19, 102.63)	372	0.33	(0.26, 0.42)
	Proportion of subjects with a ≥ 3-fold rise	349	89.40%	(85.68%, 92.42%)	356	10.11%	(7.18%, 13.72%)

PPI: Evaluable subjects are those who receive their scheduled doses without intervening laboratory-confirmed disease specific to the antigen earlier than the blood sample collection Postdose 3, adhere to the guidelines for administration of vaccine, and have valid values available for analysis within specified day ranges.
N = Number of subjects in Per-Protocol Immunogenicity for ROTATEQ® population.
n = Number of subjects contributing to the per-protocol analyses (for ≥ 3 fold rise, limited to per-protocol subjects with both Predose 1 and Postdose 3 serology).
GMT = Geometric mean titer.
CI = Confidence interval. The two-sided 95% CI for the GMTs is based on the natural log-transformed titers and t-distribution. The two-sided 95% CI for binomial responses is provided using the exact method by Clopper-Pearson.

Table 7
Immunogenicity Summary of Response to Serum Neutralizing Antibody Serotypes G1, G2, G3, G4 and P1A [8] (Per-Protocol Immunogenicity for ROTATEQ® Population, Staggered Use Group)

Antigen (Assay)	Parameter	ROTATEQ® (N=175)			Placebo (N=180)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
Serotypes G1	Predose 1 GMT	175	43.41	(38.69, 48.71)	180	49.65	(44.33, 55.60)
	Postdose 3 GMT	175	141.88	(120.49, 167.07)	180	17.94	(15.93, 20.20)
	Proportion of subjects with a ≥ 3-fold rise	175	51.43%	(43.77%, 59.04%)	180	0.00%	(0.00%, 2.03%)
Serotypes G2	Predose 1 GMT	175	24.03	(20.76, 27.81)	180	30.35	(25.62, 35.95)
	Postdose 3 GMT	175	25.16	(20.96, 30.21)	180	10.67	(9.37, 12.17)
	Proportion of subjects with a ≥ 3-fold rise	175	19.43%	(13.85%, 26.08%)	180	0.56%	(0.01%, 3.06%)
Serotypes G3	Predose 1 GMT	175	23.93	(20.11, 28.47)	180	23.73	(19.87, 28.34)
	Postdose 3 GMT	175	21.97	(18.64, 25.89)	180	8.33	(7.39, 9.38)
	Proportion of subjects with a ≥ 3-fold rise	175	13.71%	(8.99%, 19.72%)	180	0.00%	(0.00%, 2.03%)
Serotypes G4	Predose 1 GMT	175	33.82	(29.99, 38.14)	180	43.34	(37.23, 50.44)
	Postdose 3 GMT	175	76.94	(67.25, 88.01)	180	14.84	(13.18, 16.72)
	Proportion of subjects with a ≥ 3-fold rise	175	37.14%	(29.97%, 44.76%)	180	0.00%	(0.00%, 2.03%)
Serotypes P1A[8]	Predose 1 GMT	175	39.18	(33.88, 45.31)	180	43.73	(37.69, 50.72)
	Postdose 3 GMT	175	125.01	(103.00, 151.72)	180	11.98	(10.44, 13.74)
	Proportion of subjects with a ≥ 3-fold rise	175	46.86%	(39.29%, 54.53%)	180	0.56%	(0.01%, 3.06%)

PPI: Evaluable subjects are those who receive their scheduled doses without intervening laboratory-confirmed disease specific to the antigen earlier than the blood sample collection Postdose 3, adhere to the guidelines for administration of vaccine, and have valid values available for analysis within specified day ranges.
N = Number of subjects in Per-Protocol Immunogenicity for ROTATEQ® population.
n = Number of subjects contributing to the per-protocol analyses (for ≥ 3 fold rise, limited to per-protocol subjects with both Predose 1 and Postdose 3 serology).
GMT = Geometric mean titer.
CI = Confidence interval. The two-sided 95% CI for the GMTs is based on the natural log-transformed titers and t-distribution. The two-sided 95% CI for binomial responses is provided using the exact method by Clopper-Pearson.

Safety:

The study included a secondary objective to evaluate the safety of RotaTeq™ with respect to all AEs within 30 days after each dose of RotaTeq™/placebo. The safety for concomitant vaccination of RotaTeq™ together with OPV and DTaP in the Concomitant Use Group (including immunogenicity subgroup and non-immunogenicity subgroup) was also assessed.

