Application Type	Efficacy Supplement
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Division / Office	DVRPA/OVRR
Committee Chair	Luba Vujcic, M.S.
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Priority Review	No
Reviewer Name(s)	Mridul Chowdhury, Ph.D.
Review Completion Date / Stamped Date	January 26, 2017
Supervisory Concurrence	Tsai-Lien Lin, Ph.D., Team Leader, VEB
	Dale Horne, Dr.P.H., Chief, VEB
Applicant	Merck Sharp & Dohme Corp.
Established Name	Rotavirus Vaccine, Live, Oral, Pentavalent
(Proposed) Trade Name	RotaTeq™
Pharmacologic Class	Active immunizer (vaccine)
Formulation(s), including Adjuvants, etc	RotaTeq (2-mL) consists of 5 live human-bovine reassortant rotavirus strains and contains a minimum of 2.0 to 2.8 × 10^6 infectious units per reassortant dose, depending on the serotype, and not greater than 116 × 10^6 infectious units per aggregate dose.
Dosage Form(s) and Route(s) of Administration	Oral solution
Dosing Regimen	The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals.
Indication(s) and Intended Population(s)	RotaTeq is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3,-G4, and G9P1A[8]. RotaTeq is approved for use in infants 6 weeks to 32 weeks of age.

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GLOSSARY

Abbreviation	Definition
AN	Allocation number
AGRC	Acute gastroenteritis report card
CI	Confidence interval
EIA	Enzyme immunoassay
FAS	Full Analysis set
G	Refers to the rotavirus VP7 glycoprotein ; defines VP7 serotypes
G1	Rotavirus serotype G1 or simplified name of the WI79-9 G1 reassortant strain contained in V260
G2	Rotavirus serotype G2 or simplified name of the SC2-9 G2 reassortant strain contained in V260
G3	Rotavirus serotype G3 or simplified name of the WI78-8 G3 reassortant strain contained in V260
G4	Rotavirus serotype G4 or simplified name oftheBrB-9 G4 reassortant strain contained in V260
G9	Rotavirus serotype G9
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IU	Infectious units
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRL	Merck Research Laboratories
OPV	Oral poliovirus vaccine
P	Refers to the rotavirus VP4 protein (a protease-sensitive protein; defines VP4 serotypes)
P1A	Rotavirus serotype P1A (sometimes abbreviated P1 in this document)
PCR	Polymerase chain reaction
PFU	Plaque-forming units
PP	Per Protocol
REST	Rotavirus Efficacy and Safety Trial (Protocol 006)
SD	Standard deviation
VE	Vaccine Efficacy
VP4	Viral protein 4, referred to as the protease-sensitive “P” protein
VP7	Viral protein 7, referred to as the glycoprotein “G” protein

1. EXECUTIVE SUMMARY

The submission is intended to provide support for expanding the indication for RotaTeq™ to include efficacy against rotavirus serotype G9. Currently, RotaTeq is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by serotypes G1, G2, G3, and G4. The applicant provided a summary of studies included in the integrated efficacy analysis from RotaTeq phase 3 studies, conducted in the U.S. and Finland (Protocols 006 and 007, ref. Clinical Review of BLA STN 125122 dated January 30, 2006) and Japan (Protocol 029). The latter (Japan) was conducted following US licensure of RotaTeq. Please refer to Table 10 for the applicant's descriptive summaries of these three studies.

The submitted efficacy studies analyzed subjects with incidence of rotavirus gastroenteritis in RotaTeq versus placebo recipients. The applicant concluded that RotaTeq was efficacious "against rotavirus gastroenteritis of any severity caused by serotype G9 and as well as for serotype P1A[8]" (ref. Statistical Report, Integrated analysis of efficacy in protocols 006, 007, and 029, page 5). The applicant also stated that, in pre-licensure studies (Protocols 006 and 007), the study endpoints did not include efficacy of G-serotypes associated with serotype P1A[8] because of lack of a validated assay for P1A[8]. Following the development of the assay for P1A[8], P1A[8] was prospectively identified as a study endpoint for Protocol 029, and testing was performed on stool samples from protocols 006 and 007. To calculate vaccine efficacy related to G9P1A[8] in the current submission, the data from all three phase 3 protocols (006, 007, and 029) were combined, and from the pooled data the vaccine efficacy (VE) estimate for G9P1A[8] was stated as 88.5% (95% CI: 17.1%, 99.7%). The applicant viewed this VE as significant because the confidence lower bound exceeded zero. In individual studies, however, the VE confidence lower bounds were below zero, i.e., VEs were not significant (Table 11).

The applicant's decision to pool the data for protocols 029, 006, and 007 was made post hoc, in order to produce, presumably, robust results for efficacy with respect to G9P1A[8]. The applicant pointed out several important ways in which the study protocols were similar, to justify the pooling. However, post hoc pooling may render the analysis results less rigorous than had they resulted from a prospectively planned pooled analysis.

For efficacy based on Protocol 029 alone, the VE for RotaTeq against rotavirus gastroenteritis, regardless of severity, due to all reported serotypes was 74.5% (95% CI: 39.9%, 90.6%) (Table 4). For serotype G9P1A[8], the VE estimate was 100% with lower confidence bound -9.0%, a value relatively closer to zero than the negative lower bounds for other G-serotypes included in the pre-licensure studies (Table 11). However, failure to demonstrate efficacy for all serotypes in a multivalent vaccine is common, because those efficacy trials are not typically powered for serotype-specific efficacy. It has sometimes been sufficient to demonstrate efficacy with respect to some (sometimes pre-specified) serotypes, and only trends toward efficacy for certain others contained within the vaccine, if there are enough cases of disease due to the relevant serotypes. This

reviewer defers to the medical officer regarding the decision on the expanded clinical indication for the package insert.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied
Rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, and G-serotypes associated with P1A[8] (e.g., G9) in infants.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

RotaTeq (Merck) and Rotarix (GSK).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Please see the medical officer's review.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

To support the licensure of RotaTeq in the U.S., the primary efficacy was assessed in 2 double-blind, placebo-controlled, randomized trials: Protocol 006 and Protocol 007. Please refer to Clinical Review (BLA STN 125122), dated January 30, 2006, for details. Protocol 029 was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a 3-dose regimen of RotaTeq to support the licensure of RotaTeq in Japan. This study was not conducted under US IND, but to support the study's inclusion, the applicant referred to information outlined in 21 CFR 312.120 and in the "Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical studies not Conducted under an IND, Frequently Asked Questions, March 2012." A Type C meeting on June 18, 2015 discussed the plan for including Study 029 in the submission. Please refer to the medical officer's report for greater details.

