Application Type	Efficacy Supplement
STN	125122/1309
CBER Received Date	April 25, 2016
PDUFA Goal Date	February 23, 2017
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Gueorgui Dubrocq, MD
Review Completion Date / Stamped Date	February 23, 2017
Supervisory Concurrence	Lucia Lee MD Jeff Roberts MD
Applicant	Merck Sharp & Dohme Corp.
Established Name	Rotavirus Vaccine, Live, Oral, Pentavalent
(Proposed) Trade Name	RotaTeq
Pharmacologic Class	Vaccines
Formulation(s), including Adjuvants, etc.	A dose (2 mL) contains 5 live human-bovine reassortant rotavirus strains. Each dose contains a minimum of 2.0 to 2.8 × 10^6 infectious units per reassortant dose, depending on the reassortant, and not greater than 116 × 10^6 infectious units per aggregate dose.
Dosage Form(s) and Route(s) of Administration	Solution administered orally
Dosing Regimen	Three doses; the first dose is administered at 6 to 12 weeks of age and then at 4 to 10 week intervals. The third dose should not be given after 32 weeks of age.
Indication(s) and Intended Population(s)	Current Indication: RotaTeq is indicated for the prevention of rotavirus gastroenteritis caused by G1, G2, G3, and G4 serotypes contained in the vaccine. Proposed new indication: RotaTeq is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9. RotaTeq is approved for use in infants 6 weeks to 32 weeks of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

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 types
G1	Rotavirus type G1 or simplified name of the WI79-9 G1 reassortant strain contained in V260
G2	Rotavirus type G2 or simplified name of the SC2-9 G2 reassortant strain contained in V260
G3	Rotavirus type G3 or simplified name of the WI78-8 G3 reassortant strain contained in V260
G4	Rotavirus type G4 or simplified name of the BrB-9 G4 reassortant strain contained in V260
G9	Rotavirus type 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 types)
P1A	Rotavirus type 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)
RVGE	Rotavirus gastroenteritis
SD	Standard deviation
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

RotaTeq (Rotavirus, Live Oral Pentavalent Vaccine) is composed of 5 human bovine reassortants which include G1, G2, G3, G4 and P1A[8]. Merck & Co., Inc submitted a Biologics License Application supplement (sBLA) to support the use of Rotavirus, Live Oral Pentavalent Vaccine (RotaTeq) to prevent rotavirus gastroenteritis (RVGE) caused by type G-serotypes associated with P1A[8] (e.g., G9) when administered as a 3 dose series to infants between the ages of 6 and 32 weeks. RotaTeq is currently indicated for the prevention of RVGE caused by types G1, G2, G3 and G4.

The efficacy of RotaTeq against RVGE caused by G types associated with P1A[8] (e.g., G9) in infants 6 to 32 weeks of age was evaluated prospectively in study 029 and retrospectively in studies 006 and 007. Study 029 was a phase 3 randomized, multicenter, double blind, placebo controlled, parallel group comparison clinical trial to evaluate the safety and immunogenicity of RotaTeq in healthy Japanese infants aged 6 to 12 weeks after birth. The subjects were randomized (1:1) into 2 groups to receive either RotaTeq or placebo. Study 006 was a phase 3 double-blinded, randomized, placebo-controlled, international multicenter study to evaluate the efficacy, immunogenicity, and safety of RotaTeq. Study 007 evaluated the efficacy of RotaTeq at expiry potency.

Studies 006 and 007 were reviewed as part of the original licensure of RotaTeq; the assay to detect P serotypes was not yet available at that time. Study 029 was conducted after the P serotype assay was developed. Study 029 was submitted for review under the current BLA to support the new claim for prevention of P1A[8] associated (e.g., G9) RVGE. For Study 029, the primary objective was to demonstrate the efficacy of a 3 dose regimen of RotaTeq against rotavirus gastroenteritis caused by rotavirus types G1, G2, G3, G4 and G types associated with type P1A[8] (e.g., G9) occurring at least 14 days following the third dose in healthy infants. The primary objective was met as RotaTeq was shown to prevent rotavirus gastroenteritis caused by G1, G2, G3, G4 and G-types associated with P1A[8] (i.e., G9) as the vaccine efficacy was 74% (95% Confidence Interval (CI): 39%, 90%). RVGE associated with G9P1A[8] was observed as follows: in study 029, it was observed in 0/356 and 5/354 subjects in the RotaTeq and placebo groups (100% (95% CI: -9%, 100%)), in study 006, it was observed 1/2203 and 3/2287 subjects (65% (95% CI: -331%, 99%)), and in study 007, it was observed in 0/551 and 1/562 subjects (100% (95% CI: -3895%, 100%)).

In addition to the new data on G9 from Study 029, the sponsor submitted a supportive analysis of all cases of G9 associated RVGE from in a pooled dataset from Studies 006, 007, and 029. The rationale for pooling the efficacy data included the similarity of the conduct of the studies, the populations included, and the concomitant infant vaccines administered. The evaluable (per-protocol) efficacy populations for the three studies (029, 006, 007) combined included a total of 6329 subjects. The combined vaccine efficacy against G9P1A[8] in Protocols 006, 007, and 029 was 88.5% (95% CI:17%, 99%).

Safety data in study 029 was reviewed in this sBLA; safety data in study 006 and 007 was previously reviewed as part of the original BLA (STN 125122/0) for licensure submitted in 2006. The safety evaluation in study 029 included assessments of solicited adverse events (AEs), unsolicited AEs, and serious adverse events (SAEs). A total of

761 subjects were included in the safety populations. The rates and severities of solicited adverse reactions were comparable between RotaTeq and placebo groups. The most frequent solicited adverse reaction reported after any vaccination within 7 days was fever (25% in the RotaTeq group, 27% in the placebo group), followed by diarrhea (10% in each group) and vomiting (7% in each group). There were no reported cases of intussusception in either group. One subject in the RotaTeq group died (b) (6) days after receiving the second dose due to complications of respiratory syncytial virus bronchiolitis. In this reviewer's assessment, the event does not appear to be related to the study vaccine.

The applicant's plan to monitor for unanticipated safety issues via routine pharmacovigilance is acceptable. No post-marketing studies are required.

Together, the submitted data, which include a new study (029) in which G9 was included in the pre-specified composite primary endpoint, support the effectiveness of RotaTeq in the prevention of RVGE associated with serotype G9.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Subgroup Analysis by Gender

Rotavirus gastroenteritis efficacy in study 029, which was pre-specified, caused by types G1, G2, G3, G4 and G9P1A[8] at least 14 days after the third dose was observed in 5 of 195 males in the group that received RotaTeq and 10 of 183 males in the placebo group (52% (95% CI: -51%, 87%). Rotavirus gastroenteritis occurred in 2 of 160 females in the group that received RotaTeq and 17 of 173 females in the placebo group (87% (95% CI: 48%, 98%)) (Source: CSR V260 Protocol 029, Section 14.2.3.1, Table 1_3 and 1_4, pages 178-9).

Incidences of diarrhea, vomiting, irritability, and fever occurring within 7 days following any dose of the study vaccine showed that the incidences of diarrhea and vomiting in females were numerically higher in the group that received RotaTeq than in the placebo group (9% vs 7%). The safety profile appeared comparable between males and females receiving RotaTeq except for the fever rate ($T \geq 38.1°C$), which was numerically higher in males than females (27% vs 22%) (Source: CSR V260 Protocol 029, Section 14.3.1.6.1 pages 243-9). The number of subjects in each subgroup was too small to make definitive conclusions about differences in safety by gender.

Subgroup Analysis by Race/Ethnicity

Subgroup analyses by race and ethnicity cannot be made as the study population was homogeneous (100% Japanese infants).

Subgroup Analysis by Gestational Age (≤36 weeks, >36 weeks)

Subgroup analyses by gestational age cannot be made as none of the subjects ≤36 weeks (20 in the RotaTeq group and 11 in the placebo group) developed rotavirus gastroenteritis.

Incidences of diarrhea, vomiting, irritability and fever occurring within 7 days following any dose of the study vaccine showed that the incidences in the subjects with a gestational age of ≤36 weeks were numerically higher compared to those subjects with a gestational age of > 36 weeks. The incidences for subjects in the treatment group in comparison to the placebo group were as follows: vomiting (15% vs 10%), vomiting

(15% vs 7%), irritability (5% vs 0%), and fever (40% vs 24%) (Source: CSR V260 Protocol 029, Section 14.3.1.6.2 pages 276-282).