All AEs (non-serious and serious) regardless of causality were collected for all randomized subjects for 30 days following each vaccination of RotaTeq™/placebo. The safety data were collected for Day 1 (day of vaccination) to Day 14 using a standardized VRC (vaccine report card). All safety follow-up periods include the day of vaccination. The VRC was reviewed with parent/legal guardian at Study Visits 2, 4, and 6. All AEs reported by the parent/legal guardian from Day 15 to Day 30 following each dose of RotaTeq™/placebo were also collected. All the subjects who received at least 1 vaccination are included in the summaries of AEs.

The safety of RotaTeq™ with attention to elevated temperature (axillary temperature $\geqslant$37.5°C, or equivalent), vomiting, diarrhoea (within 30 days following vaccination) and intussusception (IS) was also analysed. Maximum axillary temperatures were measured daily through 7 days following each vaccination and recorded on the VRC. Pre-specified solicited AEs of diarrhoea and/or vomiting were collected through 14 days following each vaccination and recorded on the VRC.

Subjects with SAEs were followed until resolution or the end of study. SAEs, deaths, and/or cases of IS were reported from the time of consent until the end of the study for all subjects (last subject's last study visit) and were reported immediately to study personnel regardless of causality. The broad AE categories consisting of the percentage of subjects with any AE, a vaccine-related AE, an SAE, an AE which is both vaccine-related and serious, and those who discontinued due to an AE were summarized and analysed.

Adverse Events Among All Subjects in the Study

Table 8 displays a summary of AEs according to study vaccination received for all vaccinated subjects that occurred within 30 days following any vaccination. There were 1,079 subjects (53.5%, 1,079/2,015) with 1 or more AEs in the group that received RotaTeq™, and 1,077 subjects (53.3%, 1,077/2,019) in the placebo group. In the group that received RotaTeq™, 116 subjects experienced SAEs, and the same number of subjects had SAEs in the placebo group. A total of 29 subjects discontinued due to an AE.

The incidences of subjects with AEs, SAEs, deaths, vaccine-related AEs, vaccine-related SAEs, and any discontinuation due to AEs, appeared comparable within the 2 vaccination groups.

No deaths were reported within 30 days following any vaccination for all subjects. However, one (<0.1%) death was reported during the study follow-up period, which occurred in the placebo group and was considered to be unrelated to the study vaccination. Two (2) IS cases were reported during the trial, and both were observed in the group that received RotaTeq™, but were considered by the study investigator to be unrelated to the study vaccination.

Table 8
Analysis of Adverse Event Summary (within 30 Days Following any Vaccination Visit) (All Subjects as Treated Population)

	ROTATEQ®		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	2,015		2,019		
with one or more adverse events	1,079	(53.5)	1,077	(53.3)	0.2 (-2.9, 3.3)
with no adverse events	936	(46.5)	942	(46.7)	-0.2 (-3.3, 2.9)
with vaccine-related‡ adverse events	359	(17.8)	354	(17.5)	0.3 (-2.1, 2.6)
with serious adverse events	116	(5.8)	116	(5.7)	0.0 (-1.4, 1.5)
with serious vaccine-related adverse events	0	(0.0)	3	(0.1)	-0.1 (-0.4, 0.0)
who died	0	(0.0)	0	(0.0)	0.0 (-0.2, 0.2)
discontinued§ due to an adverse event	17	(0.8)	12	(0.6)	0.2 (-0.3, 0.8)
discontinued due to a vaccine-related adverse event	4	(0.2)	4	(0.2)	0.0 (-0.3, 0.3)
discontinued due to a serious adverse event	10	(0.5)	5	(0.2)	0.2 (-0.1, 0.7)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.2, 0.2)

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the vaccine.
§ Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
All events were collected within 30 days after any vaccination and before next vaccination.
CI = Confidence Interval

Summary of Adverse Events Among Subjects Who Received DTaP and OPV Concomitantly

The AEs for all subjects in the Concomitant Use Group that occurred within 30 days following any vaccination in the group that received RotaTeq™ and the placebo group are summarized in Table 9. Table 9 also provides an analysis of AEs between the recipients of RotaTeq™ and placebo in the Concomitant Use Group (ASaT). For subjects with one or more AEs, no significant difference was observed between the group that received RotaTeq™ and the placebo group. Furthermore, there were a similar number of subjects with an SAE reported in the group that received RotaTeq™ (5%) and the placebo group for the Concomitant Use Group (5.5%).