2.6 Other Relevant Background Information

None.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The applicant stated that all trials were conducted following appropriate Good Clinical Practice standards.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the medical officer's report.
Sections 4.1 through 4.6 do not apply for this statistical review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This reviewer was the sole statistical reviewer for the clinical statistics.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

1. Integrated efficacy statistical report (phase 3 studies: Protocols 006, 007, and 029).
2. Clinical Overview.
3. Clinical study report (phase 3 Protocol 029 Japan, study not conducted under US IND).

All the above were included in modules 2 and 5 of the BLA submission.

The applicant, in a recent response to the IR of September 29, 2016, provided summary results from two additional studies (b) (4) which evaluated G9 efficacy for (b) (4) from studies 006, 007, and 029 to a notable extent. These studies were not included in the earlier integrated efficacy analysis. Please refer to the medical officer's report for the clinical team's perspectives and considerations regarding relevance of these studies for the current submission.

Reviewer's comment: Protocols 006 and 007, being pre-licensure studies for RotaTeq BLA STN 125122, provide post-hoc data in the current submission.

5.3 Table of Studies/Clinical Trials

Please refer to section 5.2.

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting (if applicable)

None.

5.4.2 External Consults/Collaborations (if applicable)

None.

5.5 Literature Reviewed (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: P029

Phase III Randomized Multi-center Placebo-Controlled Trial to study the Efficacy and Safety of V260 in Healthy Infants in Japan

6.1.1 Primary Objectives

Efficacy

Endpoint: Incidence rate of rotavirus gastroenteritis (any severity, ref. Table 1) caused by G1, G2, G3, G4, and G serotypes associated with serotype P1A[8] (e.g., G9) occurring at least 14 days following the third dose.

Objective: To evaluate the efficacy of a 3-dose regimen of RotaTeq against naturally occurring rotavirus gastroenteritis of any severity caused by rotavirus serotypes G1, G2, G3, G4, and G-serotypes associated with P1A[8] (e.g., G9) occurring at least 14 days following the third dose in healthy Japanese infants.

Hypothesis: RotaTeq is efficacious against rotavirus gastroenteritis caused by rotavirus serotypes G1, G2, G3, G4, and those associated with serotype P1A that occurs at least 14 days following the third dose in healthy Japanese infants.

The statistical criterion corresponds to the lower bound of the 95% confidence interval on vaccine efficacy being > 0%.

Safety

Endpoints: All adverse experiences for 14 days following each vaccination. Deaths and serious vaccine-related adverse experiences, as well as events of clinical interest (intussusception) occurring during the study period.

Objective: To assess the safety of RotaTeq with respect to all adverse experiences occurring within 14 days of any dose in healthy Japanese infants.

Hypothesis: RotaTeq is generally safe and well tolerated in healthy Japanese infants with respect to all adverse experiences occurring within 14 days of any dose.

6.1.2 Design Overview

This study is a phase III, double-blind, placebo-controlled study with 762 healthy infants aged 6 through 12 weeks at enrollment. The subjects were from 32 sites across Japan. The parents/legal guardians provided written informed consent for study participation. The planned number of subjects was 744 (RotaTeq group: 372, placebo group: 372). The

primary objective of the study was to compare the efficacy, safety, and tolerability of a 3-dose regimen of oral RotaTeq with the placebo.

The severity of rotavirus gastroenteritis was evaluated using the clinical scoring system shown in Table 1.

Table 1 Clinical Scoring System

Score to be Summed According to Evaluation of Symptoms and Durations	1	2	3
Diarrhea			
No. of stools/day†	2 to 4 1 to 4	5 to 7 5 to 7	>7 >7
Vomiting			
No. of emeses/day§	1 to 3 2	4 to 6 3 to 5	>6 >5
Rectal Temperature			
Degrees in Celsius‖	38.1 to 38.2 1 to 2	38.3 to 38.7 3 to 4	≥38.8 ≥5
Behavioral Symptoms			
Description¶	Irritable/less playful	Lethargic/listless	Seizure
Duration in	1 to 2	3 to 4	≥5

† Maximum number of watery or looser-than-normal stools/day on any given day over the course of the episode.
‡ Number of days in which the subject had a symptom of any score. Total days did not need to be consecutive. Duration is self-reported by parents.
§ Maximum number of emeses on any given day over the course of the episode.
‖ Highest rectal equivalent temperature over the course of the episode which is >38ºC as reported by parents.
¶ If a subject is reported to have 2 or more symptoms, only the one with the highest score is counted.

Source: Adapted from CSR (V260 Prot. No.029) , Table 9-3, page 38.

6.1.3 Population

The study subjects were healthy Japanese infants, with parents/ legal guardians providing informed consent. The infants were from 6 to exactly 12 weeks old (≥42 days to ≤84 days from Date of Birth) upon the day of receipt of the first study vaccination (Day 1). Please see the medical officer's review for details on the inclusion and exclusion criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each experimental dose contained 2 mL of study vaccine (in a 2 mL single-dose tube), was administered orally at intervals of 28 to 70 days. The third dose was to be completed by 32 weeks of age.

Please refer to the medical officer's report for further details.

