MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Date: January 30, 2006

Subject: Clinical Review of New Biologics License Application STN #125122 RotaTeq®

Date of submission: April 6, 2005

Amendments reviewed: 125122/0 (clinical sections, case report forms, label sections and ------- datasets) 125122/ 2-4, 125122/ 7-8, 125122/11-15, 125122/17-23, 125122/25-33, 125122/35

From: Rosemary Tiernan, MD, MPH
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To: Laraine Henchal, M.S.
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Through: R. Douglas Pratt, MD, MPH
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Product: Human-Bovine Rotavirus Reassortant Pentavalent (G1, G2, G3, G4, P1; Vero Cells) Vaccine, Live, Oral

Sponsor: Merck & Co., Inc.

1 RotaTeq™ BLA Review

1.1	Medical Officer's Review	
1.11	BLA #	STN 125122
1.12	Related IND #(s):	---- series
1.13	Medical Reviewer:	Rosemary Tiernan, MD, MPH Division of Vaccines and Related Product Applications, HFM 475
1.14	Submission Received:	April 5, 2005
1.15	Review for Licensure Completed:	January 30, 2006
1.2	Product	
1.2.1	Proper Name:	Rotavirus, vaccine, live, oral, pentavalent
1.2.2	Proposed Trade Name:	RotaTeq™
1.2.3	Product Formulation:	

Human Bovine reassortants which include:
G1 2.2 x10^6 infectious units,
G2 2.8 x 10^6 infectious units,
G3 2.2 x 10^6 infectious units,
G4 2.0 x 10^6 infectious units,
P1 2.3 x 10^6 infectious units.
Reassortants are propagated in Vero cells in the absence of antifungal agents and suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrated, sodium monobasic monohydrate, sodium hyrdroxide, polysorbate 80 and also tissue culture media. There are no preservatives or thimerosal.

1.3	Applicant:	Merck & Co., Inc., Whitehouse Station, N.J.
1.4	Pharmacologic Category:	Vaccine
1.5	Proposed Indication(s):	Prevention of rotavirus disease
1.6	Proposed Population(s):	Infants
1.7	Dosage Form(s):	Oral dose in ready-to use liquid which comes in an individual latex-free dosing tube with a twist-off cap allowing for direct oral dosing and should not be diluted or mixed with any other vaccines or solutions. Store at 4^oC

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3 Executive Summary

This BLA review contains a summary of the efficacy, immunogenicity and safety data provided by Merck to support approval of their pentavalent rotavirus vaccine, RotaTeq™. This is a live, oral vaccine for administration in a 3 dose series with the first dose to be given to healthy infants at 6-12 weeks of age followed by two subsequent doses separated by 4-10 week intervals.

The Biologics Licensing Application (BLA) contains three phase 3 trials: study 006, the rotavirus efficacy and safety trial (REST), study 007 the end-expiry dose trial and study 009 the lot-consistency trial. In order to rule out an increased risk to develop intussusception, which had been seen in the post-marketing period for a previously licensed live oral rotavirus vaccine, the Applicant enrolled over 70,000 infants in the pivotal phase 3 trials which were conducted in the United States and abroad.

Efficacy
The two phase 3 trials that contributed data for the efficacy evaluation were study 006 (REST) and study 007 (end-expiry).

Study 006 was a phase 3 double-blinded, randomized, placebo-controlled, international multicenter study to evaluate the efficacy, immunogenicity and safety of RotaTeq™. There were four protocol amendments submitted to study 006 which are discussed in Section 8.1.1.1.5 of this BLA review. The primary objective of study 006 was to evaluate the efficacy of a 3 dose regimen of RotaTeq™ against rotavirus gastroenteritis caused by serotypes 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 serotypes in the vaccine through the first rotavirus season post-vaccination was 74% (95% CI: 67%, 79%) (Table 1)