Table 9 Analysis of Adverse Event Summary (within 30 Days Following any Vaccination Visit) (All Subjects as Treated Population, Concomitant Use Group)

	ROTATEQ®		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	400		400		
with one or more adverse events	188	(47.0)	199	(49.8)	-2.8 (-9.6, 4.2)
with no adverse events	212	(53.0)	201	(50.3)	2.8 (-4.2, 9.6)
with vaccine-related‡ adverse events	101	(25.3)	118	(29.5)	-4.2 (-10.4, 1.9)
with serious adverse events	20	(5.0)	22	(5.5)	-0.5 (-3.7, 2.7)
with serious vaccine-related adverse events	0	(0.0)	1	(0.3)	-0.3 (-1.4, 0.7)
who died	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)
discontinued§ due to an adverse event	1	(0.3)	0	(0.0)	0.3 (-0.7, 1.4)
discontinued due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)
discontinued due to a serious adverse event	1	(0.3)	0	(0.0)	0.3 (-0.7, 1.4)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.0, 1.0)

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the vaccine.
§ Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
All events were collected within 30 days after any vaccination and before next vaccination.
CI = Confidence Interval

Analysis of Overall Adverse Events in Overall Study Population

The analysis of subjects with AEs (incidence ≥1% in one or more vaccination groups), by system organ class, within 30 days following any vaccination is provided in Table 10. The overall AE profile and incidences were generally comparable between the group that received RotaTeq™ and the placebo group.

The most common (incidence ≥10%) AEs were pyrexia (20.5% in RotaTeq™ recipients vs. 20.8% in placebo recipients), diarrhea (20.1% in RotaTeq™ recipients vs. 20.1% in placebo recipients) and nasopharyngitis (11.3% in RotaTeq™ recipients vs. 11.5% in placebo recipients).

For these AEs, the incidences in the group of RotaTeq™ were comparable with that of the placebo group.

Table 10
Analysis of Subjects With Adverse Events (Incidence ⩾1% in One or More Vaccination Groups) (within 30 Days Following any Vaccination Visit) (All Subjects as Treated Population)

	ROTATEQ[a]		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population with follow-up	2,015		2,019		
with one or more adverse events	1,079	(53.5)	1,077	(53.3)	0.2 (-2.9, 3.3)
with no adverse events	936	(46.5)	942	(46.7)	-0.2 (-3.3, 2.9)
Gastrointestinal disorders	491	(24.4)	497	(24.6)	-0.2 (-2.9, 2.4)
Diarrhoea	406	(20.1)	406	(20.1)	0.0 (-2.4, 2.5)
Enteritis	46	(2.3)	32	(1.6)	0.7 (-0.2, 1.6)
Vomiting	54	(2.7)	71	(3.5)	-0.8 (-1.9, 0.2)
General disorders and administration site conditions	419	(20.8)	422	(20.9)	-0.1 (-2.6, 2.4)
Pyrexia	414	(20.5)	419	(20.8)	-0.2 (-2.7, 2.3)
Infections and infestations	454	(22.5)	464	(23.0)	-0.5 (-3.0, 2.1)
Bronchitis	35	(1.7)	49	(2.4)	-0.7 (-1.6, 0.2)
Bronchopneumonia	33	(1.6)	40	(2.0)	-0.3 (-1.2, 0.5)
Gastroenteritis	23	(1.1)	26	(1.3)	-0.1 (-0.9, 0.5)
Nasopharyngitis	228	(11.3)	233	(11.5)	-0.2 (-2.2, 1.7)
Pharyngitis	34	(1.7)	27	(1.3)	0.4 (-0.4, 1.1)
Upper respiratory tract infection	98	(4.9)	111	(5.5)	-0.6 (-2.0, 0.7)
Respiratory, thoracic and mediastinal disorders	153	(7.6)	129	(6.4)	1.2 (-0.4, 2.8)
Cough	115	(5.7)	92	(4.6)	1.2 (-0.2, 2.5)
Rhinorrhoea	32	(1.6)	24	(1.2)	0.4 (-0.3, 1.2)

[†] Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
All events were collected within 30 days after any vaccination and before next vaccination.
CI = Confidence Interval

Analysis of Overall Adverse Events in Concomitant Use Group

The analysis of subjects with AEs (incidence ≥1% in one or more vaccination groups) by system organ class, within 30 days following any vaccination in the Concomitant Use Group is summarized in Table 11. The incidences of AEs appeared to be generally comparable between the group that received RotaTeq™ and the placebo group.