6.1.6 Sites and Centers

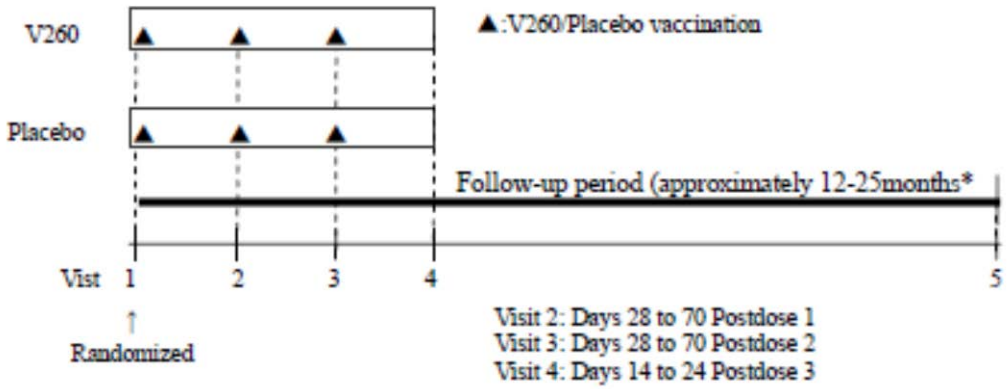
The study was conducted in 32 study sites (in Japan). The total number of study subjects was 762, and the number of subjects in individual sites ranged from 4 to 69 (CSR Prot. 029, Table 10-1, page 53).

6.1.7 Surveillance/Monitoring

The diagram below provides precise details on the monitoring. In essence,

> "the investigator, etc. or study coordinator confirmed symptoms of suspected acute gastroenteritis with the parent (guardian) at each visit and by telephone or e-mail on Days 8 and 15 following the first and second doses and on Day 8 following the third dose. After Visit 4, the occurrence of gastroenteritis was monitored by telephone or e-mail bi-weekly during the rotavirus season (January 1st through June 30th) and every 4 weeks during the period after the rotavirus season. If symptoms of suspected acute gastroenteritis occurred (3 or more looser-than-normal stools within a 24-hour period, or one or more watery stool or forceful vomiting), the determination of each episode of symptoms" (CSR, Prot. No. 029, page 35)

was based on daily information kept by parents or guardians on report cards as instructed by the study coordinator.



Source: CSR (V260 Prot. No.029) , Figure 9-1, page 26.

6.1.8 Endpoints and Criteria for Study Success

Efficacy

Primary endpoint
The incidence rate of rotavirus gastroenteritis of any severity caused by rotavirus serotypes G1, G2, G3, G4, and G-serotypes associated with serotype P1A (including G9) occurring at least 14 days following the third dose.

The primary hypothesis is that vaccine efficacy against rotavirus gastroenteritis relative to placebo ([1 - relative risk] x 100[%]) is >0.

The case definition of rotavirus gastroenteritis required subjects to meet both of the following criteria: (a) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting (acute gastroenteritis episode [AGE]); and (b) detection of wild-type rotavirus in a stool specimen collected within 7 days after the onset of symptoms.

The events evaluated for primary efficacy analysis were defined as any rotavirus gastroenteritis episodes that satisfied the 2 definition criteria above and were caused by serotypes G1, G2, G3, G4, and G-serotypes associated with serotype P1A (including G9) occurring at least 14 days following the third dose.

Secondary endpoints
(1) Moderate and severe rotavirus gastroenteritis caused by rotavirus serotypes G1, G2, G3, G4, and those associated with serotype P1A occurring at least 14 days following the third dose.
(2) Rotavirus gastroenteritis caused by any rotavirus serotype occurring at least 14 days following the third dose.
(3) Rotavirus gastroenteritis (moderate-severe, severe, and any severity, respectively) occurring following the first dose caused by i) rotavirus serotypes G1, G2, G3, G4, and those associated with serotype P1A and by ii) any rotavirus serotype.

Safety

(1) All adverse experiences within 14 days following any vaccination.
(2) Deaths, serious vaccine-related adverse experiences, and events of clinical interest (intussusception) occurring during the entire study period.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Efficacy: The stated primary hypothesis is that vaccine efficacy against rotavirus gastroenteritis ([1 - relative risk] x 100[%]) is >0, with relative risk being the ratio of the incidence rates in Rotateq vs Placebo arms. The confidence intervals (2-sided 95% CIs) for vaccine efficacy were calculated using an exact conditional method based on the Poisson distribution, which evaluated the

number of subjects with rotavirus cases in the RotaTeq group conditional on the total number of subjects with rotavirus cases, taking into account the person-time differences in follow-up between the two groups.

Reviewer's comment:
For efficacy against rotavirus of any severity due to serotypes G1-G4 and those G-serotypes associated with P1A in study 029, which was conducted to satisfy the requirement of the (b) (4) *regulatory agency, the applicant's statistical criterion for success corresponds to the VE 95% confidence lower bound being > 0%. In pre-licensure study 006, however, the VE confidence lower bound was 35% (per pre-specification) for rotavirus of any severity due to serotypes G1-G4. The reviewer defers this issue to the medical officer for clinical perspective.*

Safety: Descriptive statistics were calculated to show the proportion of subjects reporting with adverse events, for given total number of subjects under study, by treatment groups.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
Informed consent was available for 768 subjects; 762 subjects were randomized with equal allocation in both arms; 761 subjects received at least one vaccination; and 734 subjects completed follow-up until the last study visit regardless of the number of vaccinations received (Table 2).

Table 2: Subject Disposition

	RotaTeq		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Obtained informed consent	-		-		768	
Not Randomized	-	-	-	-	6	-
Randomized Subjects	381		381		762	
Completed†	368	(96.6)[a]	366	(96.1)[a]	734	(96.3)[a]
Discontinued	13‡	(3.4)	15	(3.9)	28	(3.7)
Per-Protocol (Primary Efficacy Analysis)	355	-	356	-	711	-
Safety Analysis	380	-	381	-	761	-
Vaccinated at						
Vaccination 1	380	(99.7)	381	(100.0)	761	(99.9)
Vaccination 2	373	(97.9)	374	(98.2)	747	(98.0)
Vaccination 3	371	(97.4)	369	(96.9)	740	(97.1)

† Completed: the number of subjects who continued the follow-up until the last study visit (Visit 5) regardless of number of vaccinations received.

