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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/P46/044

Note

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

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Introduction

On 15 January 2016, the MAH submitted a completed paediatric study Prot. No. 035, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development programme

The MAH stated that the study, entitled:

- A Double-Blind, Randomized, Controlled, Multicentre Study to Evaluate the Safety, Tolerability, and Immunogenicity of a New Formulation of RotaTeq™

is a standalone study.

1.2. Information on the pharmaceutical formulation used in the studies

The pharmaceutical formulation used in the studies was an oral solution. RotaTeq (Rotavirus vaccine, Live, Oral, Pentavalent) is administered as a 2 mL solution per dose for oral administration for both groups. The vaccine is contained in a single-dose plastic tube. Each dose of study vaccine (new or current formulation of RotaTeq™) consisted of a 2-mL, oral solution of 5 live human-bovine reassortant rotaviruses which contains a minimum of 2.0 to 2.8 x 106 infectious units (IU) per reassortant dose, depending on the serotype, and not greater than 116 x 106 IU per aggregate dose.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- V260-035; NCT01600092 A Double-Blind, Randomized, Controlled, Multicentre Study to Evaluate the Safety, Tolerability, and Immunogenicity of a New Formulation of RotaTeq™

The current formulation of RotaTeq™ must be stored at 2 to 8°C for the duration of its shelf-life (24 months). While there are some allowances for temperature excursions, the vaccine is unstable at temperatures >25°C. A more thermostable formulation of RotaTeq™, referred to as New Formulation (also referred to as the “Vaccine Vial Monitor Compatible [VVMC] formulation”), has been developed and used in the clinical study protocol (V260-035; NCT01600092). This new formulation of RotaTeq™ has the ability to meet the stability requirements of an existing Vaccine Vial Monitor (VVM). The new formulation of RotaTeq™ also has increased shelf-life of 3 years.

1.3.2. Clinical studies

Clinical study number and title

- V260-035; NCT01600092 A Double-Blind, Randomized, Controlled, Multicentre Study to Evaluate the Safety, Tolerability, and Immunogenicity of a New Formulation of RotaTeq™

Description

Methods

Objectives

Primary Objective:

To summarize and compare the vaccine-induced serum neutralizing antibody (SNA) to human rotavirus serotypes G1, G2, G3, G4, and P1A[8] at 42 days post dose 3 between recipients of the new formulation and recipients of the current formulation of RotaTeq™.

Secondary Objectives:

(1) To assess the safety and tolerability of the new formulation of RotaTeq™.

(2) To summarize the geometric mean titres (GMTs) of vaccine-induced serum anti-rotavirus IgA at

42 days post dose 3 in recipients of the new formulation and recipients of the current formulation of RotaTeq™.

(3) To summarize the proportion of subjects with a ≥3-fold rise in SNA titre against human rotavirus serotypes G1, G2, G3, G4, and P1A[8] as well as antibody titre for serum anti-rotavirus IgA from baseline to 42 days post dose 3 in recipients of the new formulation and recipients of the current formulation of RotaTeq™.

Study design

This was a double-blind, randomized, controlled, multicentre trial to primarily demonstrate the non-inferiority of the new formulation of RotaTeq™ relative to the current formulation of RotaTeq™ on the basis of immunogenicity. The primary purpose of the study was to demonstrate the noninferiority of the new formulation of RotaTeq™ when compared with the current formulation of RotaTeq™ on the basis of immunogenicity.

Study population /Sample size

Approximately 924 healthy, eligible infants between 6 and 12 weeks of age (42 to 84 days) at receipt of the first study vaccination (Date of Birth is age Day 1) A total of 462 subjects per vaccination group were to be enrolled and vaccinated in the study.

Treatments

Subjects were randomly assigned to 1 of 2 vaccination groups: new formulation of RotaTeq™ and current formulation of RotaTeq™. Each subject received a total of three 2- mL oral doses of study vaccine. The first dose was administered between 6 and 12 weeks (42 to 84 days) of age and the third dose was administered before 32 weeks of age or per local regulation. Each dose of study vaccine was separated by a minimum of 4 weeks (28 days).

Other approved routine paediatric vaccines (such as diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, inactivated poliovirus vaccine [IPV], hepatitis B vaccine [HBV], pneumococcal conjugate vaccines and Haemophilus influenzae type b [Hib] conjugate vaccines) could have been administered during the study per country and study site practice.

Outcomes/endpoints

Immunogenicity Endpoints

Primary immunogenicity endpoint

The primary immunogenicity endpoints were the SNA titres to human rotavirus serotype G1, G2, G3, G4, and P1A[8] included in the vaccine.

Secondary immunogenicity endpoints

The secondary immunogenicity endpoints included serum anti-rotavirus IgA, and proportion of subjects with a ≥3-fold rise from baseline for SNA to human rotavirus serotypes G1, G2, G3, G4, and P1A[8], as well as for serum anti-rotavirus IgA.

Safety Endpoints

Safety endpoints included incidence of AEs collected for 42 days following each dose. In addition, all SAEs regardless of causality, all deaths, and any cases of intussusception (ECI) were to be reported from the time of consent until the end of the entire study.

Statistical Methods

Immunogenicity:

For non-inferiority regarding the geometric mean titres (GMTs) for all 5 immunogenicity endpoints, the GMT ratio and associated 95% CI were calculated from a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [Ref. 5.4: 03QK6K] on the log-transformed baseline and post-vaccination titre values. This analysis was adjusted for country and baseline titres and used all available data at both baseline and post vaccination.

Success criteria required that the lower bound of the 95% confidence interval (CI) of the GMT ratio be >0.67 (corresponding to a no more than 1.5-fold decrease in the GMT of the [New] VVMC formulation compared with the current formulation). The primary immunogenicity endpoints were the SNA titres to human rotavirus serotype G1, G2, G3, G4, and P1A[8] included in the vaccine. The secondary immunogenicity endpoints included serum anti-rotavirus IgA, and proportion of subjects with a ≥3-fold rise from baseline for SNA to human rotavirus serotypes G1, G2, G3, G4, and P1A[8], as well as for serum antirotavirus IgA.

The per-protocol (PP) population served as the primary population for the immunogenicity analysis in this study. The PP population is 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 would substantially affect the results of the primary immunogenicity endpoints. Analyses and summaries of Post dose 3 assay values included subjects who had Post dose 3 assay results. The final determination of protocol violations and thereby the composition of PP population was made prior to the final unblinding of the database. A supportive immunogenicity summary and analysis were done on the Full Analysis Set (FAS) population that included all randomized subjects with available serology data, for each serology time point for all endpoints associated with the primary hypothesis. Subjects were included in the vaccine group to which they were randomized for immunogenicity analyses.