The most common (incidence ≥10%) AEs observed in the group of RotaTeq™ were diarrhoea (22.0%) and pyrexia (19.5%). The most common (incidence >10%) AEs in the group of placebo were diarrhea (27.5%) and pyrexia (20.5%).

Table 11

Analysis of Subjects With Adverse Events (Incidence ⩾1% in One or More Vaccination Groups) (within 30 Days Following any Vaccination Visit) (All Subjects as Treated Population, Concomitant Use Group

	ROTATEQ®		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	400		400		
with one or more adverse events	188	(47.0)	199	(49.8)	-2.8 (-9.6, 4.2)
with no adverse events	212	(53.0)	201	(50.3)	2.8 (-4.2, 9.6)
Gastrointestinal disorders	101	(25.3)	116	(29.0)	-3.7 (-9.9, 2.4)
Diarrhoea	88	(22.0)	110	(27.5)	-5.5 (-11.5, 0.5)
Enteritis	7	(1.8)	3	(0.8)	1.0 (-0.6, 2.9)
Vomiting	8	(2.0)	5	(1.3)	0.8 (-1.1, 2.8)
General disorders and administration site conditions	78	(19.5)	82	(20.5)	-1.0 (-6.6, 4.6)
Pyrexia	78	(19.5)	82	(20.5)	-1.0 (-6.6, 4.6)
Infections and infestations	53	(13.3)	58	(14.5)	-1.2 (-6.1, 3.6)
Bronchitis	7	(1.8)	7	(1.8)	0.0 (-2.0, 2.0)
Bronchopneumonia	5	(1.3)	6	(1.5)	-0.2 (-2.1, 1.6)
Candida infection	1	(0.3)	4	(1.0)	-0.8 (-2.3, 0.5)
Nasopharyngitis	14	(3.5)	17	(4.3)	-0.8 (-3.6, 2.0)
Pharyngitis	15	(3.8)	11	(2.8)	1.0 (-1.6, 3.7)
Upper respiratory tract infection	11	(2.8)	19	(4.8)	-2.0 (-4.9, 0.7)
Respiratory, thoracic and mediastinal disorders	16	(4.0)	16	(4.0)	0.0 (-2.8, 2.8)
Cough	11	(2.8)	15	(3.8)	-1.0 (-3.7, 1.6)

†Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
All events were collected within 30 days after any vaccination and before next vaccination.
CI = Confidence Interval

Serious Adverse Events

The safety of RotaTeq™ with respect to SAEs was evaluated for all subjects throughout the entire study.

Table 12 presents the number (%) of subjects with SAEs (incidence ≥1% in one or more vaccination groups). The most common (incidence ≥1%) SAEs were bronchopneumonia (6.4% in RotaTeq™ recipients and 7.0% in placebo recipients), followed by bronchitis (4.2% in RotaTeq™ recipients and 5.0% in placebo recipients) and enteritis (2.3% in RotaTeq™ recipients and 2.0% in placebo recipients). The overall incidences of SAE appeared to be comparable between recipients of RotaTeq™ and placebo.

A total of 984 SAEs were reported in a total of 667 subjects during the study.

There were 3 SAEs considered to be vaccine-related by the investigator in this study (intestinal obstruction, rotavirus enteritis and infectious diarrhoea). All vaccine-related SAEs occurred in subjects who received placebo.

There was no report of overdose throughout the trial.

Table 12

Subjects With Serious Adverse Events (Incidence ⩾ 1% in One or More Vaccination Groups) (All Subjects as Treated Population)

	ROTATEQ®		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	2,015		2,019		4,034	
with one or more adverse events	339	(16.8)	338	(16.7)	677	(16.8)
with no adverse events	1,676	(83.2)	1,681	(83.3)	3,357	(83.2)
Gastrointestinal disorders	53	(2.6)	58	(2.9)	111	(2.8)
Enteritis	47	(2.3)	41	(2.0)	88	(2.2)
Infections and infestations	307	(15.2)	310	(15.4)	617	(15.3)
Bronchitis	84	(4.2)	101	(5.0)	185	(4.6)
Bronchopneumonia	129	(6.4)	141	(7.0)	270	(6.7)
Diarrhoea infectious	20	(1.0)	21	(1.0)	41	(1.0)
Gastroenteritis rotavirus	7	(0.3)	24	(1.2)	31	(0.8)
Pharyngitis	21	(1.0)	23	(1.1)	44	(1.1)
Pneumonia	30	(1.5)	14	(0.7)	44	(1.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Death

One death (in the placebo group) due to thalassemia was reported during the study follow-up period. The death occurred on Day 124 Postdose 3 of placebo and was considered to be unrelated to the study vaccination by the investigator.