2. Clinical and Regulatory Background

On February 6, 2006, approval of RotaTeq was granted by the FDA for the prevention of rotavirus gastroenteritis in infants and children caused by the types G1, G2, G3 and G4 when administered as a 3 dose series to infants between the ages of 6 to 32 weeks. Licensure of RotaTeq was supported by two phase 3 trials (study 006 and study 007) that contributed data for the efficacy evaluation.

Study 006, the "Rotavirus Efficacy and Safety Trial" (REST) was a phase 3 double-blinded, randomized, placebo controlled, international multicenter study to evaluate the efficacy, immunogenicity, and safety of RotaTeq. The primary objective of study 006 was to evaluate the efficacy of a 3 dose regimen of RotaTeq against rotavirus gastroenteritis caused by types G1,G2, G3 and G4 occurring at least 14 days following the third vaccination. The efficacy of RotaTeq against rotavirus gastroenteritis of any severity caused by the types in the vaccine through the first rotavirus season post-vaccination was 74% (95% Confidence Interval (CI): 66%, 79%).

Study 007 was a phase 3 double blinded, randomized, multi-center, placebo controlled, efficacy trial conducted in the United States and Finland to evaluate the safety, Immunogenicity, and efficacy of RotaTeq at end expiry potential. The efficacy of a 3 dose regimen of RotaTeq at expiry potency against naturally occurring rotavirus disease caused by the composite of the types contained within the vaccine (G1, G2, G3 and G4) occurring at least 14 days following the third dose which was 72% (95% CI: 50%, 85%). In the original licensure review, efficacy against rotavirus gastroenteritis was analyzed by type, based on VP7 (G) typing assays (including typing for G9) for stool specimens collected in studies 006 and 007. Globally, nearly all G9 rotavirus types are associated with P1A[8].

2.1 Disease or Health-Related Condition(s) Studied

Rotavirus infection is the leading cause of severe gastroenteritis among infants and young children worldwide (1, 2). Before the introduction of rotavirus vaccine in the United States in 2006, rotavirus infection caused significant morbidity among U.S. children, with an estimated 55,000–70,000 hospitalizations and 410,000 clinic visits annually (3). The disease showed a characteristic winter-spring seasonality and geographic pattern, with annual seasonal activity beginning in the West during December-January, extending across the country, and ending in the Northeast during April-May (4). Although most rotavirus infections occur in the first and second years of life, the age group at greatest risk of severe gastroenteritis includes children 4 to 23 months of age (5). Subsequent infections usually result in much milder disease (6).

A marked and sustained decline in rotavirus activity was seen nationally in all seven rotavirus reporting years from 2007 to 2014 following the implementation of routine rotavirus vaccination of U.S. children (7). Though rotavirus vaccine coverage among children aged 19–35 months has increased nationally since the vaccine was introduced, from 43% in 2009 to 72% in 2013, some children remain unvaccinated (8). During 2007–2011 more than 176,000 hospitalizations, 242,000 emergency department visits, and 1.1

million outpatients visits due to diarrhea were averted, resulting in costs savings of $924 million over this 4-year period (9).

Rotavirus is classified according to a binary system based on two protein types: G (glycoprotein) types and P (protease protein) types. In the US, viruses containing six distinct P and G combinations are most prevalent: G1P[8], G2P[4], G3P[8], G4P[8], G9 P[8], and G9P[6], although more than 40 rare or regional strains have been identified in the US and globally (10). In North America, Europe and Australia, G1P[8], G2P[4], G3P[8], and G4P[8] represent over 90% of rotavirus infections (11).

During the 1990s and 2000s at least 2 novel strains, G9P[8] and G12P[8], emerged to become medically important globally in addition to the historically well-known four endemic strains, G1P[8], G2P[4], G3P[8], and G4P[8] (12). In fact, the emerging variants of G9 and G12 strains were inferred to have spread worldwide over the course of a decade to become, respectively, the 5^{h} and 6th most commonly reported rotavirus strains (13). Worldwide regional G9P[8] prevalence range from 7 to 16% as follows: Americas 16%, Eastern Mediterranean 16%, Europe 14%, Southeast Asia 11%, Africa 9%, and Western Pacific region 7%. All other common genotype worldwide regional prevalences ranged as follows: G1P[8], 20.4–47.7%; G2P[4], 10.0–29.2%; G3P[8], 2.6–34.4%; G4P[8], up to 15.5%; G9P[8], 7.9–16.6%; G12P[8], 0.1–10.1%). While there are regional variations, the literature suggests that globally approximately 90% of G9 is associated with P[8] (12). From 2007 to 2012, the non-P[8] G9 type isolated from humans, which were uncommon have been associated with P[4], P[6], P[9], P[10], P[11], and P[19] (12).

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

The first U.S. licensed rotavirus vaccine was RotaShield® in 1998, a tetravalent (G1-4) rhesus-human reassortant vaccine given in a 3-dose schedule (14). However, this vaccine was withdrawn from the US market in 1999 due to the development of an unexpected association with intussusception (15).

Rotarix®, a live attenuated monovalent G1P1A[8] human rotavirus strain, was licensed in the United States in April, 2008. The oral vaccine was indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9) in infants and children when administered as a two-dose series between the ages of 6-24 weeks (16). All types indicated in the Rotarix vaccine were associated with P1A[8].

2.3 Safety and Efficacy of Pharmacologically Related Products

Safety and efficacy of Rotarix® is included in the clinical review of STN# 125265/0. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133580.pdf

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

Please refer to the RotaTeq package insert and/or the clinical BLA review for STN 125122/0 for more information regarding previous human experience with RotaTeq in infants.

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

Relevant Meetings and Teleconferences between CBER and the Applicant:
June 18th, 2015: Type C sBLA Teleconference to discuss study 029 and pooling of studies 006, 007, 029 to expand indication to include type G9.
June 3st, 2016: Teleconference to discuss Pediatric Study Plan (PSP) request to address Pediatric Research Equity Act (PREA) and request document validation for VP4 and VP7 PCR fecal assays.

Post-submission Relevant Communications by CBER
September 29th, 2016: Request for:

a. Pooled and individual data from all RotaTeq clinical studies where type G9 was evaluated for efficacy.
b. Data on percentage of how many type G9 cases were associated with P1A[8] and non-P1A[8]. Asked to provide a separate analysis of efficacy in the prevention of non-P1A[8] associated G9 disease, both from individual studies and pooled.
c. A summary of published literature with data on RotaTeq efficacy of type G9 and its association with P1A[8] and non-P1A[8].
d. A summary of global epidemiologic data on isolates of type G9 in association with P1A[8] and non-P1A[8].

Clinical Reviewer: A PSP was requested of the sponsor as there was a new indication for the product. PREA was not addressed during the BLA review in 2006 as licensure of RotaTeq pre-dated PREA.

During the Type C meeting held with applicant on June, 2015, the applicant proposed combining the data from an efficacy and safety study in Japan (study 029), a study prospectively defined to assess the efficacy of rotavirus gastroenteritis including G9P1A[8], with previous studies used to support licensure in the United States (studies 006 and 007) to extend the indication for prevention of G type containing P1A[8] e.g. type G9. During the meeting, CBER indicated that review of the data from study 029 was needed before any decision could be made regarding the proposed expanded indication, and that the wording of the indication required further discussion.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty or an unreasonable number of information requests.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring (BIMO) data audit inspections were previously reviewed at 4 sites for study 006. For summary and additional details, please see clinical review (STN 125122/0) by Dr. Rosemary Tiernan, Medical Officer, Vaccines Clinical Trials Branch Division of Vaccines and Related Product Applications.

3.3 Financial Disclosures

The applicant certified that they had not entered into any financial arrangements with any of the 172 investigators in study 029 whereby the value of compensation of the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Financial disclosures are not listed for study 006 and 007 as it has been previously reviewed as part of the BLA.

Covered clinical study (name and/or number): V260-029		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 172		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 172		

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

4.1 Chemistry, Manufacturing, and Controls

Please refer to the original BLA submission (STN 125122/0 http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094063.htm). The product formulation selected for use in subjects 6 to 12 weeks of age is identical to the pediatric formulation which was approved in the original RotaTeq BLA.