Safety:

Statistical analysis followed a tiered approach to evaluate the safety data. The tiers differed with respect to the analyses that were performed. Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that were subject to inferential testing for statistical significance with p-values.

For Tier 1 safety endpoints analysis, 95% CI was used for between-group comparisons. Other safety parameters were included in 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 vaccine group were provided for Tier 3 safety parameters. P-values and 95% CI for the percentage differences between the 2 vaccine groups were calculated using the Miettinen and Nurminen method. AEs (specific terms as well as system organ class terms) that were not prespecified as Tier 1 endpoints, were classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Tier 2 included only AEs which were exhibited by at least 4 subjects in any vaccine group. All other AEs belonged to Tier 3. The threshold of at least 4 events was chosen because the 95% CI would not show a statistically significant difference between the 2 vaccine groups if the events were <4 in each vaccine group. For safety evaluation, all statistical tests were conducted at the $\alpha = 0.05$ (2-sided) level, unless otherwise stated.

Results

Recruitment/ Number analysed

Of the 1039 subjects screened, 1020 subjects were randomized (513 in the New formulation group and 507 in the current formulation group). Inability to obtain blood specimen at randomization was the most common reason for subjects not randomized (n=12).

Of the 1020 subjects randomized, 1014 subjects received at least 1 dose of study vaccine. The 6 randomized subjects who were not vaccinated included 3 subjects who were determined by the investigator to be screen failures and 3 subjects who were withdrawn by his/her parent/legal guardian prior to study vaccination. Overall, 98% of the subjects completed the 3 dose vaccination series. The number (%) of subjects discontinued from the study was low (<3%) and were similar in the 2 vaccination groups. The most common reason for study discontinuation was parent withdrew consent (1.4%). Details in summarised in Table 1 and baseline characteristics in Table 2.

Table 1

Disposition of Subjects

	RotaTeq™ New Formulation		RotaTeq™ Current Formulation		Total	
	n	(%)	n	(%)	n	(%)
Screened					1039	
Randomized	513		507		1020	
Vaccinated	510		504		1014	
Vaccinated at[1]						
Vaccination 1	510	(100.0)	504	(100.0)	1014	(100.0)
Vaccination 2†	505	(99.0)	497	(98.6)	1002	(98.8)
Vaccination 3	500	(98.0)	494	(98.0)	994	(98.0)
Subject Study Medication Disposition[2]						
Did not get full dose (2mL) at						
Vaccination 1	4	(0.8)	3	(0.6)	7	(0.7)
Vaccination 2	3	(0.6)	2	(0.4)	5	(0.5)
Vaccination 3	6	(1.2)	3	(0.6)	9	(0.9)
End of Treatment Disposition[1]						
Received all 3 doses†	500	(98.0)	494	(98.0)	994	(98.0)
Discontinued	10	(2.0)	10	(2.0)	20	(2.0)
Adverse Event	2	(0.4)	0	(0.0)	2	(0.2)
Lost To Follow-Up	1	(0.2)	4	(0.8)	5	(0.5)
Parent/Guardian Withdrew Consent	5	(1.0)	6	(1.2)	11	(1.1)
Physician Decision*	2	(0.4)	0	(0.0)	2	(0.2)
Trial Disposition (End of Study)[1]						
Completed	495	(97.1)	491	(97.4)	986	(97.2)
Received all 3 Doses† and Completed‡	494	(96.9)	491	(97.4)	985	(97.1)
Discontinued	15	(2.9)	13	(2.6)	28	(2.8)
Adverse Event	2	(0.4)	0	(0.0)	2	(0.2)
Lost To Follow-Up	4	(0.8)	6	(1.2)	10	(1.0)
Parent/Guardian Withdrew Consent	8	(1.6)	6	(1.2)	14	(1.4)
Physician Decision*	1	(0.2)	1	(0.2)	2	(0.2)

Each subject is counted once for Trial Disposition and Subject Study Medication Disposition.

† Included 1 subject who received non-study RotaTeq™ instead of study vaccine at Dose 2.

‡ Completed = completing safety followup/study procedures at Visit 4.

* One subject (AN 100998) discontinued treatment (physician decision) after dose 2 but returned to complete the last study visit and blood draw (Visit 4).

[1] Percentages were based on the number of randomized subjects who received at least one dose of study vaccine.

[2] Percentages based on subjects who were vaccinated at each vaccination visit.

n = Number of subjects included in each category.

Table 2

Subject Characteristics
(All Randomized Subjects)

	RotaTeq™ New Formulation		RotaTeq™ Current Formulation		Total	
	n	(%)	n	(%)	n	(%)
Randomized Subjects	513		507		1,020	
Gender						
Male	281	(54.8)	267	(52.7)	548	(53.7)
Female	232	(45.2)	240	(47.3)	472	(46.3)
Age (Weeks)*						
Under 6 weeks	0	(0.0)	0	(0.0)	0	(0.0)
6 to 12 weeks	513	(100.0)	507	(100.0)	1,020	(100.0)
Over 12 weeks	0	(0.0)	0	(0.0)	0	(0.0)
Mean	8.4		8.3		8.3	
SD	1.4		1.4		1.4	
Median	8.0		8.0		8.0	
Range	6 to 12		6 to 12		6 to 12	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.2)	1	(0.1)
Asian	3	(0.6)	2	(0.4)	5	(0.5)
Black Or African American	24	(4.7)	21	(4.1)	45	(4.4)
Multi-Racial	56	(10.9)	58	(11.4)	114	(11.2)
White	430	(83.8)	425	(83.8)	855	(83.8)
Ethnicity						
Hispanic or Latino	50	(9.7)	58	(11.4)	108	(10.6)
Not Hispanic or Latino	441	(86.0)	423	(83.4)	864	(84.7)
Not Reported/Unknown	22	(4.3)	26	(5.1)	48	(4.7)
Birth Weight (kg)						
Subjects with data	510		505		1015	
Mean	3.3		3.3		3.3	
SD	0.5		0.5		0.5	
Median	3.3		3.3		3.3	
Range	1.4 to 4.8		1.4 to 5.0		1.4 to 5.0	
Gestational Age at Birth						
38 weeks or more	438	(85.4)	442	(87.2)	880	(86.3)
33 to 37 weeks	67	(13.1)	62	(12.2)	129	(12.6)
28 to 32 weeks	5	(1.0)	1	(0.2)	6	(0.6)
Not provided/Unknown	3	(0.6)	2	(0.4)	5	(0.5)

* Age at enrollment.
Percentages were based on the number of randomized subjects.
n = Number of subjects included in the analysis.