Adverse Events of Special Interest

Adverse Event of Special Interest Excluding Intussusception

Table 13 presents the results of these comparisons, and includes the number and percentage of subjects in each group reporting the AEs of special interest excluding IS (elevated temperature [axillary temperature ≥ 37.5ºC, or equivalent], vomiting and diarrhea), as well as the risk differences (RotaTeq™ minus placebo), 95% CIs, and p-values for those differences. As shown in Table 13, all p-values were greater than 0.05, two-sided.

Overall, there was no clinical evidence of a difference between the group that received RotaTeq™ and the placebo group with respect to the incidences of these AEs of special clinical interest.

Table 13
Analysis of Subjects with Protocol-Specified Solicited Adverse Events within 30 Days Following Any Vaccination (All Subjects as Treated Population)

	ROTATEQ®			Placebo			Risk Difference ROTATEQ®-Placebo (95% CI)†	P-Value (2-sided)
	n	m	%	n	m	%		
Elevated Temperature								
Post Dose 1	154	2015	7.64%	165	2019	8.17%	-0.53% (-2.20%, 1.14%)	
Post Dose 2	146	1946	7.50%	173	1959	8.83%	-1.33% (-3.06%, 0.39%)	
Post Dose 3	191	1932	9.89%	182	1946	9.35%	0.53% (-1.33%, 2.40%)	
Post Any Dose	440	2015	21.84%	461	2019	22.83%	-1.00% (-3.57%, 1.57%)	0.4473
Vomiting								
Post Dose 1	40	2015	1.99%	49	2019	2.43%	-0.44% (-1.37%, 0.47%)	
Post Dose 2	11	1946	0.57%	16	1959	0.82%	-0.25% (-0.82%, 0.29%)	
Post Dose 3	5	1932	0.26%	11	1946	0.57%	-0.31% (-0.78%, 0.11%)	
Post Any Dose	54	2015	2.68%	71	2019	3.52%	-0.84% (-1.93%, 0.24%)	0.1252
Diarrhoea								
Post Dose 1	218	2015	10.82%	189	2019	9.36%	1.46% (-0.40%, 3.33%)	
Post Dose 2	143	1946	7.35%	162	1959	8.27%	-0.92% (-2.61%, 0.77%)	
Post Dose 3	97	1932	5.02%	124	1946	6.37%	-1.35% (-2.83%, 0.11%)	
Post Any Dose	406	2015	20.15%	406	2019	20.11%	0.04% (-2.44%, 2.52%)	0.9748

Calculation of percentage: The number of subjects evaluated divided by the number of subjects with follow-up.
Elevated temperature is defined as axillary temperature $\geq 37.5^{0}$C.
m = Number of subjects with follow-up; n = Number of subjects with event;
† Based on Miettinen & Nurminen method.
All events were collected within 30 days after any vaccination and before next vaccination.
CI = Confidence interval

Adverse Event of Special Interest In Concomitant Use Group

The incidences of AEs of special interest excluding IS (elevated temperature [axillary temperature ≥37.5ºC, or equivalent], vomiting and diarrhea), were also compared in the Concomitant Use Group of RotaTeq™/placebo with OPV and DTaP. There was no difference in the incidences of these events of special interest between the group that received RotaTeq™ and the placebo group in the Concomitant Use Group.

Intussusception

There were two cases of intussusception reported in this study, both in the group that received RotaTeq™. Neither event of intussusception was considered vaccine related by the investigator.

Of the two cases of IS, one case was observed in the Concomitant Use group. The first case of IS occurred in a 77-day old female on Day 32 Postdose 1. Per the protocol, this subject did not receive subsequent doses of RotaTeq™. The second case occurred in a 173-day old male on Day 53 Postdose 3. Both subjects recovered after receiving treatment (air enema and air enema/surgical reduction, respectively).

Maximum Temperatures

Maximum Temperatures in Overall Study Population

Axillary temperatures were collected and reported for all subjects on Days 1-7 following the receipt of each of the 3 doses of RotaTeq™/placebo. Temperatures collected via other methods were converted to axillary-equivalent temperatures. If the subject presented with an elevated temperature or had a reported AE of AGE and dehydration rehydration (DERE), the temperature was recorded. Any unscheduled assessment or symptom-driven assessment of temperature was also recorded. Fever >38.1°C was reported for 80.5% of subjects who received RotaTeq™ within 7 days following any vaccination visit and 81.0% for placebo.