4.2 Assay Validation

Licensure of RotaTeq in the USA was based on the results from phase 3 study Protocols 006 and 007. In these two studies, the VP7 assay was used to determine the VP7 glycoprotein types of the rotavirus in the clinical samples. Subsequent to the validation of the new VP4 assay in 2005, the applicant performed post-hoc serotyping for the VP4 protease sensitive protein on these clinical samples. During 2008-2009, when the applicant conducted clinical study 029, both the VP4 and VP7 assays were used to test stool samples. The validation reports demonstrated accuracy and precision for determining types G1, G2, G3, G4, G5 and G9 using the VP7 assay and P1a, (b) (4) using the VP4 assay. In addition, the VP7 and VP4 assays did not show any evidence that negative samples would be falsely determined as positives. The serotypes of the infected subjects in the submitted clinical reports were included in the list of serotypes that were validated. Based on these findings, we consider that the VP7 and VP4 assays were suitable for the use in determining the serotypes for the clinical isolates to support the proposed indication. For additional details, please refer to the review memo of Dr. Charles (Yin Kiu) Cheung, Vaccine Evaluation Branch, Division of Biostatistics, CBER.

4.3 Nonclinical Pharmacology/Toxicology

This submission contained no new or revised nonclinical pharmacology/toxicology information.

4.4 Clinical Pharmacology

Not applicable

4.5 Statistical

As per the statistics review memo, the applicant's pooling for the G9P1A[8] information was a post hoc combining of data from pre-licensure studies 006 and 007 with new data from study 029. 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. For efficacy based on Protocol 029 alone, the vaccine efficacy for RotaTeq against rotavirus gastroenteritis, regardless of severity, due to all reported serotypes was 74.5% (95% CI: 39%, 90%). For serotype G9P1A[8], the VE estimate was 100% with lower confidence bound -9%, a value relatively closer to zero than the negative lower bounds for other G-serotypes included in the pre-licensure studies. 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. For additional details, please see the review memo by Dr. Mridul Chowdhury of Biostatistics, CBER.

4.6 Pharmacovigilance

Plans to monitor for unexpected safety risks following RotaTeq vaccination are via routine safety surveillance. Previous reviews following licensure and post-marketing data of RotaTeq concluded that no safety signals or increased risk of intussusception were identified.

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

5.1 Review Strategy

The review of reports for individual studies focuses on one study (study 029), as the individual reports for study 006 and 007 had been previously reviewed for safety and efficacy as part of the BLA. An integrated summary of efficacy for studies 006, 007, and 029 for G9P1A[8] is presented in section 7 of this review.

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

The following modules of the sBLA were reviewed:

m1.3.4	Financial Certification and Disclosures
m1.6	Meetings
m1.14	Labeling
m2.5	Clinical Overview
m5	Clinical Study Reports
m5.3.5.1	Integrated Efficacy Report
m1.9.1	Amendment 1-Request for Waiver of Pediatric Studies
m1.11.3	Amendment 4-Respose to G9 Epidemiologic Data
m1.14.1	Amendment 5-Response to Label Comments
m1.14.1	Amendment 6-Final Label

5.3 Table of Studies/Clinical Trials

Table 1. Summary of Clinical Studies 006, 007, and 029

Study	Study Design and Objectives	Location	Study Vaccine	Population	Subject Exposure
006	Phase 3 randomized (1:1), double blinded, placebo controlled study. Primary objective was to assess the safety and efficacy of RotaTeq in infants.	Europe, North America, Central America, Caribbean, East Asia	RotaTeq administered as a 3 dose series to infants between the ages of 6 and 32 weeks. The first dose is administered at 6 to12 weeks of age followed by two subsequent doses separated by 4 to 10 week intervals.	Infants 6 to 12 weeks of age	RotaTeq: 31,938 Placebo: 34,896 Efficacy subset RotaTeq: 2834 Placebo: 2839
007	Phase 3 randomized (1:1), double blinded, placebo controlled study. Primary objective was to assess the safety and efficacy of RotaTeq in infants.	United States and Finland	RotaTeq administered as a 3 dose series to infants between the ages of 6 and 32 weeks. The first dose is administered at 6 to12 weeks of age followed by two subsequent doses separated by 4 to 10 week intervals.	Infants 6 to 12 weeks of age	RotaTeq: 651 Placebo: 661
029	Phase 3 randomized (1:1), double blinded, placebo controlled study. Primary objective was to assess the safety and efficacy of RotaTeq in infants.	Japan	RotaTeq administered as a 3 dose series to infants between the ages of 6 and 32 weeks. The first dose is administered at 6 to12 weeks of age followed by two subsequent doses separated by 4 to 10 week intervals.	Infants 6 to 12 weeks of age	RotaTeq: 381 Placebo: 381

Source: Adapted from Tabular Listings of All Clinical Studies

5.4 Consultations

Not applicable

5.5 Literature Reviewed

1. Tate JE, Burton AH, Boschi-Pinto, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Inf Dis 2012;12:136–41.

2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565–72.

3. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2009;58(No. RR-02):1–25.

4. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. 2011 Peds Inf Dis Supp; 30(1).

5. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR02):1-25.

6. Ehlken B, Laubereau B, Karmaus W, Petersen G, Rohwedder A, Forster J and the RoMoD Study Group. Prospective population-based study on rotavirus disease in Germany. Acta Paediatr. 2002;91:769-75.

7. Aliabadi N, et al. Sustained decrease in laboratory detection of rotavirus after implementation of routine vaccination—United States, 2000-2014. Centers for Disease Control and Prevention (CDC), MMWR Morb Mortal Wkly Rep. 2015 Apr 10;64(13):337-42.

8. Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19–35 months — United States, 2013. 2014 MMWR Morbid Mortal Wkly Rep 2014;63;741–8.

9. Leshem E, Moritz RM, Curns AT et al. Rotavirus vaccines and health care utilization for diarrhea in the United States (2007-2011). Pediatrics 2014;134(1)

10. Gentsch JR, Laird AR, Bielfelt B, Griffin DD, Banyai K, Ramachandran M, et al. Serotype diversity and reassortmant between human and animal rotavirus strains: implications for rotavirus vaccine programs. *J Infect Dis* 2005;192:S146-59

11. Santos H, Hoshino Y. Global distribution of rotavirus serotype/genotypes and its implication for the development and implication of an effective rotavirus vaccine. Rev Med Virol. 2005;15:29-56.

12. Dóró R et al. Review of global rotavirus strain prevalence data from six years post vaccine licensure surveillance: is there evidence of strain selection from vaccine pressure? Infect Genet Evol. 2014 Dec;28:446-61. doi: 10.1016/j.meegid.2014.08.017. Epub 2014 Sep 16.

13. Matthijnssens, J., Heylen, E., Zeller, M., Rahman, M., Lemey, P., Van Ranst, M., 2010. Phylodynamic analyses of rotavirus genotypes G9 and G12 underscore their potential for swift global spread. Mol. Biol. Evol. 27, 2431–2436.

14. CDC. Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 1999;48:1-20.

15. CDC. Withdrawal of rotavirus vaccine recommendation. Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 1999;48(43):1007.

16. Rotarix [package insert]. Research Triangle Park, NC: GlaxoSmithKline Biologicals; 2016
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm133920.htm

17. Van Damme P, Giaquinto C, Huet F, Gothefors L, Maxwell M, Van Der Wielen M, et al. Multicenter prospective study of the burden of Rotavirus Acute Gastroenteritis in Europe, 2004-2005: The REVEAL Study. J Infect Dis 2007;195(Suppl 1):S4-S16.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Clinical Study Protocol V260 P029
Clinical trials.gov registry number identifier: NCT00718237

Protocol Title: Phase III Randomized Multi-center Placebo Controlled Trial to Study the Efficacy and Safety of V260 in Healthy Infants in Japan.

Study dates: 8/22/08-8/26/09
First subject first visit: 8/22/08
Last subject last visit: 8/26/09

Clinical Reviewer: Study 029 was not conducted under US IND as it was performed to support licensure in (b) (4) regulatory agency based on the results of face-to-face advice given by the (b) (4) at a meeting held on April 17, 2008.

6.1.1 Objectives (Primary, Secondary, Exploratory, Safety)

The primary objective included:

a. Evaluating the efficacy of a 3 dose regimen of RotaTeq against naturally occurring rotavirus gastroenteritis of any severity caused by rotavirus types G1, G2, G3, G4 and G types associated with P1A[8] (e.g. G9) occurring at least 14 days following the third dose in healthy Japanese children.
b. Assessing the safety of RotaTeq with respect to all adverse experiences occurring within 14 days of any dosing in healthy Japanese children.