Table 1. Efficacy in the Per Protocol (PP) Population for Study 006 (REST)*

Study 006 (REST)	RotaTeq™	Placebo
Subjects vaccinated	2834	2839
Subjects in efficacy analysis	2207	2305
Person Days of follow-up	623880	622388
Rotavirus gastroenteritis cases caused by G1, G2, G3 or -G4 serotype	82	315
Efficacy estimate (%) and 95% confidence interval	74.0 (66.8, 79.9)	

FDA analysis*

Additional Efficacy Analyses for Study 006 (REST):
Intent-to-treat analyses (ITT) were performed in order to assess the impact of

RotaTeq™ on rotavirus antigen-positive diarrheal disease due to vaccine and non-vaccine rotavirus serotypes in all subjects who received at least one dose of vaccine. In the intent-to-treat analyses, the per protocol case definition was also used except that cases were counted starting with the day of the first vaccination rather than counting 14 days after the third vaccination as was done for the per protocol (PP) analyses.

Table 2 below shows 49.7% efficacy for RotaTeq™ in the intent-to-treat population (ITT) that includes only subjects with no vaccine-strain in the stool sample. Although the Applicant's number of EIA positive, vaccine strain negative cases differed from the FDA which had 4 fewer cases in the RotaTeq™ arm and 5 fewer cases in the placebo group, this discrepancy in case ascertainment was similarly distributed across both study arms.

Table 2. Efficacy in the Intent-to-Treat Population (ITT)* in Study 006 (REST), Rotavirus Antigen positive disease, all serotypes**

Study 006 (REST)	RotaTeq™		Placebo	
Subjects vaccinated	2834		2839	
EIA positive, vaccine-strain negative, all serotypes	Merck 202	FDA 198	Merck 400	FDA 395
Efficacy estimate (%) and 95% confidence interval***	49.7 (40.3, 57.7)			

*Intent-to-treat includes rotavirus disease cases occurring after the first dose.
**This analysis does not include cases due to the vaccine strains.
*** Applicant's efficacy estimate.

Study 007

The primary objective of study 007 was to evaluate the efficacy of a 3 dose regimen of RotaTeq™ at expiry potency against naturally occurring rotavirus disease caused by the composite of the serotypes contained within the vaccine (G1, G2, G3 and G4) occurring at least 14 days following the third dose.
An efficacy estimate of 72.5% (CI: 50.5, 85.6) was obtained by both the FDA statistical reviewer and the Applicant (see Table 3 below):

Table 3 Efficacy in the Per Protocol Population for Study 007 (End Expiry)*

Study 007 (End Expiry)	RotaTeq at expiry potency (~ 1.1 $X10^7$ IU/dose)		Placebo	
Subjects vaccinated	650		660	
Subjects in efficacy analysis	551		564	
	FDA	Merck	FDA	Merck
Days of follow-up	78,282	78,791	77,674	78,141
Rotavirus gastroenteritis cases caused by G1, G2, G3 or -G4 serotype	15	15	52	54
Efficacy estimate (%) and 95% confidence interval	71.0 (48.4, 85.0)	72.5 (50.5, 85.6)		

*FDA analysis

Although the FDA statistical reviewer's and the Applicant's numbers are different for the total follow-up time and the numbers of gastroenteritis cases, the

discrepancies are smaller. Therefore, it is highly likely RotaTeq™ has achieved the primary objective in this trial.

Immunogenicity

Immunogenicity data from trials of RotaTeq™ have been used to demonstrate manufacturing consistency and have been used in studies of the concomitant use of RotaTeq™ with other childhood vaccines. Immunogenicity has not been used in making decisions about dose (viral titer) for RotaTeq™ or in assessing protection against rotaviral disease. However, the Applicant provided data showing that RotaTeq™ induces antibodies that neutralize serotypes G1, G2, G3, G4 and a selection of serotypes that contain P1. A quantitative relationship between serum antibody responses to RotaTeq ™ and protection against rotavirus gastroenteritis has not been established. In phase 3 studies, 92.9% to 100% of 439 recipients of RotaTeq™ achieved a 3-fold or more rise in serum anti-rotavirus IgA (ELISA) after a three-dose regimen when compared to 12.3%-20.0% of 397 placebo recipients.