Maximum Temperatures in Concomitant Use Group

Fever >38.1°C was reported for 84.9% of subjects who received RotaTeq™ within 7 days following any vaccination visit and 86.5% of subjects who received placebo.

Discussion on clinical aspects

The study showed that RotaTeq was efficacious against naturally-occurring RVGE regardless of severity and serotype occurring at least 14 days following the third vaccination, and was also efficacious against naturally occurring severe RVGE regardless of serotype that occurred at least 14 days following the third vaccination. The ITT analysis was also consistent with the above observations with respect to naturally-occurring RVGE regardless of serotype and severity that occurred at least 14 days after the first vaccination.

RotaTeq was highly efficacious against RVGE caused by serotypes contained in the vaccine that occurred at least 14 days following the third vaccination.

The data regarding all-cause gastroenteritis showed that RotaTeq™ was efficacious against any severity and severe all-cause gastroenteritis that occurs at least 14 days following the third vaccination.

With respect to immunogenicity, the immune responses with respect to Postdose 3 GMTs and SPRs from baseline to Postdose 3 to diphtheria, tetanus, pertussis toxin, pertussis filamentous among recipients of RotaTeq™ were as high as those observed among recipients of placebo.

The applicant has highlighted the fact that in this study, the proportion of subjects who had a $\geqslant$ 3-fold rise post vaccination in anti-rotavirus total IgA was 89.4% which is numerically lower than those of prior phase III studies (97.3% in PN006, 95.5% in PN007, 95.5% in PN009), which were conducted in developed countries. However it is numerically comparable to those observed in other developing countries, which was 78.3% in Africa (Ghana, Kenya, Mali) (PN015), 87.8% in Asia (Bangladesh, Vietnam) (PN015), and 82.8% in India (PN021). Although the exact mechanism for these differences is not clear, it should, nevertheless, be noted that there is no proven immune correlate of protection for natural RVGE or for rotavirus vaccines. The applicant has also stated that SNA responses to G1, G2, G3, G4, and P1A[8] are generally similar to those observed in other phase III studies, including PN007 in developed countries, PN015 and PN021 in Asian countries.

As far as safety is concerned, the data would appear to indicate that Rotateq is generally well tolerated.

The incidences of AEs were comparable between subjects vaccinated with RotaTeq and placebo. The majority of reported AEs and SAEs were determined to be not related to the study vaccine. The proportion of subjects, who died, experienced a SAE, experienced a vaccine-related AE or SAE, or discontinued from the study due to a SAE were comparable between the 2 vaccination groups.

The proportion of subjects with reported AEs of special interest (elevated temperature, diarrhoea, and vomiting) were comparable between the group that received RotaTeq™ and the placebo group.

It is notable that there were 2 cases of acute intussusception reported in the Rotateq group.

One case was observed in the Concomitant Use group. The first case of IS occurred in a 77-day old female on Day 32 Postdose 1 and accordingly as per the protocol, this subject did not receive subsequent doses of RotaTeq™. The second case occurred in a 173-day old male on Day 53 Postdose 3. However, neither event was considered vaccine-related by the investigator and both subjects recovered. Nevertheless, a small risk of IS caused by Rotavirus vaccine cannot be fully excluded, however, this does not significantly impact on the positive benefit risk of vaccination.

In the Concomitant Use Group of subjects that received RotaTeq™ concomitantly with OPV and DTaP, the proportions of subjects with reported AEs of special interest (elevated temperature, diarrhoea, and vomiting) were also comparable between the group that received RotaTeq™ and the placebo group.

3. CHMP's overall conclusion and recommendation

This study appeared to demonstrate that in healthy Chinese infants, 6 to 12 weeks of age at enrolment, RotaTeq™ is efficacious against naturally-occurring RVGE regardless of serotype and severity as well as being efficacious against naturally-occurring severe RVGE regardless of serotype that occurs at least 14 days following the third vaccination. The vaccine is immunogenic with respect to anti-rotavirus total IgA response and SNA responses to G1, G2, G3, G4, P1A[8].

From a safety perspective, the vaccine is generally well-tolerated with respect to all clinical AEs, and immune responses induced by OPV and DTaP are not affected by the concomitant use of RotaTeq™. Accordingly, there is no change to the benefit/risk.

Overall conclusion

The submission is satisfactory in terms of addressing the requirements of the MAH under Article 46 of Regulation (EC) No1901/2006, as amended.

Recommendation

☒ **Fulfilled:**