The secondary objectives included:

a. Evaluating the efficacy of a 3 dose regimen of RotaTeq against moderate and severe rotavirus gastroenteritis caused by rotavirus types G1, G2, G3, G4 and those associated with type P1A occurring at least 14 days following the third dose.
b. Evaluating the efficacy of a 3 dose regimen of RotaTeq against rotavirus gastroenteritis (moderate-severe, severe, and any severity) caused by any rotavirus type occurring at least 14 days following the third dose.
c. Evaluating the cumulative efficacy following the first dose of a 3 dose regimen of RotaTeq against rotavirus gastroenteritis (moderate-severe, severe, and any severity) cause by rotavirus types G1, G2, G3, G4 and those associated with type P1A and by any rotavirus type.

The tertiary objectives included:

a. Summarizing the efficacy of RotaTeq against rotavirus gastroenteritis occurring between doses (from 14 days Post-dose 1 until the second vaccination, and from 14 days Post-dose 2 until the third vaccination) and caused by rotavirus types G1, G2, G3, G4 and those associated with type P1A and by rotavirus of any type.
b. Summarizing the effect of a 3-dose regimen of RotaTeq on health care resource utilization, including visits to emergency departments and hospitalizations for rotavirus gastroenteritis.

6.1.2 Design Overview

This was a phase 3 randomized, multicenter, double blind, placebo controlled, parallel group comparison study trial to evaluate the safety and immunogenicity of RotaTeq in healthy infants aged 6 to 12 weeks after birth. The trial enrolled a total of 744 subjects throughout Japan and randomized them (1:1) into 2 groups to receive either RotaTeq or placebo.

The subjects received 3 doses of the vaccine at intervals of 28 to 70 days, with completion of the third dose by 32 weeks of age. Follow up was continued at least until the end of the first rotavirus infection season after the enrollment of the first subject. The last visit was made when the number of subjects with rotavirus gastroenteritis reached the target number (30) needed for the primary evaluation and unblinding the treatment assignment was performed.

For randomization, after the subject was confirmed to be eligible, an allocation number was assigned, and the subject was randomized to the group receiving RotaTeq or the group receiving placebo in a 1:1 ratio according to the randomization code prepared by a computer at the US Head Office. The randomization code prepared was sealed and strictly retained at the “Randomization Code Retaining Organization” until database lock to maintain blinding.

The blinding procedures was prescribed by the US Head Office and the treatment groups were blinded against parents (guardians), investigators, study coordinators, study-related personnel and the applicant (including external agencies). Blinding was maintained using the randomization code prepared and retained by subject assignment according to the procedure set out in the randomization procedures stated above.

Table 2. Study Design for Study 029

Group	Age	Number of Subjects	Dosing Schedule	Analysis
RotaTeq	6 to 12 weeks of age	381	3 doses	Safety and Efficacy
Placebo	6 to 12 weeks of age	381	3 doses	Safety and Efficacy

Clinical Reviewer: Study design, randomization, and blinding procedures were appropriate for a phase 3 study.

6.1.3 Population

Inclusion Criteria

1. Healthy Japanese infants
2. Infants aged 6 to 12 weeks (≥42 to ≤84 days) after birth at the time of the first dose of vaccination
3. Infants whose parents (guardians) understood the study procedures, alternative treatments available, and risks associated with the study, and voluntarily agreed to participate by giving written informed consent

Exclusion Criteria

1. History of congenital abdominal disorders, intussusception, or abdominal surgery.
2. Known or suspected impairment of immunological function.
3. Hypersensitivity to any components of the rotavirus vaccine, e.g., (b) (4) sucrose, sodium hydroxide, sodium citrate, sodium phosphate, surface active agent (Polysorbate 80), and (b) (4) contained in the culture media for tissue culture used in the manufacturing process of a vaccine.
4. Prior administration of any rotavirus vaccine.
5. Rectal temperature ≥38.1°C or axillary temperature ≥37.5°C at the time of vaccination.
6. History of known prior rotavirus gastroenteritis, chronic diarrhea, or growth disorder.
7. History of active gastrointestinal illness [Note that infants with gastroesophageal reflux disease (referred to as GERD, hereinafter) may participate in the study provided the GERD is well controlled with or without medication.].
8. Receipt of intramuscular, oral, or intravenous corticosteroid treatment (Note that infants on inhaled steroids may participate in the study.).
9. Residing in a household with an immunocompromised person, including individuals with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, organ, or bone marrow transplantation, or with those receiving immunosuppressive chemotherapy including long-term systemic corticosteroids.
10. Any prior receipt of a blood transfusion or blood products including immunoglobulins.
11. Cannot be adequately followed for safety by telephone, e-mail, or clinic visit.
12. Receipt of oral poliovirus vaccine (referred to as OPV, hereinafter) or Bacille Calmette-Guerin (BCG) within 27 days prior to the first dose of study vaccine/placebo.
13. Currently participating in or are anticipated to participate in other studies (Subjects enrolled in observational studies may be included if the sponsor approves.).
14. Any condition, which, in the opinion of the investigator, etc. may interfere with the evaluation of the study objectives.

Clinical Reviewer: The inclusion criteria for study 029 are similar with study 006 and 007 in that they included healthy infants 6 to 12 weeks of age after birth at the first dose of the vaccination. Differences in the inclusion criteria for study 029 is that it only included Japanese subjects, while study 006 and 007 were performed

on 2 or more continents each. The exclusion criteria were the same for all three studies.

6.1.4 Study Treatments or Agents Mandated by the Protocol

RotaTeq (manufactured by Merck): Each 2 mL dose 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 type, and not greater than 116 × 10^6 infectious units per aggregate dose. Each dose is supplied in a container consisting of a squeezable plastic dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch.

Table 3. Product Description in Study 029

Group	Dosage Form	Potency	Lot Number	Package
RotaTeq	Oral Solution	Rotavirus G1, G2, G3, G4, and P1 12.8/7.65/18.8/14.0/11.0 x 10^6 IU, making a total potency of 64 x 10^6 Infection Unit (IU)	WL00026150	2 mL Single dose tube
RotaTeq	Oral Solution	Rotavirus G1, G2, G3, G4, and P1 9.77/9.60/27.9/13.6/11.9 x 10^6 IU, making a total potency of 73 x 10^6 IU	WL00030888	2 mL Single dose tube
Placebo	Oral Solution	NA	WL00029424	2 mL Single dose tube

Source: Adapted from STN125122/1309 CSR 029 Table 9-2 p32

Clinical Reviewer: Phase 3 clinical trials (study 007) was conducted to confirm clinically the efficacy of the assigned expiry potency of the final commercial product with favorable results, and study 006 confirmed the safety of RotaTeq in the range of release potencies (67 × 10^6 to 124 × 10^6 infectious units/dose).

Prior and Concomitant Vaccines

Prior administration of any rotavirus vaccine was prohibited before study entry. All subjects were permitted to receive licensed pediatric vaccines concomitantly with RotaTeq or placebo except for oral poliovirus vaccine (OPV) or Bacille Calmette-Guerin (BCG). OPV and BCG vaccines were permitted, but had to be administered more than 27 days before or after the study vaccine or placebo. If childhood vaccines other than RotaTeq were given during the 14 days before or after each dose, this fact was documented on the appropriate case report form (CRF). Vaccines that have not been licensed, other investigational drugs, and blood products (including immunoglobulins) were prohibited from day 1 of the first dose to day 14 after the third dose.

Reviewer Comment: Results of the phase 3 post-marketing study (study 014) showed that concomitant vaccination of RotaTeq with OPV had a negligible effect on the safety outcomes. Further seroresponse rates provided support for the inference that concomitant administration of RotaTeq with OPV would have a negligible effect on the efficacy.

Prior and Concomitant Medications
Medications whether they were prescription or over-the-counter preparations were allowed in the study. If they were given during the 14 days after each dose, they were recorded in the case report form.

6.1.5 Directions for Use

Directions for use are specified in the RotaTeq package insert.

6.1.6 Sites and Centers

Subjects were enrolled at 32 sites in Japan. Each site enrolled approximately between 4 and 69 subjects (CSR Prot. 029, Table 10-1, p53).