Efficacy results

Primary Immunogenicity Analyses

The primary immunogenicity analyses and summaries of Post dose 3 assay values included subjects who had Post dose 3 assay results (per-protocol population). The results of the primary immunogenicity analysis are summarized in Tables 3 and 4. The primary immunogenicity hypothesis was met for all 5 serotypes, and therefore non-inferiority with respect to immunogenicity can be asserted for the VVMC formulation of RotaTeq™ as compared to the current formulation of RotaTeq™. Of note, the GMT for G3 was higher in the VVMC formulation group compared to the current formulation group.

A per-protocol summary of SNA responses to serotypes G1, G2, G3, G4 and P1A measured Predose 1 and ~42 days Post dose 3 is provided for both vaccine groups in Table 4.

The observed GMTs and proportion of subjects with a ≥3-fold rise of rotavirus SNA to serotypes G1, G2, G3, G4 and P1A from baseline to ~42 days Post dose 3, as well as the associated 95% CI are also shown in Table 4. At baseline, the GMTs were comparable between the vaccine groups across all serotypes. Post dose 3, the VVMC formulation group had a higher GMT response for serotype G3, and the 95% CI and proportion of subjects with a 3-fold rise did not overlap between the 2 vaccine groups. For the other serotypes (G1, G2, G4, P1A), the 95% CIs for GMTs and proportion of subjects with a ≥3-fold rise were comparable between the 2 vaccine groups Post dose 3.

Table 3

Statistical Analysis of Non-inferiority of GMT for the SNA Responses to Reassortants Rotavirus Serotypes G1, G2, G3, G4 and P1A
(Per-Protocol Population)

Antigen	RotaTeq™ New Formulation (N=495)		RotaTeq™ Current Formulation (N=488)		Ratio of GMTs †§ (95% CI)‡	P-value	Similarity Conclusion
	N	Estimated GMT†	N	Estimated GMT†			
Serotypes G1	495	99.5	488	107.6	0.92 (0.79, 1.07)	<0.001	Similar‡
Serotypes G2	495	30.7	488	26.7	1.15 (0.99, 1.33)	<0.001	Similar‡
Serotypes G3	495	82.6	488	25.8	3.20 (2.75, 3.74)	<0.001	Similar‡
Serotypes G4	495	77.3	488	72.8	1.06 (0.94, 1.20)	<0.001	Similar‡
Serotypes P1A	495	107.2	488	92.5	1.16 (1.00, 1.35)	<0.001	Similar‡

† GMTs and their ratio were based on a model with terms for treatment and country, with the constraint that the mean baseline is the same for all treatment groups.
‡ A 95% CI on the ratio excluding a 1.5-fold decrease or more (i.e., the lower bound of CI > 0.67) and associated 1-sided p-value ≤ 0.025 implies that the difference is statistically significantly less than the pre-specified clinically relevant decrease of 1.5-fold and allows for a conclusion of non-inferiority.
§ [New Formulation group] / [Current Formulation group].
SNA = Serum neutralization assay.
N = Number of subjects vaccinated.
n = Number of subjects contributing to the per-protocol analyses.
CI = Confidence interval.

Table 4

Immunogenicity Summary for SNA Response to Serotypes G1, G2, G3, G4 and P1A
(Per-Protocol Population)

Antigen (Assay)	Parameter	RotaTeq™ New Formulation (N=495)			RotaTeq™ Current Formulation (N=488)		
		n	Observed Response.	95% CI	n	Observed Response.	95% CI
Serotypes G1	Predose 1 GMT	495	27.3	(24.7, 30.2)	487	29.3	(26.7, 32.2)
	Postdose 3 GMT	480	99.8	(89.7, 111.1)	482	106.1	(94.6, 119.0)
	Proportion of subjects with a ≥ 3-fold rise	480	56.0%(269/480)	(51.5%, 60.5%)	481	53.8%(259/481)	(49.3%, 58.4%)
Serotypes G2	Predose 1 GMT	495	15.0	(13.7, 16.5)	487	16.2	(14.8, 17.6)
	Postdose 3 GMT	480	30.0	(27.0, 33.3)	482	26.3	(23.7, 29.1)
	Proportion of subjects with a ≥ 3-fold rise	480	30.4%(146/480)	(26.3%, 34.7%)	481	26.8%(129/481)	(22.9%, 31.0%)
Serotypes G3	Predose 1 GMT	495	11.7	(10.4, 13.1)	487	13.4	(12.0, 15.0)
	Postdose 3 GMT	480	82.8	(74.2, 92.5)	482	25.2	(22.6, 28.1)
	Proportion of subjects with a ≥ 3-fold rise	480	65.8%(316/480)	(61.4%, 70.1%)	481	33.3%(160/481)	(29.1%, 37.7%)
Serotypes G4	Predose 1 GMT	495	21.4	(19.4, 23.7)	487	25.6	(23.3, 28.3)
	Postdose 3 GMT	480	78.9	(72.3, 86.1)	482	71.5	(65.4, 78.1)
	Proportion of subjects with a ≥ 3-fold rise	480	58.3%(280/480)	(53.8%, 62.8%)	481	49.7%(239/481)	(45.1%, 54.3%)
Serotypes P1A	Predose 1 GMT	495	37.6	(33.7, 41.9)	487	42.5	(38.2, 47.4)
	Postdose 3 GMT	480	106.9	(96.5, 118.4)	482	90.1	(80.2, 101.2)
	Proportion of subjects with a ≥ 3-fold rise	480	49.6%(238/480)	(45.0%, 54.2%)	481	42.6%(205/481)	(38.2%, 47.2%)

N = Number of subjects vaccinated.
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.
SNA = Serum neutralization assay.

Secondary Immunogenicity Analyses

The secondary immunogenicity analyses of serum anti-rotavirus IgA measured Predose 1 and 42 days Post dose 3 are shown in Table 5. This PP analysis showed that GMTs of serum anti-rotavirus IgA from Day 1-42 days Post dose 3 in the 2 vaccine groups were comparable. Though the proportion of subjects with a ≥3-fold rise of serum anti-rotavirus IgA in the VVMC formulation group (97.3%) was numerically higher than in the current formulation group (95.2%), the two 95% CIs overlapped.