‡ Includes 1 subject who was randomized but did not receive the study vaccine by the investigator's decision.

[a]Denominator Randomized Population

Source: Adapted from CSR (V260 Prot. No.029), Table 10-2, pages 54, 57, 58.

6.1.10.2 Demographics
From Table 3, males accounted for about 52-55% in each study arm, and 3-5% of subjects were below 36 weeks of gestation, with age ranging from 6 to 12 weeks.

Table 3: Summary of Demographic Characteristics (Randomized Subjects)

	RotaTeq		Placebo	
	n	(%)	n	(%)
Randomized	381		381	
Gender				
Male	208	(54.6)	199	(52.2)
Female	173	(45.4)	182	(47.8)
Age (Weeks)				
<6	0	(0.0)	0	(0.0)
6 to 12	381	(100.0)	381	(100.0)
>=13	0	(0.0)	0	(0.0)
Mean	7.6		7.5	
SD	1.7		1.6	
Median	7.0		7.0	
Range	6 to 12		6 to 12	
Gestation (Weeks)				
<=36	20	(5.2)	11	(2.9)
>36	360	(94.5)	370	(97.1)
Unknown	1	(0.3)	0	(0.0)

Source: CSR (V260 Prot. No.029), Table 10-5, page 59.

6.1.10.3 Medical/Behavioral Characterization of the Enrolled Population
The subjects were healthy Japanese infants of consenting parents/legal guardians. The infants were age 6 through exactly 12 weeks (≥42 days to ≤84 days from Date of Birth) upon the day of receipt of the first study vaccination (Day 1). Please refer to the medical officer's report on details relating to the infant requirement for neonatal vaccines and or concomitant medications in the study area.

6.1.10.4 Subject Disposition
Please see Table 2.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)
The primary analysis of the primary endpoint, vaccine efficacy against rotavirus gastroenteritis of any severity caused by any serotypes G1, G2, G3, G4, and G-serotypes associated with P1A[8] (e.g., G9) occurring at least 14 days Postdose 3 relative to placebo, is presented in Table 4 . The reported results show that vaccine efficacy was 74.5% (95%CI: 39.9%, 90.6%), with the confidence lower bound about 40%. Based on the criterion specified in study 029, this VE was significant with the confidence lower bound being > 0%. The observed serotype specific results are presented in Table 5. The VEs were not significant for serotypes G3 and G9.

Table 4: Analysis of Efficacy Against Rotavirus Gastroenteritis of Any Severity Caused by Rotavirus Serotypes G1, G2, G3, G4, and G-Serotypes Associated With P1A[8] (e.g., G9), Per Protocol Population.

	RotaTeq	Placebo
Subjects vaccinated	380	381
Protocol violators†	10	16
Subjects with no follow-up	0	0
Subjects classified as unevaluable per case definition‡	15	9
Subjects contributing to efficacy analysis	355	356
Days of efficacy follow-up	64823	63839
Subjects classified as rotavirus cases	7	27*
Efficacy estimate (%) and 95% confidence interval	74.5 (39.9, 90.6)	-

† Subjects who had less than 3 vaccinations or less than 28 days between vaccinations, who received BCG within 27 days prior or later any dose

‡ Subjects were classified as unevaluable due to wild-type rotavirus-positive prior to 14 days Postdose 3, incomplete clinical and/or laboratory results, or stool samples collected out of day range

Source: Adapted from CSR (V260 Prot. No.029), Table 11-1, page 61. *Reported number of cases were 26 in the applicant's Clinical Overview, Table 2.5.10, page 29-30.

Table 5: Analysis of Efficacy Against Rotavirus Gastroenteritis by Serotype in Protocol P029, Per-Protocol Population

Serotype in P029	Subjects in V260 contributing to efficacy analysis	Subjects in V260 classified as rotavirus gastro enteritis cases	Subjects in Placebo contributing to efficacy analysis	Subjects in Placebo classified as rotavirus gastro enteritis cases	Vaccine Efficacy estimate (%) and 95% confidence interval
G1 P1A[8]	356	3	355	16	81.4 (35.1, 96.5)
G3 P1A[8]	357	4	354	5	20.0 (-271.8, 84.1)
G9 P1A[8]	356	0	354	5	100.0 (-9.0, 100.0)

Source: Adapted from Clinical Overview, Table 2.5.10, page 29.

6.1.11.2 Analyses of Secondary Endpoints

The results of the secondary endpoint evaluation showed that the vaccine efficacy estimate of RotaTeq against moderate and severe rotavirus gastroenteritis (clinical score > 8) caused by any G serotypes associated with serotype P1A[8] occurring at least 14 days following the third dose was 80.2% (95% CI: 47.4%, 94.1%). With severe only level of the disease (clinical score >16), vaccine efficacy was 100% (95% CI: 55.4%, 100%) (ref. Table 11-2 and Table 11-3, CSR Prot. No.029, pages 62-63).

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the primary endpoint by sex was performed for descriptive purposes and presented in Table 6. Among male vaccinees, 5 out of 195 developed rotavirus gastroenteritis in the V260 arm, compared to 10 out of 183 in the placebo arm.

For females, these respective numbers were 2/160 and 17/173. The study, conducted in Japan, involved only one race (e.g., Asian).