Safety

Intussusception

Safety data from the three pivotal phase 3 clinical trials demonstrate that administration of RotaTeq™, when compared to placebo, conferred no increased risk for intussusception during the 42 and 60 day periods post vaccination. No evidence of clustering of intussusception cases within a 7-day or 14-day window post-vaccination was observed.

In study 006 (REST), for the pre-specified 42-day post-vaccination endpoint, 6 cases of intussusception were observed in the RotaTeq™ group versus 5 cases of intussusception in the placebo group. Based on these case numbers, an estimated relative risk of 1.2 with a 95% confidence interval of (0.3, 5.0) was obtained. The upper bound of the 95% confidence interval of the relative risk is less than 10, which satisfies the prospectively specified primary safety objective of REST. In the package insert, the relative risk is reported as 1.6 with a 95% confidence interval of (0.4-6.4) which reflects adjustment for the group sequential design.

The relative risk of intussusception identified in these phase 3 clinical trials must be considered in terms of the infant subjects enrolled who were mainly from industrialized nations. The safety and efficacy of this product may be different in children who reside in developing countries. Safety results from these clinical trials do not address use in infant populations who were not studied such as those with a history of HIV infection or underlying gastrointestinal disease or co-infection with intestinal parasites. There are insufficient data regarding the administration of this vaccine on a schedule other than that utilized in the randomized, placebo-controlled trials. The clinical study data do not address the safe administration of a first dose of vaccine to infants at an age greater than 12 weeks or administration of a third dose beyond approximately 32 weeks of age.

While not applicable to the United States, it should be noted that these data do not address administration of this product to infants who live in areas where the standard of care is to give live, oral polio vaccine.

Adverse Experiences

There did not appear to be an increased incidence of fever in infants who received RotaTeq™ when compared to placebo. The incidence of fever (temperature greater than 100.5^{o}F) was comparable in the vaccine and placebo groups during the week after any dose.

Within the 42 days after any dose, infants who received RotaTeq™ when compared to placebo experienced diarrhea and vomiting at a statistically higher rate. Across the three phase 3 studies, the incidence of diarrhea was RotaTeq™ (24%) compared to placebo (21%) and for vomiting the incidence was RotaTeq™ (15%) compared to placebo (14%).

Rates of other adverse experiences that were statistically significantly greater in the vaccine as compared with the placebo groups were nasopharyngitis (7.0% vs 6.0%), otitis media (15.0% versus 13%) and bronchospasm (1.1% versus 0.7%).

Concomitant Administration with Other Vaccines Administered During Childhood

All subjects in the phase 3 studies were permitted to receive licensed pediatric vaccines concomitantly (on the same day or within 42 days of vaccination) with RotaTeq™ or placebo.

A subset of 1358 infants (662 RotaTeq™ and 696 placebo subjects) participated in the U. S. Concomitant Use Sub-study of Protocol 006 (REST) in which they were administered RotaTeq™ and the following childhood vaccines on the same day according to the U.S. licensed schedule. These pre-specified childhood vaccines included: COMVAX®, INFANRIX®, IPOL® and PREVNAR®. The antibody responses to these vaccines were compared between recipients of placebo and RotaTeq™ to ensure that RotaTeq™ did not interfere with the immune response to these vaccines.

The non-inferiority statistical criteria for declaring similarity of immune responses between the RotaTeq™ and placebo group were met for poliovirus 1, 2, 3, hepatitis B, *H. influenza* type b, and pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, diphtheria and tetanus.

In an unvalidated assay, the pre-specified non-inferiority statistical criteria were met for pertussis toxin and pertussis FHA. Non-inferiority criteria were not satisfied for the pertussis pertactin antibody response (LL of 2-sided 95% CI for the GMT ratio must be >0.5). In addition, pertussis assay validation remains under review. Consequently, at this time, insufficient data are available to confirm lack of interference of immune responses when RotaTeq™ is co-administered with childhood vaccines to prevent pertussis.