Table 5

Immunogenicity Summary for Serum Anti-rotavirus IgA
(Per-Protocol Population)

Antigen (Assay)	Parameter	RotaTeq™ New Formulation (N=495)			RotaTeq™ Current Formulation (N=488)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
Serum Anti-rotavirus IgA	Predose 1 GMT	490	0.2	(0.1, 0.2)	484	0.2	(0.2, 0.2)
	Postdose 3 GMT	474	240.5	(210.4, 274.8)	474	235.5	(204.1, 271.8)
	Proportion of subjects with a ≥ 3-fold rise	475	97.3%(462/475)	(95.4%, 98.5%)	477	95.2%(454/477)	(92.9%, 96.9%)

N = Number of subjects vaccinated.
n = Number of subjects contributing to the per-protocol analyses (for ≥ 3 fold rise, limited to per-protocol subjects with both Dose 1 and Postdose 3 serology).
GMT = Geometric mean titer.
CI = Confidence interval.

Supportive Immunogenicity Analyses

Immunogenicity analysis of the non-inferiority of GMT for the SNA responses to reassortants rotavirus serotypes G1, G2, G3, G4 and P1A were done in FAS population also.

The method used for this analysis was the same as that used for the primary PP analysis of non-inferiority of GMTs for the SNA responses to reassortant rotavirus serotypes G1, G2, G3, G4 and P1A. The FAS results indicate that the statistical criterion for non-inferiority was met for all 5 serotypes, which was consistent with the results from the primary PP analysis.

The FAS for the measurement of SNA responses to serotypes G1, G2, G3, G4 and P1A and serum anti-rotavirus IgA were also done Predose 1 and ~42 days Post dose 3 for both vaccine groups. Consistent with the PP analysis, results for serotype G3 were higher in the VVMC formulation group and the 95% CI for GMTs Post dose 3 and the proportion of subjects with a ≥3-fold rise did not overlap with that of the current formulation. For the other serotypes (G1, G2, G4, P1A) and IgA, the 95% CIs for GMTs and proportion of subjects with a ≥3-fold rise were comparable between the 2 vaccine groups [Ref. 5.3.5.1: P035].

Safety:

The safety objective for this study was to assess the safety and tolerability of the VVMC formulation of RotaTeq™. All adverse events (AEs, nonserious and serious) regardless of causality were collected for 42 days following each study vaccine dose. In addition, all SAEs regardless of causality and any cases of intussusception (Event of Clinical Interest [ECI]) were reported from the time of consent until the end of entire study (defined as the last scheduled visit of the last subject enrolled in the study). At each vaccination visit, the parent/legal guardian received a vaccine report card (VRC) which prompted for recording of AEs of special interest which included the subject's temperature, presence of vomiting, and/or diarrhoea daily for 7 days post-vaccination. The VRC also collected any other AEs, as well as concomitant medications and concomitant vaccinations for 42 days post-vaccination. Intensity/severity (mild, moderate, or severe) were collected for all AEs. "Mild" was defined as an awareness of symptom in the subject, but easily tolerated; "moderate" was defined as subject definitely acting like something was wrong; and "severe" was defined as the subject appearing

extremely distressed or unable to do usual activities. Stool samples (~5 grams) were collected for subjects who experienced moderate-to-severe diarrhoea and/or vomiting (defined as 3 or more looser-than-normal stools in 24 hours, 1 watery stool in 24 hours, and/or forceful vomiting) within 14 days of study vaccination for rotavirus testing. If positive for rotavirus, further testing was done to characterize any strains identified by genotype.

Safety Evaluation and Results

The safety evaluation was based on the ASaT (All Subjects as Treated) population, which included all randomized subjects who received at least 1 vaccine dose and who had safety follow-up. For the analysis of safety data, subjects were included in the vaccine group corresponding to the vaccine that they actually received. For most subjects, this group was the vaccine group to which they were randomized.

Of the 1014 subjects vaccinated in this study, 510 subjects were randomized to the VVMC formulation of RotaTeq™, and 504 subjects to the current formulation of RotaTeq™. After adjusting for subjects who were cross-treated and therefore included in the group corresponding to the study vaccine they received at Day 1/Dose 1, there were a total of 509 and 505 subjects included in the VVMC formulation and current formulation groups, respectively, for the safety analysis based on the ASaT population.

The statistical analysis of clinical AEs that occurred after any study vaccination showed that the VVMC formulation group and current formulation group had comparable safety profiles Table 6. In the VVMC formulation group, 86.4% of subjects (439/508) reported 1 or more AE compared to 87.8% of subjects (438/499) in the current formulation group during Day 1 to Day 42 following any vaccination. Overall, 51% of the subjects in both vaccine groups reported a vaccine-related AE and the distribution of AEs was generally similar between the 2 vaccine groups. The incidence of SAEs any time after vaccination for the entire study period was low (3.9% in the VVMC formulation group and 2.4% in the current formulation group). There were no deaths and no vaccine-related SAEs in this study.

A total of 2 subjects discontinued the study as a result of an SAE. Both subjects were in the VVMC formulation group and both discontinued due to intussusception.

Table 6

Analysis of Adverse Event Summary
Following Any Vaccination
(All Subjects as Treated Population)

	RotaTeq™ New Formulation (N=509)		RotaTeq™ Current Formulation (N=505)		Difference†† in % vs RotaTeq™ Current Formulation
	n	(%)§§	n	(%)§§	Estimate (95% CI)†
Subjects in population	509		505		
Subjects in population with follow-up	508		499		
with one or more adverse events (Day 1 to Day 42)	439	(86.4)	438	(87.8)	-1.4 (-5.5, 2.8)
with no adverse events	69	(13.6)	61	(12.2)	1.4 (-2.8, 5.5)
with vaccine-related‡ adverse events (Day 1 to Day 42)	259	(51.0)	256	(51.3)	-0.3 (-6.5, 5.8)
with serious adverse events (Any time after Vaccination)	20	(3.9)	12	(2.4)	1.5 (-0.7, 3.9)
with serious vaccine-related adverse events (Any time after Vaccination)	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.8)
who died	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.8)
discontinued§ due to an adverse event	2	(0.4)	0	(0.0)	0.4 (-0.4, 1.4)
discontinued due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.8)
discontinued due to a serious adverse event	2	(0.4)	0	(0.0)	0.4 (-0.4, 1.4)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.8, 0.8)

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the vaccine.
§ Study medication withdrawn.
†† Difference was New Formulation Group minus Current Formulation Group. Risk difference and confidence intervals are based on the pooled incidence rates across all study centers for Tier 2 events.
§§ Percentages were based on the number of subjects in the population with follow-up.
All serious adverse events regardless of causality and deaths were collected for the duration of the study. Solicited adverse events were collected Day 1 to Day 7 after each vaccination. Other adverse events were collected from Day 1 to Day 42 after vaccination.
N = Number of vaccinated subjects, n = Number of subjects in each category.
This table includes 3 cross-treated subjects: AN 100470, AN 100323 and AN 101054. They are included in the group corresponding to the study vaccine received at Dose 1.