6.1.7 Surveillance/Monitoring

1. All adverse experiences were collected for 14 days following each vaccination dose.
2. A vaccination report card was distributed to parents or guardians at each visit for vaccination and collected at the designated visit.
3. The parents or guardians were to record body temperature and the frequency of episodes of vomiting and diarrhea every day for 7 days following each vaccination. Other adverse experiences including behavioral changes, concomitant drugs taken, and vaccination were also recorded for 14 days following each vaccination.
4. Any events that occurred at other time points were confirmed with parents or guardians by telephone or e-mail on days 8 and 15 following the first and second doses and on day 8 following the third dose.
5. At and after visit 4 (day 15 after 3rd dose), adverse experiences and acute gastroenteritis were 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.
6. 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 parents or guardians were instructed to:

    A. Record body temperature, symptoms, and use of any medication daily until there was improvement of symptoms noted in the acute gastroenteritis report card. The highest body temperature of the day was recorded. The severity of rotavirus gastroenteritis was evaluated according to the Clinical Scoring System (Table not shown: CSR Study 029, Table 9-3, p38).
    B. The parent or guardian was to collect a stool sample using the stool sample collection kit provided by the study site within 3 days and not later than 7 days after onset of symptoms.
    B. The parent or guardian visited a medical institution with the subject.
    C. The investigator then confirmed the details of the report card were completed when the stool sample was submitted. If the symptoms had resolved at the time of submission, the report card was also collected. If the symptoms persisted, the parent or guardian kept the report card and continued to record information associated with the episode until resolution.
    D. Stool samples obtained from subjects with acute gastroenteritis symptoms were evaluated for rotavirus gastroenteritis. First, stool samples were tested for presence of rotavirus antigen by EIA. All the stool samples shown to contain rotavirus antigens by EIA were analyzed by PCR to identify serotypes. Rotavirus gastroenteritis used as the primary efficacy endpoint was defined as those cases

confirmed to be rotavirus antigen-positive by EIA and were confirmed to be wildtype rotavirus (by PCR) caused by serotype G1, G2, G3, G4, and G serotypes associated with serotype P1A[8] (e.g. G9).

7. Serious adverse events, deaths, and events of clinical interest such as intussusception were collected from the time of informed consent through the end of the study.

Clinical Reviewer Note: The safety monitoring plan was appropriate and consistent with previous rotavirus studies.

Table 4. Study Flowchart in Study 029

Vaccination	Dose 1			Dose 2			Dose 3			Surveillance Period[1]	Final Study Visit[2]
Day	1	8	15	1	8	15	1	8	15		
Clinic Visit	1			2			3		4		5
Informed Consent	X										
Review Inclusion and Exclusion Criteria	X										
Review Medical History	X			X			X		X		X
Review of prior and concomitant therapy	X			X			X		X		
Vital Signs	X			X			X		X		X
Clinical Follow Up	X	X	X	X	X	X	X	X	X	X	X
Vaccination (RotaTeq or Placebo)	X			X			X				
Distribute Vaccination Report Card	X			X			X				
Collect Vaccination Report Card				X			X		X		
Review of Adverse Experiences	X	X	X	X	X	X	X	X	X	X	X
Distribute Acute Gastroenteritis Report Card	X			X			X		X		
Contact Parents or Guardians to Inquire about Acute Gastroenteritis		X	X	X	X	X	X	X	X	X	X

1. Active surveillance with bi-weekly should be conducted by either phone or e-mail during the rotavirus season (from January 1st through June 30th). Active surveillance should be conducted every 4 weeks by either phone or e-mail during the period after rotavirus season.
2. Visit 5 should be conducted within 60 days after being informed by applicant that the study will be finished
Source: Adapted from STN125122/1309 CSR 029 Table 9-1 p27-28

6.1.8 Endpoints and Criteria for Study Success

1) Primary Endpoint

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

Clinical Reviewer: For efficacy against rotavirus gastroenteritis of any severity due to types G1, G2, G3, G4 and G9P1A[8] in study 029, which was conducted to satisfy the requirement of the Japanese regulatory agency, the applicant's statistical criterion for success corresponds to the vaccine efficacy 95% confidence lower bound being > 0%.

2) Secondary Endpoints

a. Incidence rate of rotavirus gastroenteritis (moderate and severe or severe) caused by G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9) occurring at least 14 days following the third dose.
b. Incidence rate of any type-related rotavirus gastroenteritis occurring at least 14 days following the third dose.

c. Incidence rate of rotavirus gastroenteritis caused by G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9) or any type occurring following the first dose.

3) Tertiary Endpoints

a. Incidence rate of rotavirus gastroenteritis caused by G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9) or any type occurring between doses (from a time point at least 14 days following the first dose to the time of the second dose, and from a time point at least 14 days following the second dose to the time of the third dose).
b. Incidence rate of rotavirus gastroenteritis occurring at least 14 days following the third dose by type.
c. Occurrence of healthcare resource utilization for rotavirus gastroenteritis (including emergency visits or hospitalization) caused by G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9).
d. Presence of clinical evidence of dehydration or the administration of rehydration therapy (intravenous, nasogastric, oral) for rotavirus gastroenteritis caused by G1, G2, G3, G4 and G type associated with type P1A[8] (e.g. G9).

4) Safety Endpoint

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary efficacy analysis set in this study is the per protocol set. Supportive analyses were performed for primary and some secondary efficacy endpoints using the full analysis set (FAS).

The per protocol (PP) set excluded subjects who failed to receive 3 vaccination doses in accordance with the schedule within the acceptable time windows, failed to receive 3 doses of the study vaccine in the vaccination group allocated, failed to meet the inclusion criteria at the time of first vaccination, met any of the exclusion criteria at the time of any one of the vaccination doses, received OPV or BCG vaccines in a 27 day period before or after administration of any vaccination dose, received an unapproved vaccine or a blood product (including immunoglobulin) from the time of the first dose until 14 days following the third dose, and deviated from the protocol due to other unforeseeable reasons.

The FAS was defined as the group of subjects excluding those who never received vaccination of RotaTeq or placebo from among all subjects randomized.

The safety analysis set consisted of all randomized subjects who received at least one dose of the study vaccine. Subjects were included in the group corresponding to the vaccination they actually received for the analysis of safety data. Subjects who received a study vaccine that was different from that of the group to which they were allocated throughout the entire study period were included in the group corresponding to the vaccination they actually received.

Primary Analysis

Demonstrate vaccine efficacy against rotavirus gastroenteritis (G1, G2, G3, G4 and G types associated with type P1A[8]) being greater than the lower bound 95% confidence interval of 0% on the number of subjects with the event in the group that received RotaTeq relative to the total number of cases.

The efficacy estimate of the vaccine was defined as (1-R RotaTeq / Rplacebo) × 100 [%], where R RotaTeq and R placebo were the incidence rates of rotavirus gastroenteritis in the respective groups. The 95% confidence interval for the efficacy estimate of the vaccine was calculated based on the proportion of subjects with the event in the group that received RotaTeq among all cases.

Secondary Analysis

The secondary efficacy endpoints and tertiary efficacy endpoints were to be analyzed by the same procedure used for the primary efficacy endpoint. The analyses for the secondary and tertiary endpoint were defined as follows:

- Secondary endpoint included cases of rotavirus of any type from stool samples in the PP analysis set. It included cases of rotavirus of types G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9) from stool samples following the first dose in the PP analysis set and FAS, and cases of rotavirus of any type from stool samples following the first dose in the PP analysis set and FAS.
- Tertiary endpoint included cases of rotavirus of types G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9) from stool samples from at least 14 days following the first dose to the second dose, or from at least 14 days following the second dose to the third dose in PP analysis set, and cases of rotavirus of any type from stool samples for the same periods in the PP analysis set.

The tertiary endpoints (b), (c) and (d) were to be analyzed in the PP analysis set. For tertiary endpoint (b), the efficacy estimate of the vaccine was calculated by type [G1, G2, G3, G4 and G types associated with type P1A[8] (e.g. G9)] while Fisher's exact test was performed for the tertiary endpoint (c).

Clinical Reviewer Note: The efficacy estimates were based on the results of study 006 and 007. The sample size of 744 subjects assumed that the incidence of gastroenteritis in the placebo group would be 10% and that 30 cases would be expected if there were 298 subjects per group. Assuming an exclusion rate of 20% due to protocol violations and loss of cases, with 30 cases, the applicant assumed there would be 92% power for detection of efficacy.

6.1.10 Study Population and Disposition

Of the 768 subjects screened, 761 subjects were randomized 1:1 and received at least one dose of either RotaTeq or placebo group. Of the randomized subjects, 734 subjects (96%) completed the study. The disposition of discontinued subjects was comparable between these groups. The main reason for study discontinuation was withdrawal by subject.