Table 6: Rotavirus Serotype G1, G2, G3, G4, and Those Associated with Serotype P1A Occurring at Least 14 Days Following the Third Dose, Subgroup Analysis (Per Protocol Population)

Subgroups	Subjects* vaccinated in V260 (and days of efficacy followup)	Subjects as rotavirus cases	Subjects* vaccinated in Placebo (and days of efficacy followup)	Subjects as rotavirus cases in Placebo	VE (95% CI)
Male	195 (35310)	5	183 (33296)	10	52.9 (-51.4, 87.4)
Female	160 (29513)	2	173 (30543)	17	87.8 (48.7, 98.6)

*Subjects contributing to efficacy analysis.
Source: Adapted from CSR (V260 Prot. No.029), Table_4 and Table_3, pages 178-179, section 14.2.3.1.

Subgroup analysis for the primary endpoint also included gestational age (≤36 weeks, >36 weeks). The study reported (section 11.4.3.2, CSR V260 Prot. No.029) that subjects with gestational age of 36 weeks or less [20 (5.2%) subjects in the group that received RotaTeq and 11 (2.9%) subjects in the placebo group] did not develop rotavirus gastroenteritis.

6.1.11.4 Dropouts and/or Discontinuations
Please refer to Table 2, block 3. Although 368 subjects in the RotaTeq arm and 366 subjects in the placebo arm received all three scheduled doses, the protocol violators and those classified as unevaluable were excluded, resulting in 355 and 356 subjects in the respective arms contributing to efficacy analyses (Table 4).

6.1.11.5 Exploratory and Post Hoc Analyses
None in study Protocol 029.

6.1.11.6 Efficacy Conclusion
Vaccine efficacy against rotavirus gastroenteritis of any severity caused by any serotype G1, G2, G3, G4, and G-serotypes associated with P1A[8] (e.g., G9) occurring at least 14 days Postdose 3 relative to placebo was 74.5% (95%CI: 39.9%, 90.6%), with confidence lower bound of about 40% (Table 4). Additionally, based on the observed serotype specific results in Table 5, the VEs were not significant for serotypes G3 and G9.

6.1.12 Safety Analyses

The objective is to assess the safety of RotaTeq with respect to all adverse experiences occurring within 14 days of any dose in healthy Japanese infants.

Hypothesis: RotaTeq is generally safe and well tolerated in healthy Japanese infants with respect to all adverse experiences occurring within 14 days of any dose.

1. Safety Population

The study had a total of 762 subjects randomized with equal allocation to the RotaTeq and placebo arms. Of these, the safety population comprised 761 subjects (ref. Table 2), with 380 subjects in the RotaTeq arm and 381 subjects in the placebo arm.

2. Demographic characteristics and number of vaccinations received

Please refer to Table 3 and Table 2.

3. Summary of Adverse Events

Adverse experiences observed in all subjects (761) who received at least one vaccine dose within 14 days following any dose are summarized in Table 7. Overall 50% of subjects in either treatment group had one or more adverse experiences. The vaccine related adverse experiences were reported in 14.5% of RotaTeq vaccinees compared to 8.9% in the placebo group. In the respective groups, the serious adverse experiences occurred to 7 (1.8%) and 9 (2.4%) subjects. Please refer to the medical review for clinical description of the serious events. However, the submission reported no causal relationship of the events with the study vaccine. It appeared that from the overall summary of adverse experiences reported within the 14 days of any dose, the treatment groups showed comparable profiles of safety experience.

Table 7: Summary of Adverse Experiences (14 days following any dose) (Safety Analysis Set)

	RotaTeq		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	380		381	
with one or more adverse experiences	189	(49.7)	191	(50.1)
with no adverse experience	191	(50.3)	190	(49.9)
with vaccine-related† adverse experiences	55	(14.5)	34	(8.9)
with serious adverse experiences	7	(1.8)	9	(2.4)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died§	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	0	(0.0)	3	(0.8)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	3	(0.8)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator or subinvestigators to be possibly, probably, or definitely related to the study vaccine.

‡ Discontinued = Subject discontinued from the study.

§ There was 1 death (b) (6) who was allocated to receive RotaTeqTM) occurred on Day (b) (6) Postdose 2.

Source: CSR (V260 Prot. No.029), Table 12-1, page 71.

4. Intussusception and deaths

The study reported no case of intussusception from monitoring, but the study was not powered to evaluate the risk of intussusception. One death case was reported. The subject (Gender=F, Race=ASIAN, Age=2 MONTHS) received RotaTeq and was reported to have died from respiratory syncytial virus bronchiolitis on Day (b) (6) following

the second dose. Any causal relationship of death to the study vaccine was ruled out by the investigator.

5. Adverse experiences, diarrhea, vomiting, and fever within 7 days of any dose

The incidences of diarrhea, vomiting, and fever, i.e., elevated temperature (38.1°C, rectal equivalent) occurring within 7 days following each dose of the study vaccine (first, second, or third dose) are shown by treatment group in Table 8. These AEs in respective order occurred overall in about 10%, 8%, and 26% of subjects, and showed no substantive differences between treatment groups. Elevated temperature (fever) was more frequent than diarrhea and vomiting. The AE of irritability was relatively rare, occurring in only 1 (0.3%) subject in the RotaTeq and 3 subjects (0.8%) in the placebo group, and is not shown in this review.

Table 8: Incidence of diarrhea, vomiting and fever (temperature ≥38.1°C, rectal equivalent), Rotateq vs Placebo, within 7 Days following any dose, Safety Population.

	RotaTeq	Placebo	Difference in % (95% CI)
Subjects in safety analysis, N	380	381	-
Diarrhea, n (%)	41 (10.8)	38 (10.0)	0.8 (-3.6, 5.2)
Vomiting, n (%)	30 (7.9)	28 (7.3)	0.5 (-3.3, 4.4)
Fever, n/N (%)	95/379 (25.1)	105/380 (27.6)	-2.6 (-8.8, 3.7)

Source: Adapted from CSR (V260 Prot. No.029), Table 12-7, pages 88.