Analysis of Overall Adverse Events

The analysis of subjects with AEs (incidence ⩾4 subjects in one or more vaccination groups) by system organ class (SOC) Days 1 to 42 following any vaccination is shown in Table 7. Overall, 87% of the subjects reported 1 or more AEs from days 1 to 42 following any vaccination. The proportion of subjects reporting specific AEs were comparable between the 2 vaccine groups. The most common AE in the [New] ~~VVMC~~ formulation vs. current formulation of vaccine groups respectively were diarrhoea (33.9% vs. 31.1%), pyrexia (29.5% vs. 30.3%), vomiting (20.1% vs. 21.2%), nasopharyngitis (14.8% vs. 15.0%), upper respiratory tract infection (15.4% vs. 13.2%), and irritability (12.8% vs. 15.4%). The majority of the AEs reported were of mild-to-moderate intensity. The frequency of AEs was generally similar between the 2 vaccine groups; the incidence of dermatitis and urticaria was greater in the VVMC formulation group. The difference in percentage between the VVMC and current formulation groups was 1.6% (95% CI: 0.1, 3.3) for dermatitis and 1.2% (95% CI: 0.1, 2.6) for urticaria, respectively.

Table 7

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Vaccination Groups)
by System Organ Class
(Days 1 to 42 Following Any Vaccination)
(All Subjects as Treated Population)

	RotaTeq™ New Formulation (N=509)		RotaTeq™ Current Formulation (N=505)		Difference[††] in % vs RotaTeq™ Current Formulation
	n	(%)[‡‡]	n	(%)[‡‡]	Estimate (95% CI)[†]
Subjects in population	509		505		
Subjects in population with follow-up	508		499		
with one or more adverse events	439	(86.4)	438	(87.8)	-1.4 (-5.5, 2.8)
with no adverse events	69	(13.6)	61	(12.2)	1.4 (-2.8, 5.5)
Blood and lymphatic system disorders	**4**	**(0.8)**	**2**	**(0.4)**	**0.4 (-0.7, 1.7)**
Congenital, familial and genetic disorders	**4**	**(0.8)**	**1**	**(0.2)**	**0.6 (-0.4, 1.8)**
Eye disorders	**13**	**(2.6)**	**8**	**(1.6)**	**1.0 (-0.9, 2.9)**
Eye discharge	3	(0.6)	6	(1.2)	-0.6 (-2.1, 0.7)
Gastrointestinal disorders	**272**	**(53.5)**	**250**	**(50.1)**	**3.4 (-2.7, 9.6)**
Abdominal distension	5	(1.0)	5	(1.0)	-0.0 (-1.5, 1.4)
Abdominal pain	19	(3.7)	12	(2.4)	1.3 (-0.8, 3.6)
Abdominal pain upper	6	(1.2)	12	(2.4)	-1.2 (-3.1, 0.5)
Constipation	30	(5.9)	22	(4.4)	1.5 (-1.3, 4.3)
Diarrhoea	172	(33.9)	155	(31.1)	2.8 (-3.0, 8.6)
Faeces discoloured	4	(0.8)	0	(0.0)	0.8 (0.0, 2.0)
Flatulence	11	(2.2)	7	(1.4)	0.8 (-1.0, 2.6)
Gastrooesophageal reflux disease	14	(2.8)	12	(2.4)	0.4 (-1.7, 2.4)
Infantile spitting up	4	(0.8)	1	(0.2)	0.6 (-0.4, 1.8)
Regurgitation	17	(3.3)	8	(1.6)	1.7 (-0.2, 3.9)
Teething	16	(3.1)	9	(1.8)	1.3 (-0.6, 3.5)
Vomiting	102	(20.1)	106	(21.2)	-1.2 (-6.2, 3.8)
General disorders and administration site conditions	**183**	**(36.0)**	**188**	**(37.7)**	**-1.7 (-7.6, 4.3)**
Crying	16	(3.1)	11	(2.2)	0.9 (-1.1, 3.1)
Discomfort	4	(0.8)	3	(0.6)	0.2 (-1.1, 1.5)
Injection site erythema	6	(1.2)	1	(0.2)	1.0 (-0.1, 2.4)

	RotaTeq™ New Formulation (N=509)		RotaTeq™ Current Formulation (N=505)		Difference†† in % vs RotaTeq™ Current Formulation
	n	(%)§§	n	(%)§§	Estimate (95% CI)†
General disorders and administration site conditions	**183**	**(36.0)**	**188**	**(37.7)**	**-1.7 (-7.6, 4.3)**
Injection site pain	14	(2.8)	19	(3.8)	-1.1 (-3.4, 1.2)
Pyrexia	150	(29.5)	151	(30.3)	-0.7 (-6.4, 4.9)
Vaccination site pain	11	(2.2)	13	(2.6)	-0.4 (-2.5, 1.5)
Infections and infestations	**274**	**(53.9)**	**274**	**(54.9)**	**-1.0 (-7.1, 5.2)**
Bronchiolitis	21	(4.1)	18	(3.6)	0.5 (-1.9, 3.0)
Bronchitis	7	(1.4)	7	(1.4)	-0.0 (-1.7, 1.6)
Candida infection	7	(1.4)	7	(1.4)	-0.0 (-1.7, 1.6)
Conjunctivitis	27	(5.3)	23	(4.6)	0.7 (-2.0, 3.5)
Croup infectious	4	(0.8)	6	(1.2)	-0.4 (-1.9, 1.0)
Ear infection	5	(1.0)	6	(1.2)	-0.2 (-1.7, 1.2)
Exanthema subitum	5	(1.0)	3	(0.6)	0.4 (-0.9, 1.8)
Gastroenteritis	9	(1.8)	13	(2.6)	-0.8 (-2.8, 1.0)
Influenza	6	(1.2)	3	(0.6)	0.6 (-0.7, 2.0)
Laryngitis	9	(1.8)	6	(1.2)	0.6 (-1.0, 2.3)
Nasopharyngitis	75	(14.8)	75	(15.0)	-0.3 (-4.7, 4.2)
Oral candidiasis	3	(0.6)	7	(1.4)	-0.8 (-2.3, 0.5)
Otitis media	18	(3.5)	27	(5.4)	-1.9 (-4.6, 0.7)
Otitis media acute	4	(0.8)	3	(0.6)	0.2 (-1.1, 1.5)
Pharyngitis	18	(3.5)	13	(2.6)	0.9 (-1.3, 3.2)
Respiratory tract infection	13	(2.6)	13	(2.6)	-0.0 (-2.1, 2.0)
Respiratory tract infection viral	11	(2.2)	11	(2.2)	-0.0 (-2.0, 1.9)
Rhinitis	41	(8.1)	40	(8.0)	0.1 (-3.4, 3.5)
Sinusitis	4	(0.8)	3	(0.6)	0.2 (-1.1, 1.5)
Upper respiratory tract infection	78	(15.4)	66	(13.2)	2.1 (-2.2, 6.5)
Urinary tract infection	9	(1.8)	6	(1.2)	0.6 (-1.0, 2.3)
Viral infection	6	(1.2)	12	(2.4)	-1.2 (-3.1, 0.5)
Viral upper respiratory tract infection	4	(0.8)	1	(0.2)	0.6 (-0.4, 1.8)