Table 5. Disposition of Subjects Receiving RotaTeq or Placebo in Study 029

Disposition of Subjects	RotaTeq Number (%)	Placebo Number (%)	Total Number (%)
Randomized	381 (100)	381 (100)	762 (100)
Vaccination 1	380 (99)	381 (100)	761 (99)
Vaccination 2	373 (97)	374 (98)	747 (98)
Vaccination 3	371 (97)	369 (96)	740 (97)
Completed Study	368 (96)	366 (96)	734 (96)
Discontinuation: Withdrawal by Subject	9 (2)	10 (2)	19 (2)
Discontinuation: Adverse Experience	1 (<1)	3 (<1)	4 (<1)
Discontinuation: Loss to Follow Up	2 (<1)	2 (<1)	4 (<1)
Discontinuation: Physician Decision	1 (<1)	0	1 (<1)
Total Number Discontinued	13 (3)	15 (3)	28 (3)

Source: Adapted from STN125122/1309 CSR 029 Table 10-2 p54

Clinical Reviewer: Overall, the quality of the study was good as the percentages of subjects who were discontinued were small, and the reasons for discontinuation were balanced among both groups. The percentage of subjects who were discontinued over the course of the study was less than the 20% anticipated rate assumed in the sample size calculation. One subject in the RotaTeq group was randomized, but did not receive the vaccine as per the investigator's decision and no further information is provided.

6.1.10.1 Populations Enrolled/Analyzed

Of the 768 subjects enrolled, 762 were randomized to receive either RotaTeq or placebo. Of the randomized subjects, 761 were in the FAS population, and 711 in the PP population. The PP set was used as the primary population for the analysis of efficacy data in this study. Analyses using the FAS were also performed for the primary efficacy endpoint and some secondary efficacy endpoints.

Table 6. Safety and Efficacy Populations in Study 029

Population	RotaTeq	Placebo	Total Number (%)
Randomized	381	381	762 (100)
Safety Population	380	381	761 (99)
Per Protocol Population	355	356	711 (93)

Source: Adapted from STN125122/1309 CSR 029 Table 10-2 and 10-4 p57-8

6.1.10.1.1 Demographics

The demographic characteristics of the safety population are presented in the table below. Males accounted for 54% in the RotaTeq group and 52% in the placebo group. All subjects were Asian, 6 to 12 weeks of age at the time of first vaccination, and over 94% on infants were born at greater than 36 weeks gestation.

Table 7. Demographic Characteristics of Subjects in the RotaTeq or Placebo 6 to 12 Weeks of Age (Safety Population) in Study 029

Demographic Characteristic	RotaTeq Number (%)	Placebo Number (%)
Number of Subjects	381	381
Male	208 (54)	199 (52)
Gestation >36 Weeks	360 (94)	370 (97)

Source: Adapted from STN125122/1309 CSR 029 Table 10-5 p59

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical histories for subjects were consistent with those of healthy Japanese infants. The most common diagnoses by category based on previous history at the time of the first dose in the RotaTeq and placebo group were skin and subcutaneous tissue disorders (26%, 24%), hepatobiliary disorders (7% in each group), and infections and infestations (6%, 5%). The most common individual diagnoses were eczema (8% in each group), eczema infantile (6%, 8%), dermatitis diaper (5%, 2%), and hyperbilirubinemia (3% in each group) (Source; Data not shown CSR 029 Section 14.1.3.1).

No subject received a concomitant vaccination that was not approved in the pediatric population. The number of subjects who received concomitant vaccination of an approved pediatric vaccine in a 14 day period before or after any dose of the study vaccine included 113 subjects (29%) in the RotaTeq group and 104 subjects (27%) in the placebo group.

6.1.10.1.3 Subject Disposition

Subject disposition is described in the table below.

Table 8. Subject Disposition in Per Protocol Analysis Set in Study 029

Subject Disposition	RotaTeq Number (%)	Placebo Number (%)
Subjects vaccinated	380 (100)	381 (100)
Evaluable PP Population	355 (93)	356 (93)
Excluded from PP Population	25 (6)	25 (6)
Unevaluable[1]	15 (3)	9 (2)
Protocol Deviations	10 (2)	16 (4)
Less than 3 vaccinations	9 (2)	12 (3)
Less than 28 days between vaccinations	1 (<1)	0
With known or suspected impairment of immunological function	0	1 (<1)
Less than 27 days between RotaTeq vaccination and BCG	0	4 (1)

[1]Subjects were classified as unevaluable due to wild-type rotavirus-positive prior to 14 days Post-dose 3, incomplete clinical and/or laboratory results, or stool samples collected out of day range
Source: Adapted from STN125122/1309 CSR 029 Table 10-4 p57

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Efficacy endpoint for incidence of rotavirus gastroenteritis of any severity caused by G1, G2, G3, G4 and G9P1A[8] occurring at least 14 days following the third dose are presented in the table below.

Table 9. Efficacy of RotaTeq Against Rotavirus Gastroenteritis of Any Severity Caused by G1, G2, G3, G4 and G9P1A[8] at Least 14 Days Following the Third Dose in the Per Protocol Population in Study 029

Subject Disposition	RotaTeq	Placebo
Number of Subjects	355	356
Number of Rotavirus Cases	7	27
Efficacy (95% CI)	74 (39, 90)	74 (39, 90)

Source: Adapted from STN125122/1309 CSR 029 Table 11-1 p61

The results showed that there is efficacy of RotaTeq against rotavirus gastroenteritis of any severity caused by G1, G2, G3, G4 and G9 P1A[8] types as the lower bound 95% confidence interval was 39%, which is greater than 0%.

Clinical Reviewer: The results for efficacy against rotavirus gastroenteritis of any severity in the PP population in this study appear consistent with previous studies such as study 006 where the efficacy estimate against caused by G1, G2, G3 and G4 was 74% (95% CI: 66%, 79%), and study 007, where the efficacy estimate was 72% (95% CI: 50%, 85%).

6.1.11.2 Analyses of Secondary Endpoints

Efficacy endpoint for incidence of moderate and severe rotavirus or severe gastroenteritis caused by G1, G2, G3, G4 and G9P1A[8] occurring at least 14 days following the third dose are presented in the tables below.

Table 10. Efficacy of RotaTeq Against Moderate and Severe Rotavirus Gastroenteritis Caused by G1, G2, G3, G4 and G9P1A[8] at Least 14 Days Following the Third Dose in the Per Protocol Population in Study 029

Subject Disposition	RotaTeq	Placebo
Number of Subjects	354	356
Number of Rotavirus Cases	5	25
Efficacy (95% CI)	80 (47, 94)	80 (47, 94)

Source: Adapted from STN125122/1309 CSR 029 Table 11-2 p62

The results showed that there is efficacy of RotaTeq against moderate and severe rotavirus gastroenteritis caused by G1, G2, G3, G4 and G9 P1A[8] types as the lower bound 95% confidence interval was 47%.

Table 11. Efficacy of RotaTeq Against Severe Rotavirus Gastroenteritis Caused by G1, G2, G3, G4 and G9P1A[8] at Least 14 Days Following the Third Dose in the Per Protocol Population in Study 029

Subject Disposition	RotaTeq	Placebo
Number of Subjects	354	355
Number of Rotavirus Cases	0	10
Efficacy (95% CI)	100 (55, 100)	100 (55, 100)

Source: Adapted from STN125122/1309 CSR 029 Table 11-3 p63

The results showed that there is efficacy of RotaTeq against severe rotavirus gastroenteritis caused by G1, G2, G3, G4 and G9 P1A[8] types as the lower bound 95% confidence interval was 55%.

Clinical Reviewer: The results for efficacy against rotavirus gastroenteritis of severe severity in the PP population in this study appear consistent with previous studies such as study 006 where the efficacy estimate against caused by G1, G2, G3 and G4 was 98% (95% CI: 88%, 100%), and study 007, where the efficacy estimate was 100% (95% CI: 13%, 100%).

6.1.11.3 Analyses of Tertiary Endpoints

The analysis results of the efficacy of RotaTeq against rotavirus gastroenteritis occurring at least 14 days following the third dose by type are presented below.