6. Vaccine-related adverse experiences occurring within 14 days of any dose

Of the vaccine-related adverse experiences reported occurring within 14 days of any dose (ref. Table 7: n=55, RotaTeq; n=34, placebo), the most frequent were diarrhea (n=21, 5.5%), vomiting (n=16, 4.2%), and gastroenteritis (n=13, 3.4%) in the RotaTeq group. In the placebo group as well these AEs were most frequent: diarrhea (n=15, 3.9%), vomiting (n=13, 3.4%), and gastroenteritis (n=4, 1.0%). The experiences of irritability, pyrexia, and sluggishness altogether happened to 7 (1.8%) subjects in the RotaTeq group compared to 4 (1.0%) subjects in the placebo recipients (CSR, Prot. No.029, Table 12-3, page 77). Gastroenteritis within 14 days of any dose was more frequent in the RotaTeq group compared to placebo (RR=3.26, 95% CI: 1.13, 13.79 for the 13/380 vs 4/381 comparison using an exact statistical method) (CSR, Prot. No.029, Table 12-3, page 77).

7. Serious adverse experiences within 14 days of any dose

The study reported a total of 16 subjects having serious adverse experiences within 14 days of any dose. Seven (1.8%) of 380 subjects were in the RotaTeq group and 9 (2.4%) of 381 subjects were in the placebo group. The incidence included bronchitis, asphyxia, pneumonia, UTI, gastroenteritis, atopic dermatitis, etc. Any causal relationship with the study vaccine was ruled out by the study investigator. Also, the incidences were comparable between groups (RR=0.78, 95% CI: 0.27, 2.11).

8. Adverse experiences within 14 days following each dose

Table 9 shows the number and proportion of subjects having one or more AEs following each dose, by treatment group. From the descriptive information, it appeared that a distinct trend in proportion from first dose was not discernible, regardless of the study groups.

Table 9: Summary and inter-group comparison of adverse experiences (within 14 days following each dose)

	RotaTeq		Placebo	
	n	(%)	n	(%)
Days 1 to 14 Post 1st Vaccination				
Subjects in population with follow-up	380		381	
with one or more adverse events	95	(25.0)	85	(22.3)
Days 1 to 14 Post 2nd Vaccination				
Subjects in population with follow-up	373		374	
with one or more adverse events	74	(19.8)	99	(26.5)
Days 1 to 14 Post 3rd Vaccination				
Subjects in population with follow-up	371		369	
with one or more adverse events	103	(27.8)	83	(22.5)

Source: CSR (V260 Prot. No.029), Section 14.3.1.1.2, pages 190-193.

9. Summary of Safety Conclusions

i. The study reported no case of intussusception from monitoring, but the study was not powered to evaluate the risk of intussusception.

ii. One death case was reported. Any causal relationship of death to the study vaccine was ruled out by the investigator.

iii. The incidences of diarrhea, vomiting, and fever, i.e., elevated temperature (38.1°C, rectal equivalent) occurring within 7 days following each dose of the study vaccine (first, second, or third dose) occurred overall in about 10%, 8%, and 26% of subjects respectively and were comparable between treatment groups (Table 8).

iv. Adverse experiences occurring within 14 days of any dose were reported from about 50% of subjects in each study group (Table 7). Of these AEs, the vaccine related experiences occurred to 14.5% of subjects in the RotaTeq group, compared to 8.9% of subjects in the placebo group (RR=1.62, 95% CI: 1.09, 2.42). The submission reported that these AEs were mild or moderate and did not cause study discontinuation.

v. The serious AEs (<14 days of any dose) reported for 7 (1.8%) and 9 (2.4%) subjects in the RotaTeq and placebo groups, respectively, were regarded as not related to the study vaccine by the study investigator.

vi. Additionally, the overall percentage of subjects with AEs after individual doses did not show marked trends over doses, in any study group (Table 9).

6.1.12.1 Methods
All broad clinical adverse experiences, including diarrhea, fever, irritability, and vomiting, during 14 days following each dose were captured. All deaths, vaccine related serious adverse experiences, and intussusception were monitored from the time the consent form was signed until the end of the study (see 6.1.7). The 95% confidence intervals were used for describing between-treatment differences in the percentage of subjects with AEs.

Reviewer's comment: Since no hypotheses for safety outcomes were tested, these confidence intervals may be viewed as flagging devices rather than inferential tools.

6.1.12.2 Solicited Adverse Events
Please refer to point 5 in section 6.1.12 and Table 8.

6.1.12.3 Deaths
Please refer to point 4 in section 6.1.12.

6.1.12.4 Nonfatal Serious Adverse Events
Please refer to point 7 in section 6.1.12

6.1.12.5 Adverse Events of Special Interest (AESI)
Please refer to point 5 in section 6.1.12 and Table 8.

6.1.12.6 Clinical Test Results
Not relevant for this review

6.1.12.7 Dropouts and/or Discontinuations
Please refer to Table 2 for discontinuations. Three subjects (ages 6, 7, and 8 weeks) in the placebo group discontinued due to adverse experiences (infantile spasms, congenital absence of bile ducts, gastroenteritis).

7. INTEGRATED OVERVIEW OF EFFICACY

The applicant pooled efficacy sub-studies from original protocols 006 (n=70,018, Finland 33%, U.S.+Puerto Rico 48%, Costa Rica + Guatemala + Mexico + Jamaica + Taiwan + Belgium + Germany + Italy + Sweden 19%) and 007 (n=1312, 30 sites in U.S., 3 sites in Finland). The sub-studies were conducted in the U.S. and Finland (Table 10). (ref. Clinical Review, BLA STN 125122, January 30, 2006). To this pool was added another phase 3 Protocol 029 (n=762, Japan 100%) for efficacy. The applicant provided brief summaries of these studies in Table 10.