	RotaTeq™ New Formulation (N=509)		RotaTeq™ Current Formulation (N=505)		Difference†† in % vs RotaTeq™ Current Formulation
	n	(%)§§	n	(%)§§	Estimate (95% CI)†
Injury, poisoning and procedural complications	**8**	**(1.6)**	**12**	**(2.4)**	**-0.8 (-2.8, 1.0)**
Vaccination complication	4	(0.8)	5	(1.0)	-0.2 (-1.6, 1.1)
Investigations	**6**	**(1.2)**	**5**	**(1.0)**	**0.2 (-1.3, 1.7)**
Body temperature increased	4	(0.8)	3	(0.6)	0.2 (-1.1, 1.5)
Metabolism and nutrition disorders	**13**	**(2.6)**	**17**	**(3.4)**	**-0.8 (-3.1, 1.3)**
Decreased appetite	11	(2.2)	12	(2.4)	-0.2 (-2.2, 1.7)
Musculoskeletal and connective tissue disorders	**10**	**(2.0)**	**4**	**(0.8)**	**1.2 (-0.3, 2.9)**
Pain in extremity	6	(1.2)	3	(0.6)	0.6 (-0.7, 2.0)
Nervous system disorders	**16**	**(3.1)**	**18**	**(3.6)**	**-0.5 (-2.8, 1.9)**
Somnolence	6	(1.2)	10	(2.0)	-0.8 (-2.6, 0.8)
Psychiatric disorders	**80**	**(15.7)**	**93**	**(18.6)**	**-2.9 (-7.6, 1.8)**
Insomnia	4	(0.8)	3	(0.6)	0.2 (-1.1, 1.5)
Irritability	65	(12.8)	77	(15.4)	-2.6 (-7.0, 1.7)
Restlessness	7	(1.4)	15	(3.0)	-1.6 (-3.7, 0.2)
Reproductive system and breast disorders	**4**	**(0.8)**	**2**	**(0.4)**	**0.4 (-0.7, 1.7)**
Respiratory, thoracic and mediastinal disorders	**62**	**(12.2)**	**76**	**(15.2)**	**-3.0 (-7.3, 1.2)**
Cough	35	(6.9)	44	(8.8)	-1.9 (-5.3, 1.4)
Nasal congestion	17	(3.3)	15	(3.0)	0.3 (-1.9, 2.6)
Rhinorrhoea	11	(2.2)	17	(3.4)	-1.2 (-3.5, 0.8)
Wheezing	3	(0.6)	6	(1.2)	-0.6 (-2.1, 0.7)

	RotaTeq™ New Formulation (N=509)		RotaTeq™ Current Formulation (N=505)		Difference†† in % vs RotaTeq™ Current Formulation
	n	(%)§§	n	(%)§§	Estimate (95% CI)†
Skin and subcutaneous tissue disorders	**56**	**(11.0)**	**54**	**(10.8)**	**0.2 (-3.7, 4.1)**
Dermatitis	11	(2.2)	3	(0.6)	1.6 (0.1, 3.3)
Dermatitis atopic	5	(1.0)	8	(1.6)	-0.6 (-2.3, 0.9)
Dermatitis diaper	8	(1.6)	13	(2.6)	-1.0 (-3.0, 0.8)
Eczema	7	(1.4)	5	(1.0)	0.4 (-1.1, 1.9)
Erythema	3	(0.6)	5	(1.0)	-0.4 (-1.8, 0.8)
Rash	5	(1.0)	7	(1.4)	-0.4 (-2.0, 1.1)
Urticaria	7	(1.4)	1	(0.2)	1.2 (0.1, 2.6)

† Based on Miettinen & Nurminen method.

†† Difference was New Formulation Group minus Current Formulation Group. Risk difference and confidence intervals are based on the pooled incidence rates across all study centers for categories with at least 4 subjects in either group reporting events in that category.

§§ Percentages were based on the number of subjects in the population with follow-up.

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.

This table includes 3 cross-treated subjects: AN 100470, AN 100323 and AN 101054. They are included in the group corresponding to the study vaccine received at Dose 1.

N = Number of vaccinated subjects, n = Number of subjects in each category.

Vaccine-Related Adverse Events

The analysis of number (%) of subjects with AEs (incidence ⩾2%) - overall and vaccine-related, by SOC and preferred terms, showed that 51% of the subjects reported 1 or more AEs Days 1 to 42 following any vaccination that were considered vaccine-related by the investigator. The most common vaccine-related AE in the VVMC formulation vaccine group vs. current formulation vaccine group were diarrhoea (26.0% vs. 22.8%), pyrexia (16.9% vs. 16.2%), and vomiting (13.8% vs. 14.4%) respectively. The proportion of subjects reporting specific vaccine-related AEs were comparable between the 2 vaccine groups.

Serious adverse events

In Protocol 035-02, all SAEs regardless of causality were collected from the time of consent until the end of the study. Prior clinical trials of RotaTeq collected SAEs for 42 days or 14 days post-vaccination. To assist in the interpretation of the SAE data from this study, the SAE by SOC table is presented by day ranges (Days 1 to 14, Days 1 to 42, and anytime post vaccination) in Table 8. The most common SAE was bronchiolitis [3 (0.6%) in the VVMC formulation and 1 (0.2%) in the current formulation group].

There were no vaccine-related SAEs reported in this study.

There were no AEs that led to death during this study.