Table 12. Efficacy of RotaTeq Against Rotavirus Gastroenteritis of Any Severity Caused by G1, G2, G3, G4 and G9P1A[8] by Type at Least 14 Days Following the Third Dose in the Per Protocol Population in Study 029

Type Identified by PCR	Number of Cases RotaTeq	Number of Cases Placebo	Efficacy by Type (95% CI)
G1P1A[8]	3	16	81 (35, 96)
G3P1A[8]	4	5	20 (-272, 84)
G9P1A[8]	0	5	100 (-9, 100)

Source: Adapted from STN125122/1309 CSR 029 Section 14.2.1.6 Table 6

Clinical Reviewer: All of the G types in the study were associated with P1A[8], including G9. There were no G9 types associated with other P types. Type G1 was the most prevalent type in Japan. Efficacy against G3 was not significant. Although the lower 95% CI for efficacy against G9P1A[8] was -9%, there were no cases of rotavirus gastroenteritis due to the G9-associated P1A[8] in the RotaTeq group.

6.1.11.3 Subpopulation Analyses

See section 1.1 (Demographic Information: Subgroup Demographics and Analysis Summary) and 6.1.11.5 (Exploratory and Post Hoc Analyses)

6.1.11.4 Dropouts and/or Discontinuations

See Table 5 in section 6.1.10 (Study Population and Disposition) and Table 8 in section 6.1.10.1.3 (Subject Disposition).

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable as there were no post-hoc analyses in study 029.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please see section 6.1.7 for information regarding safety monitoring. The safety analysis population included all subjects who received one dose of RotaTeq or placebo.

Safety was considered in terms of intussusception as well as general safety issues such as deaths, serious adverse events, and discontinuations. In addition, solicited adverse events such as fever, diarrhea, vomiting, and irritability were evaluated.

6.1.12.2 Overview of Adverse Events

Solicited Adverse Events
Detailed safety information was collected from 761 infants. A Vaccination Report Card was used by parents or guardians to record the child's temperature and any episodes of diarrhea, vomiting, irritability (fussiness) on a daily basis during the first week following each vaccination. Frequencies of these adverse events are listed in the table below.

Table 13. Incidences of Diarrhea, Irritability, Vomiting and Fever Between the RotaTeq and Placebo Group within 7 Days Following Any Dose (Safety Analysis Set) in Study 029

Subject Disposition	RotaTeq Number (%)	Placebo Number (%)
Number of Subjects	380	381
Diarrhea	41 (10)	38 (10)
Vomiting	30 (7)	28 (7)
Irritability	1 (<1)	3 (<1)
Fever		
(≥38.1°C)	95 (25)	105 (27)
(≥39.2°C)	5 (1)	4 (1)

Source: Adapted from STN125122/1309 CSR 029 Table 12-7 p88 and Section 14.3.1.7 p351

The incidences of diarrhea, irritability, vomiting and fever (≥38.1°C) occurring within 7 days following any dose of the study vaccine (first, second or third dose) were comparable between the groups.

Clinical Reviewer: Overall, when compared to placebo, infants appeared to tolerate RotaTeq well.

Table 14. Subjects with Adverse Experiences by System Organ Class in the RotaTeq or Placebo Group Within 14 days Following Any Dose (Safety Analysis Set) in Study 029

Adverse Experiences	RotaTeq (%)	Placebo (%)
Infections and infestations	22	22
Gastrointestinal Disorders	22	20
Skin and subcutaneous tissue disorders	10	10
Respiratory, thoracic and mediastinal disorders	10	9
General disorders and administration site conditions	8	8
Eye Disorders	2	1
Metabolism and nutrition disorders	<1	<1
Injury, poisoning and procedural complications	<1	0
Blood and Lymphatic Disorders	0	<1
Congenital, Familial, and Genetic Disorders	0	<1
Nervous system disorders	0	<1
Psychiatric disorders	0	<1
Reproductive system and breast disorders	0	<1
Vascular disorders	0	<1

Source: Adapted from STN125122/1309 CSR 029 Table 12-2 p73-6

The incidences of system organ class occurring within 14 days following any dose of the study vaccine (first, second or third dose) were comparable between the groups.

The vaccine related adverse experiences (Data not shown: CSR 029 Table 12-3 p77) reported to occur within 14 days following any dose of RotaTeq or placebo in the safety analyses set with high frequency in this study were diarrhea, vomiting, and gastroenteritis. Events occurring with an incidence of greater than 1% in the RotaTeq or placebo groups were: diarrhea (5% and 3%), vomiting (4% and 3%), gastroenteritis (3% and 1%), and pyrexia (1% and <1%).

Clinical Reviewer: Although diarrhea, vomiting, and gastroenteritis occurred at higher incidences in the group that received RotaTeq than in the placebo group, they were all mild or moderate and resolved without any subject discontinuing from the study.

6.1.12.3 Deaths

One subject in the RotaTeq group died on day (b) (6) following the second dose from respiratory syncytial virus bronchiolitis. Applicant noted no causal relationship with the study vaccine.

Clinical Reviewer: Agree with applicant that there is likely no causal relationship with the study vaccine and bronchiolitis, which is an acute infection of the lower respiratory tract. Bronchiolitis is common in infants younger than 6 months of age, and the event occurred over a month after the administration of the vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal serious adverse events (SAEs) occurring within 14 days after any vaccination with RotaTeq or placebo occurred for 7 subjects (1%) reporting 8 events in the RotaTeq group and 9 (2%) subjects reporting 10 events in the placebo group. None of the SAEs reported during the study were considered by the investigator to be related to study vaccine.

No vaccine-related serious adverse experiences were reported throughout the entire study.

Clinical Reviewer: Agree with applicant that the SAEs reported during the study are unlikely to be related to study vaccine.

6.1.12.5 Adverse Events of Special Interest (AESI)

No cases of intussusception were reported in the study.

6.1.12.7 Dropouts and/or Discontinuations

See Table 5 in section 6.1.10 (Study Population and Disposition). Three subjects were discontinued from the study in the placebo group after experiencing serious adverse experiences. One subject was found to have congenital absence of bile ducts 2 days following administration of the second dose of placebo, another developed infantile spasms 10 days following administration of the second dose of placebo, and the third

subject developed gastroenteritis 2 days following administration of the first dose of placebo. None of the events were judged by the applicant to be related to the study vaccine.

6.1.13 Study Summary and Conclusions

The overall vaccine efficacy against rotavirus gastroenteritis of any severity caused by any types G1, G2, G3, G4 and G9 occurring at least 14 days after dose 3 relative to placebo was demonstrated as the lower bound of the 95% CI of the VE was 39%. There were 5 cases of G9 rotavirus gastroenteritis in the control group and none in the RotaTeq group (the efficacy estimate for G9 associated with P1A[8] was 100% with a 95% CI ranging from -9 to 100%).

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Currently, the use of a Rotavirus, Live Oral Pentavalent Vaccine (RotaTeq) is indicated for the prevention of rotavirus gastroenteritis caused by G1, G2, G3, and G4 types when administered as a 3 dose series to infants between the ages of 6 and 32 weeks. In this supplement, applicant seeks to expand the indication to include the G9 type; G9 types are most commonly associated with P1A[8], which is a component in the vaccine. While there are regional variations, the literature suggests that globally approximately 90% of G9 is associated with P1A[8] (12).

Three studies (006, 007, 029) were included in the supplement to evaluate the efficacy of the G9P1A[8] type. The main support for efficacy was study 029, which was a phase 3 randomized, multicenter, double blind, placebo controlled, parallel group comparison study trial to evaluate the safety and immunogenicity of RotaTeq in healthy Japanese infants aged 6 to 12 weeks after birth. Study 006 was a phase 3 double-blinded, randomized, placebo-controlled, international multicenter study to evaluate the efficacy, immunogenicity and safety of RotaTeq. Study 007 evaluated the efficacy of RotaTeq at expiry potency. Study 006 and 007 were previously reviewed for safety and efficacy of the G1, G2, G3 and G4 types in the original BLA for licensure in 2006.

Clinical Reviewer: A VP4 (P) assay was developed and validated after licensure, and stools from original licensure for studies 006 and 007 were analyzed retrospectively for G9P1A[8]. The applicant submitted the results of the analyses for P types, in addition to a post hoc analysis of health care utilization data, as STN 125122/201. An indication to include G9P1A[8] was not granted due to low number of cases. However, G9P1A[8] data was briefly described in section 14 (Clinical Studies) of the package insert. With the addition of new data on G9 from study 029, which was done prospectively utilizing both the VP4 and VP7 assay, the sponsor submitted a supportive analysis of all cases of G9 associated RVGE from a pooled dataset of studies 006, 007, and 029.