Table 10: Summary of Studies Included in the Integrated Efficacy Analysis

Program/ Protocol	Short Description	Study Design	Treatments (Sample Size)‡	Key Elements of Patient Population	Primary Efficacy Endpoint
006	Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human- Bovine Reassortant Rotavirus Vaccine in Healthy Infants	Phase III Randomized, multi-center, double-blinded, placebo-controlled, efficacy and safety trial. The efficacy substudy was conducted in US and Finland.	RotaTeq™ (n=34,035) Placebo (n=34,003) Efficacy substudy: Rotateq (n=2,834) Placebo (n=2,839)	Healthy infants, 6 through 12 weeks of age. Gender and age at enrollment: **Rotateq** **Placebo** **Gender** Male 51.5% 51.6% Female 48.5% 48.4% **Age (weeks)** mean (SD) 9.7 (1.6) 9.7 (1.5)	G1-, G2-, G3-, or G4-specific cases of rotavirus gastroenteritis occurring through the first rotavirus season that begins 14 or more days Postdose 3.
007	Study of the Efficacy, Safety, and Immunogenicity of RotaTeq™ at Expiry Potency in Healthy Infants	Phase III Randomized, multi-center, international, double- blinded, placebo controlled efficacy and safety trial. The study was conducted in US and Finland.	RotaTeq™ (n=650) Placebo (n=660)	Healthy infants, 6 through 12 weeks of age. Gender and age at enrollment: **Rotateq** **Placebo** **Gender** Male 53.3% 51.1% Female 46.7% 48.9% **Age (weeks)** mean (SD) 10.1 (1.5) 9.1 (1.5)	G1-, G2-, G3-, or G4-specific cases of rotavirus gastroenteritis occurring through the first rotavirus season that begins 14 or more days Postdose 3.
029	Study of the Efficacy and Safety of V260 in Healthy Infants in Japan	Phase III Randomized multicenter double-blind placebo-controlled efficacy and safety trial The study was conducted in Japan.	RotaTeq™ (n=381) Placebo (n=381)	Healthy infants, 6 through 12 weeks of age. Gender and age at enrollment: **Rotateq** **Placebo** **Gender** Male 54.6% 52.2% Female 45.4% 47.8% **Age (weeks)** mean (SD) 7.6 (1.7) 7.5 (1.6)	G1, G2, G3, G4, and G-serotypes associated With P1A[8] (e.g., G9) specific cases of rotavirus gastroenteritis that begins 14 or more days Postdose 3.

Source: Statistical Report, Integrated analysis of efficacy in protocols 006, 007, and 029, page 7.

7.1 Endpoints

The following endpoint description is taken from the Statistical Report submitted with the application:

> "In protocols 006 and 007, the primary endpoint was cases of naturally occurring RVGE caused by human rotavirus serotypes (G1, G2, G3, G4), that began at least 14 days following vaccination.
>
> *In Protocols 006 and 007, to be counted as a case, the subject must have met the following criteria: (1) Three or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting; and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms.*
>
> In Protocol 029, the primary endpoint was cases of naturally occurring RVGE caused by human rotavirus serotypes G1, G2, G3, G4 and G serotypes associated with serotype P1A[8] (e.g. G9) that began at least 14 days following vaccination.
>
> *In Protocol 029, to be counted as a case, the subject must have met the following criteria: (1) Three or more watery or looser-than-normal stools within a 24-hour*

period and/or forceful vomiting; and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 7 days after the onset of symptoms." (ref. Statistical Report, Integrated analysis of efficacy in protocols 006, 007, and 029, pages 7-9).

In protocols 006 and 007, the primary endpoint analysis did not include efficacy of G-serotypes associated with serotype P1A[8], because the assay for P1A[8] had not been validated yet. Thus, the analysis was performed post-hoc after the validated assay for P1A[8] was available, and the analysis was included in the current submission.

7.1.1 Methods of Integration

The applicant stated that protocols (P) 006, 007 and 029 were suitable for pooling for efficacy because of the following features:

- Similar designs: Phase III, randomized, placebo-controlled (RotaTeq, placebo, ratio 1:1), double-blind studies, similar primary endpoint
- Similar subject characteristics of gender and age (ref. Table 10)
- Similar treatment period visit structures: subjects received 3 doses of study vaccine 28 to 70 days apart
- Same formulation of RotaTeq; same laboratory assays for assessment of vaccine efficacy
- Similar environmental conditions, e.g., industrialized countries
- Very similar primary per-protocol efficacy results [efficacy estimate and 95% CI in P006 74.0% (66.8, 79.9); in P007 72.5% (50.6, 85.6), and in P029 74.5% (39.9, 90.6)] and similar amount of efficacy follow-up time.

(Source: Adapted from Statistical Report, Integrated analysis of efficacy in protocols 006, 007, and 029, page 8).

Reviewer's Comments:
The G9P1A[8] data from studies P006 and P007 were not available for analysis until recently due to lack of a validated assay at the time of the original BLA submission. However, the decision to pool the P029 data with pre-licensure studies P006, P007 was made post hoc rather than prospectively and thus may render the analysis results less rigorous than had they resulted from a prospectively planned pooled analysis.

7.1.2 Demographics and Baseline Characteristics

Please see Table 10.

7.1.4 Primary Efficacy Results

Please refer to the previous medical officer's review of BLA STN 125122, dated January 30, 2006 for the P006 and P007 results on serotypes G1, G2, G3, and G4. Principal focus in this review is for the reported G9P1A[8] results (Table 11). A validated assay for

P1A[8] serotype was not available in the previous BLA review. The G9P1A[8] results from P006 and P007 in the current submission are thus post-hoc. The vaccine efficacy estimates for G9 were not statistically significant within each individual study, including P029. When data from all studies were combined, 1 case of G9 was observed in the RotaTeq group compared to 9 in placebo, resulting in the reported VE point estimate of 88.5% with 17.1% as the 95% confidence lower bound. Ideally, such pooling is planned and described prospectively, to ensure validity of the statistical outcome. An alternative approach is to consider efficacy results from study P029 alone. The study stated "there is 92% power for detection for the efficacy estimate of the vaccine being higher than 0% (statistically significant)" (ref. CSR V260 Prot. No.029, page 50). The stated efficacy was with regard to serotypes G1, G2, G3, G4, and G-serotypes associated with serotype P1A (i.e., including G9) combined, not for individual serotypes. From this study alone, the reported VE estimate for G9P1A[8] was 100% (95% CI: -9.0%, 100.0%) (Table 11), and is not statistically significant. However, whether the negative lower confidence bound for G9P1A[8] is consistent with those for other serotypes already included in licensed products (ref. Table 11, G3P1A[8], G4P1A[8] for study P006) is a clinical judgment. Of note, the observed lower bound of -9.0% is closer to zero than those reported for other G-serotypes (Table 11). Such negative lower bounds often occur, since efficacy trials of multivalent vaccines are not typically powered to detect significant serotype-specific efficacy.