Table 8

Subjects With Serious Adverse Events following any Vaccination
(Incidence > 0% in One or More Vaccination Groups)
by Time, System Organ Class and Preferred Term
(All Subjects as Treated Population)

	RotaTeq™ New Formulation (N = 509)						RotaTeq™ Current Formulation (N = 505)					
	Days 1 - 14		Days 1 - 42		Anytime		Days 1 - 14		Days 1 - 42		Anytime	
	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]
Subjects in population	509		509		509		505		505		505	
Subjects in population with follow-up	508		508		508		499		499		499	
with one or more serious adverse events	9		16		20		4		12		12	
with no serious adverse events	499		492		488		495		487		487	
Gastrointestinal disorders	0	0.0	1	0.2	2	0.4	0	0.0	1	0.2	1	0.2
Intussusception	0	0.0	1	0.2	2	0.4	0	0.0	0	0.0	0	0.0
Umbilical hernia	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2
General disorders and administration site conditions	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0
Pyrexia	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0
Infections and infestations	7	1.4	13	2.6	15	3.0	3	0.6	9	1.8	9	1.8
Anal abscess	0	0.0	1	0.2	1	0.2	0	0.0	1	0.2	1	0.2
Bronchiolitis	3	0.6	3	0.6	3	0.6	0	0.0	1	0.2	1	0.2
Bronchitis	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	1	0.2
Cellulitis	0	0.0	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Gastroenteritis viral	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	1	0.2
Laryngitis	1	0.2	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Parainfluenzae virus infection	0	0.0	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Pneumonia	0	0.0	1	0.2	2	0.4	0	0.0	0	0.0	0	0.0

Subjects With Serious Adverse Events following any Vaccination
(Incidence > 0% in One or More Vaccination Groups)
by Time, System Organ Class and Preferred Term
(All Subjects as Treated Population)

	RotaTeq™ New Formulation (N = 509)						RotaTeq™ Current Formulation (N = 505)					
	Days 1 - 14		Days 1 - 42		Anytime		Days 1 - 14		Days 1 - 42		Anytime	
	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]	n	(%)[§§]
Pyelonephritis	0	0.0	1	0.2	1	0.2	0	0.0	1	0.2	1	0.2
Pyelonephritis acute	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	1	0.2
Respiratory syncytial virus bronchiolitis	0	0.0	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Respiratory tract infection viral	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2
Septic shock	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0
Upper respiratory tract infection	1	0.2	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Urinary tract infection	1	0.2	1	0.2	1	0.2	0	0.0	1	0.2	1	0.2
Viral infection	1	0.2	1	0.2	1	0.2	0	0.0	1	0.2	1	0.2
Injury, poisoning and procedural complications	0	0.0	0	0.0	0	0.0	2	0.4	2	0.4	2	0.4
Head injury	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	1	0.2
Subcutaneous haematoma	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	1	0.2
Nervous system disorders	2	0.4	2	0.4	2	0.4	0	0.0	0	0.0	0	0.0
Hypersomnia	1	0.2	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Loss of consciousness	1	0.2	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0
Psychiatric disorders	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2
Restlessness	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2

Every subject is counted a single time for each applicable row and column.
[§§] Percentages were based on the number of subjects in the population with follow-up.
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.
All serious adverse events regardless of causality and deaths were collected for the duration of the study.
N = Number of vaccinated subjects, n = Number of subjects in each category.
This table includes 3 cross-treated subjects: AN 100470, AN 100323 and AN 101054. They are included in the group corresponding to the study vaccine received at Dose 1.

Adverse Events of Special Interest

Daily temperatures, diarrhoea, and vomiting were solicited for 7 days after each study vaccination in this study. There were no statistically significant differences in any of the AEs of Special Interest between the 2 vaccine groups (Table 9).

Intussusception was considered an ECI for this study. All cases of intussusception were to be reported for the duration of the study. There were 2 cases of intussusception reported in this study, both in the

VVMC formulation group (Table 10). The 2 cases met the Brighton Collaboration Level 1 case definition of acute intussusception. Both cases occurred over 30 days Post dose 2 at ~5 months of age, the time of peak incidence for naturally-occurring intussusception in the absence of rotavirus vaccination. The first case involved a 5.1 month old male, who developed intussusception on Day 37 Post dose 2 of study vaccine. The second case involved a 4.9 month old female, who developed intussusception on Day 45 Post dose 2 of study vaccine. Neither event was considered vaccine-related by the investigator and both subjects recovered. Because of the AE of intussusception, neither subject received a further dose of study vaccine, per prescribing information for the product.

Table 9

Events of Special Interest
Days 1 to 7 Following any Vaccination
(All Subjects as Treated Population)

	Group 1: RotaTeq™ New Formulation (N = 509)				Group 2: RotaTeq™ Current Formulation (N = 505)				Risk Difference‖ (Group 1 - Group 2) (95% Confidence Interval)†	P-value†
	Overall		VR‡		Overall		VR‡			
	n	%§	n	%§	n	%§	n	%§		
Diarrhoea (post any vaccination)	144	28.3	124	24.4	128	25.7	104	20.8	2.7 (-2.8, 8.17)	0.336
Vaccination 1	102	20.1	87	17.1	84	16.8	66	13.2	3.2 (-1.6, 8.04)	0.185
Vaccination 2	58	11.6	49	9.8	58	11.6	48	9.6	-0.1 (-4.1, 3.91)	0.963
Vaccination 3	47	9.5	39	7.9	41	8.3	30	6.1	1.2 (-2.4, 4.77)	0.522
Vomiting (post any vaccination)	84	16.5	65	12.8	92	18.4	68	13.6	-1.9 (-6.6, 2.80)	0.427
Vaccination 1	57	11.2	45	8.9	56	11.2	39	7.8	-0.0 (-3.9, 3.93)	0.999
Vaccination 2	29	5.8	23	4.6	34	6.8	23	4.6	-1.1 (-4.2, 2.00)	0.494
Vaccination 3	29	5.9	22	4.4	33	6.7	24	4.9	-0.8 (-4.0, 2.23)	0.583
Elevated Temperature [rectal temperature ≥38.1° C(≥100.5° F) or equivalent] (post any vaccination)	217	42.7	84	16.5	223	44.7	79	15.8	-2.0 (-8.1, 4.15)	0.528
Vaccination 1	95	18.7	29	5.7	101	20.2	31	6.2	-1.5 (-6.5, 3.36)	0.537
Vaccination 2	107	21.3	41	8.2	111	22.3	36	7.2	-1.0 (-6.1, 4.15)	0.709
Vaccination 3	106	21.4	26	5.3	123	25.0	33	6.7	-3.6 (-8.9, 1.68)	0.182
Irritability (post any vaccination)	58	11.4	44	8.7	64	12.8	49	9.8	-1.4 (-5.5, 2.64)	0.494
Vaccination 1	24	4.7	15	3.0	28	5.6	20	4.0	-0.9 (-3.7, 1.89)	0.525
Vaccination 2	34	6.8	26	5.2	35	7.0	30	6.0	-0.3 (-3.5, 2.94)	0.874
Vaccination 3	18	3.6	12	2.4	20	4.1	15	3.0	-0.4 (-2.9, 2.05)	0.726