7.1.1 Methods of Integration

Studies 006, 007 and 029 were all phase 3, randomized, placebo-controlled, double-blind, with similar primary endpoints. The distribution of subjects was similar in gender

and age. The design was the same with regard to formulation of RotaTeq administered, dose, dosing regimen (subjects received 3 doses of RotaTeq 28 to 70 days apart), and the studies were all performed in industrialized countries.

7.1.2 Demographics and Baseline Characteristics

Not applicable

7.1.3 Subject Disposition

Not applicable

7.1.4 Analysis of Endpoint(s) for G9P1A[8]

Analysis of efficacy data for each individual study and combined is described in the tables below.

Table 15. Efficacy of RotaTeq Against Rotavirus Gastroenteritis of Any Severity Caused by G9P1A[8] at Least 14 Days Following the Third Dose in the Per Protocol Population in Studies 006, 007, and 029 Individually

Subject Disposition	Study 006 RotaTeq	Study 006 Placebo	Study 007 RotaTeq	Study 007 Placebo	Study 029 RotaTeq	Study 029 Placebo
Number of Subjects	2203	2287	551	562	356	354
Number of Rotavirus Cases	1	3	0	1	0	5
Efficacy (95% CI)	65 (-331, 99)	65 (-331, 99)	100 (-3895, 100)	100 (-3895, 100)	100 (-9, 100)	100 (-9, 100)

Source: Adapted from STN125122/1309 Clinical Overview Table 2.5 10 p29-30

Table 16. Efficacy of RotaTeq Against Rotavirus Gastroenteritis of Any Severity Caused by G9P1A[8] at Least 14 Days Following the Third Dose in the Per Protocol Population in Studies 006, 007, and 029 Combined

Subject Disposition	RotaTeq	Placebo
Number of Subjects	3110	3203
Number of Rotavirus Cases	1	9
Efficacy (95% CI)	88 (17, 99)	88 (17, 99)

Source: Adapted from STN125122/1309 Clinical Overview Table 2.5 10 p29-30

The results of the post-hoc pooled analysis utilizing data from studies 006 and 007 and combining it with prospective data from study 029 showed that the efficacy of RotaTeq against rotavirus gastroenteritis of any severity caused by G9P1A[8] type was 88%, with the lower bound of 95% confidence interval equal to 17%.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable

7.1.6 Other Endpoints

Not applicable

7.1.7 Subpopulations

Not applicable

7.1.8 Persistence of Efficacy

Not applicable

7.1.9 Product-Product Interactions

All subjects were permitted to receive licensed pediatric vaccines concomitantly with RotaTeq or placebo except for oral poliovirus vaccine (OPV) and Bacille Calmette-Guerin (BCG). OPV and BCG vaccines were permitted, but had to be administered more than 27 days before or after the study vaccine or placebo as results of the phase 3 post-marketing study (study 014) showed that concomitant vaccination of RotaTeq with OPV had a negligible effect on the safety. Seroresponse rates also assumed that concomitant administration of RotaTeq with OPV would have a negligible effect on the efficacy.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable

7.1.11 Efficacy Conclusions

In study 029, RotaTeq was shown to prevent rotavirus gastroenteritis caused by G1, G2, G3, G4 and G-types associated with P1A[8] (i.e., G9) as the vaccine efficacy was 74% (95% CI: 39%, 90%). G9P1A[8] associated gastroenteritis was observed in 0/356 and 5/354 subjects in the RotaTeq and placebo groups, respectively (VE=100% (95% CI: -9.0, 100)). In studies 006 and 007, additional cases of G9P1A[8] associated gastroenteritis were identified retrospectively, and occurred less frequently in the RotaTeq group than the placebo group. The pooled efficacy estimate for the 3 studies was 88% (95% CI: 17%, 99%). Although the pooled analysis was post hoc and is subject to several limitations, it was notable for being consistent with the results across the three studies and consistent with efficacy demonstrated against all types in the vaccine. Overall, these data indicate effectiveness of RotaTeq in the prevention of gastroenteritis due to G9.

8. INTEGRATED OVERVIEW OF SAFETY

An integrated summary of safety was not performed as the safety data from studies 006 and 007 was previously reviewed in the BLA (STN 125122\0). Please see section 6 of this clinical review for study 029 safety data.

8.6 Safety Conclusions

For study 029, a total of 761 infants aged 6 to 12 weeks of age were included in the safety population. Safety parameters evaluated in the study included solicited adverse events (fever, diarrhea, vomiting, and irritability), unsolicited adverse events, and serious adverse events. The most frequent solicited adverse reaction reported by subjects after any vaccination within 7 days was fever, which was 25% in the RotaTeq group and 27% in the placebo group, followed by diarrhea (10% in each group) and vomiting (7% in

each group). The solicited adverse reactions were comparable between both groups. The number of serious adverse events appeared comparable between both groups (8 in the RotaTeq group and 10 in the placebo group), and none appeared to have a causal relationship to the vaccine. There were no reported cases of intussusception in either group. One subject died in the RotaTeq group (b) (6) days after receiving the second dose due to complications of respiratory syncytial virus bronchiolitis and the event does not appear to be related to the study vaccine. Overall, the safety data showed that the 3 dose regimen of RotaTeq was well tolerated in healthy Japanese infants. No new safety signals were apparent in review of the data submitted to the application.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

RotaTeq is not approved for individuals 32 weeks of age and older. No human or animal data are available to assess vaccine associated risks in pregnancy.

9.1.2 Use During Lactation

No human or animal data are available to assess the impact of RotaTeq on milk production, its presence in breast milk, or its effect on the breastfed infant.

9.1.3 Pediatric Use and PREA Considerations

Currently, RotaTeq is approved in infants 6 to 32 weeks of age for the prevention of gastroenteritis caused by types G1, G2, G3 and G4. The safety and effectiveness of RotaTeq have not been established in infants less than 6 weeks of age or greater than 32 weeks of age. Data are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth and the use of in infants with controlled gastroesophageal reflux disease.

PREA applies to this supplement for a new indication as the applicant provided data to evaluate G9P1A[8]. PeRC agreed to a partial waiver in pediatric subjects 0 to less than 6 weeks of age; and greater than 32 weeks to less than 17 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric age groups. PeRC also agreed that RotaTeq has now been fully assessed in patients 6 weeks to 32 weeks of age, and that waivers can be granted for patients < 6 weeks of age and >32 weeks of age.

9.1.4 Immunocompromised Patients

RotaTeq has been studied in infants born prematurely. No other safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised. Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus have been reported in infants who were administered RotaTeq and later identified as having Severe Combined Immunodeficiency (SCID).

9.1.5 Geriatric Use

Not applicable

10. CONCLUSIONS

The safety and efficacy data support the approval of RotaTeq in subjects 6 to 32 weeks of age for the prevention of gastroenteritis caused by the G9 type.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A vaccine that protects against G9 rotavirus gastroenteritis would be beneficial to infants, who are at high risk to develop rotavirus gastroenteritis. During the 1990s and 2000s, rotavirus gastroenteritis due to G9P[8] emerged to become medically important globally. Given that the safety profile of the vaccine is unchanged, the benefit-risk assessment remains favorable.

11.2 Risk-Benefit Summary and Assessment

The overall risk-benefit of RotaTeq in infants 6 to 32 weeks of age for the prevention of RVGE associated with G1, G2, G3, G4 and G9 is favorable based on the observed efficacy and safety data submitted in the original BLA and this sBLA.

11.3 Discussion of Regulatory Options

Refer to 7.1.11 for discussion of basis for approval of the addition of indication for G9.

11.4 Recommendations on Regulatory Actions

The data submitted to this BLA supplement provide evidence to support the safety and effectiveness of three doses of RotaTeq in infants 6 to 32 weeks of age for the prevention of rotavirus gastroenteritis caused by G9.

11.5 Labeling Review and Recommendations

CBER communicated with the applicant to achieve consistency with CBER's current guidance on the content and format of package inserts. Important revisions to the label included updates to section 1 (Indications and Usage), section 8 for PLLR compliance, and section 14.5 (which describe the G9 efficacy data from study 029 in more detail). The final label was reviewed by the clinical team and found to be acceptable.

11.6 Recommendations on Postmarketing Actions

Clinical review of the data from study 029 did not identify safety or immunogenicity concerns that would prompt the need for any additional postmarketing study other than routine pharmacovigilance.