Table 11: Efficacy by Serotype in Protocol 006, 007, 029 and combined (Per-protocol Population)

Protocol	Serotype	RotaTeq Subjects contributing to efficacy analysis	RotaTeq Subjects classified as rotavirus gastro-enteritis cases	Placeo Subjects contributing to efficacy analysis	Placeo Subjects classified as rotavirus gastro-enteritis cases	Efficacy estimate(%) and 95% confidence interval
P006[†]	G1 P1A[8]	2206	72	2296	286	74.9 (67.3, 80.9)
	G2 P1[4]	2204	6	2294	17	63.4 (2.6, 88.2)
	G3 P1A[8]	2203	1	2288	6	82.7 (-42.6, 99.6)
	G4 P1A[8]	2203	3	2288	6	48.1 (-143.2, 91.6)
	G9 P1A[8]	2203	1	2287	3	**65.4 (-331.1, 99.3)**
P007[‡]	G1 P1A[8]	551	13	564	53	75.8 (55.0, 87.9)
	G3 P1A[8]	551	2	562	1	<0
	G9 P1A[8]	551	0	562	1	**100.0 (-3895.1, 100.0)**
P029[§]	G1 P1A[8]	356	3	355	16	81.4 (35.1, 96.5)
	G3 P1A[8]	357	4	354	5	20.0 (-271.8, 84.1)
	G9 P1A[8]	356	0	354	5	**100.0 (-9.0, 100.0)**
P006, P007, and P029	G1 P1A[8]	3113	88	3215	355	75.3 (68.7, 80.7)
	G2 P1[4]	3111	6	3210	17	63.5 (3.0, 88.2)
	G3 P1A[8]	3111	7	3204	12	39.7 (-66.1, 79.9)
	G4 P1A[8]	3110	3	3204	6	48.3 (-142.2, 91.6)
	G9 P1A[8]	3110	1	3203	9	**88.5 (17.1, 99.7)**

combined	All P1A[8], e.g. G1, G3, G4 and G9*	3111	99	3218	383	74.2 (67.8, 79.6)

Note: No cases with G2 or G4 identified from P007 or P029.

† P006: Safety, Immunogenicity and Efficacy of RotaTeq™ (REST; Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, U.S.)

Note: In P006 there were 26 per-protocol cases (11 RotaTeq™, 15 placebo) that were rotavirus-antigen positive via EIA but negative or non-typeable via PCR. These are not included in this table.

‡ P007: Safety, Immunogenicity and Efficacy of RotaTeq™ at End Expiry Potency (US, Finland)

Note: In P007 there were 4 per-protocol cases (1 RotaTeq™, 3 placebo) for which the G serotype was not identified (e.g., missing data, antigen-positive but negative serotype, or not-typeable). These are not included in this table.

§ P029: Safety and Efficacy of RotaTeq™ in Japanese Subjects (Japan)

*Note: In P029, there was one case that was identified as P1A[8], but the G serotype was not identified. It is included here.

Source: Statistical Report, Integrated analysis of efficacy in protocols 006, 007, and 029, page 11.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable in this review.

7.1.6 Other Endpoints

Not applicable in this review.

7.1.7 Subpopulations

Not applicable in this review.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable in this review.

7.1.11 Efficacy Conclusions

The applicant's pooling for the G9P1A[8] information was a post hoc combining of data from pre-licensure studies P006 and P007 with new data from study P029. Analysis results that are based on post hoc decisions rather than prospective planning are not ordinarily viewed as having the same level of validity as those based on pre-specification. Consequently, such results are often viewed as being descriptive in nature, to some extent, and may provide supportive information.

When data from study P029 alone were considered for efficacy evaluation, the VE lower bound for G9P1A[8] serotype was reported as -9.0%, which does not demonstrate statistical significance. The negative lower confidence bound, however, appears consistent with that for other serotypes already included in the previous BLA for licensure. Compared to lower bounds already reported with other G-serotypes (Table 11), the observed lower bound of -9.0% is closer to zero (i.e. , is closer to being statistically significant). Note that negative lower bounds for serotype-specific efficacy are common for multivalent vaccines, since clinical trials of these vaccines are not typically powered to detect statistically significant VE for all individual serotypes.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable in this review. Please refer to medical officer's report.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

See section 7.1.11 above.

10.2 Conclusions and Recommendations

A validated assay for P1A[8] serotype was not available for the previous BLA review. Following the development of the validated assay, the G9P1A[8] data from pre-licensure studies P006 and P007 were available for analysis in the current submission.

Based on study P029 alone, from the per-protocol population, the overall VE for RotaTeq against rotavirus gastroenteritis of any severity due to reported serotypes (G1, G3, G9) was 74.5% (95% CI: 39.9%, 90.6%), and for serotype G9P1A[8] the reported VE was 100% with 95% CI: -9.0%, 100.0%. The reviewer defers to the medical officer to consider this negative lower confidence bound in view of the lower bounds already reported for other G-serotypes in the vaccine.

This reviewer defers to the medical officer regarding the applicant's intended indication, based on the totality of the statistical and clinical evidence.