† Based on Miettinen and Nurminen method.
‡ VR = Vaccine-related. Vaccine relationship is determined by the investigator.
‖ Difference was New Formulation Group minus Current Formulation Group. Risk difference, confidence intervals and p-value are based on the pooled incidence rates across all study centers.
§ Percentages were based on the number of subjects in the population with follow-up at the corresponding visit.
N = Number of vaccinated subjects, n = Number of subjects in each category.
This table includes 3 cross-treated subjects: AN 100470, AN 100323 and AN 101054. They are included in the group corresponding to the study vaccine received at Dose 1.

Table 10

Adverse Events of Special Interest-Intussusception
Anytime During the Study
(All Subjects as Treated Population)

	Group 1: RotaTeq™ New Formulation (N = 509)				Group 2: RotaTeq™ Current Formulation (N = 505)				Risk Difference‖ (Group 1 - Group 2) (95% Confidence Interval)†	P-value†
	Overall		VR‡		Overall		VR‡			
	n	%§	n	%§	n	%§	n	%§		
Intussusception (post any vaccination)	2	0.4	0	0.0	0	0.0	0	0.0	0.4 (-0.4, 1.42)	0.161
Vaccination 1	0	0.0	0	0.0	0	0.0	0	0.0	N/A	N/A
Vaccination 2	2	0.4	0	0.0	0	0.0	0	0.0	0.4 (-0.4, 1.44)	0.159
Vaccination 3	0	0.0	0	0.0	0	0.0	0	0.0	N/A	N/A

† Based on Miettinen and Nurminen method.
‡ VR = Vaccine-related. Vaccine relationship is determined by the investigator.
‖ Difference was New Formulation Group minus Current Formulation Group. Risk difference, confidence intervals and p-value are based on the pooled incidence rates across all study centers.
§ Percentages were based on the number of subjects in the population with follow-up at the corresponding visit.
N = Number of vaccinated subjects, n = Number of subjects in each category.
This table includes 3 cross-treated subjects: AN 100470, AN 100323 and AN 101054. They are included in the group corresponding to the study vaccine received at Dose 1.

Stool Testing For Rotavirus

Stool samples were collected from subjects who experienced moderate-to-severe diarrhoea and/or vomiting (defined as 3 or more looser-than-normal stools in 24 hours, 1 watery stool in 24 hours, and/or forceful vomiting) within 14 days of study vaccination for rotavirus testing. Stool samples that were positive for rotavirus using an enzyme immunoassay (EIA) rotavirus antigen test, were further tested using real-time rotavirus polymer chain reaction assay (RT-PCR), assays specific for rotavirus VP6 genotype, VP4 genotype, and VP7 genotype. Of the 1014 subjects who received at least 1 dose of study vaccine, 115 (54 in the VVMC formulation and 61 in the current formulation group) had an AE of moderate-to severe diarrhoea and/or vomiting within 14 days of vaccination. Stool was tested for 51 subjects with moderate or severe diarrhoea and/or vomiting within 14 days of vaccination. Of the 51 subjects who had stool samples tested, 47 (92.2%) were negative for rotavirus by EIA. All 4 subjects (2 subjects Post dose 1 and 1 subject Post dose 2 in the VVMC formulation group; and 1 subject Post dose 1 in the current formulation group) with rotavirus EIA-positive stool specimens were determined to have vaccine strain rotavirus by RT-PCR. This was not an unexpected occurrence since faecal shedding of vaccine virus is known to occur post vaccination

Discussion on clinical aspects

The data demonstrated that the VVMC formulation of RotaTeq was non-inferior to the current formulation of RotaTeq with respect to immunogenicity. The primary immunogenicity hypothesis of non-inferiority was met for all 5 serotypes. The IgA GMT and the proportion of subjects with $\geqslant$ 3-fold rise in antibody titre (SNA and IgA) at 42 days post dose 3 were also similar in the new formulation and the current formulation groups. However, the GMT for G3 was 3.2 fold higher in the new formulation group compared to the current formulation group. It is the applicant's opinion that the increased immunogenicity of the G3 reassortant may be due to improved stability in the VVMC formulation at multiple temperatures as well as less potency loss over time compared to the current formulation.

Over 95% of subjects (97.3% in the new formulation and 95.2% in the current formulation group) had a $\geqslant$ 3-fold rise in serum anti-rotavirus IgA after completing the 3 dose regimen, and the 95% CIs overlapped.

Although the VVMC formulation of RotaTeq™ appeared to be well-tolerated and had a generally similar safety profile as the current formulation of RotaTeq™, the incidence of adverse events like injection site erythema, dermatitis and urticaria appeared to be slightly higher in the VVMC formulation.

The incidence of serious adverse events, albeit low, appeared to be somewhat higher in the VVMC formulation (3.9% vs 2.4%), nevertheless there were no vaccine-related serious adverse experiences and no deaths.

It is notable that in a comparatively small population of patients, 2 cases of acute intussusception were reported in the VVMC formulation group. Both cases occurred more than 30 days (Day 37 and Day 45) post-dose 2 at around 5 months of age. However, it should be noted that this period is the time of peak incidence for naturally-occurring intussusception in the absence of rotavirus vaccination, as reported in the literature. Nevertheless, neither event was considered vaccine-related by the investigator and both subjects recovered. In particular, the timing of the 2 cases of intussusception relative to time post-vaccination and the age of the subjects does not appear to suggest a causal link of the cases to vaccination.

2. CHMP overall conclusion and recommendation

This study appeared to demonstrate that the VVMC formulation of RotaTeq which is thermostable with a shelf life of three years, was non-inferior to the current formulation of RotaTeq with respect to immunogenicity. The VVMC formulation of RotaTeq appeared to be well-tolerated and had a generally similar safety profile as the current formulation of RotaTeq. Accordingly, there is no change to the benefit/risk assessment between the two formulations.

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:**