Shedding and Transmission

Fecal shedding was evaluated in a subset of subjects in study 006 (the first 150 Finnish randomized subjects and the first 150 U.S. randomized subjects). Based on the timing of shedding observed in early phase studies, a single stool sample was collected from each subject during Days 4 to 6 following vaccination visits 1, 2, and 3. Shedding was evaluated using plaque assays with electrophenotyping. The percent of subjects in the RotaTeq™ arm who shed vaccine-virus strains in the stool at days 4 to 6 following vaccination visit 1 was 13%. There was no shedding of vaccine-virus strains detected at 4 to 6 days following visits 2 and 3. The vaccine-virus strains shed were either from the vaccine or reassortants.

In studies 006 and 007, fecal shedding of vaccine-virus strains was also evaluated for all potential acute gastroenteritis episodes (AGEs) for which the stools tested positive by rotavirus EIA. Fecal shedding of vaccine-virus strains at any time during these studies was detected in 9% (32 subjects) following dose 1 and in 1 subject (0.3%) at 4 days following dose 3. The longest post-dose time point at which shedding of vaccine-virus was detected was at 15 days post dose 1. The most commonly shed vaccine strains were G1 and P1 reassortants. There were 2 subjects who appeared to have shed vaccine virus following the first dose of placebo. The cause for vaccine virus shedding by 2 placebo subjects remains uncertain but the Applicant believes that this finding was due to a laboratory mislabeling error.

The Applicant did not evaluate the potential for horizontal transmission of vaccine virus.

Conclusion:

The primary efficacy and safety objectives of the phase 3 clinical trials for RotaTeq™ were satisfied. In addition, on December 14, 2005, the Vaccines and Related Biological Products Advisory Committee voted unanimously that the data were adequate to support both the safety and efficacy of RotaTeq™.

Recommendation:

APPROVAL of RotaTeq™ for the indication of prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4 administered in a 3-dose vaccine series to infants between the ages of 6 to 32 weeks. The first dose of RotaTeq™ should be administered to healthy infants between 6 and 12 weeks of age with the two subsequent doses to be administered at 4 to 10 week intervals.

Post-Licensure studies:

In a submission to the BLA dated January 25, 2006, the Applicant committed to conduct a large-scale observational post-licensure safety study to evaluate the incidence of intussusception and other safety parameters in recipients of

RotaTeq™ in approximately 44,000 subjects (adjustments to the sample size will be made based on the background rate of intussusception). The study will be designed to detect an increased risk of intussusception due to vaccine of 2.5 or greater with 80% probability. The final study protocol will be submitted by May 5, 2006. The study will be initiated no later than the third quarter of 2006, sooner if possible. The study will be completed by the fourth quarter of 2008.

In a submission to the BLA dated January 31, 2006, the Applicant committed to conduct an adequately powered non-inferiority study of the concomitant administration of RotaTeq™ with acellular pertussis vaccine in which serological endpoints will be examined using a validated assay. The study will be powered sufficiently to detect a 1.5-fold difference in GMTs. A final concept sheet for this protocol will be submitted no later than May 3, 2006.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)/Bioassay

The FDA product reviewer considered the information submitted in the CMC section to be complete for evaluation. Vaccine product characterization, methods of manufacture including raw materials and reagents, animal sourcing, cellular sources, and related adventitious agent testing, process controls, reference standards, release specifications, and analytical methods, especially the M-QPA for potency and identity analysis, test results, release specifications, stability protocols and related SOPPs as well as validation of the testing are all appropriate for this live viral vaccine and are satisfactory. The Applicant also provided commitments to ensure that 1) ---------- ---------- ---------- 2) Post-approval stability monitoring will continue as planned, and 3) Data on the stability protocol, and ---------- values of each lot manufactured will be submitted to the agency on an annual basis. Based on the evaluation of the information submitted in the BLA, and the written commitments by the sponsor, RotaTeq™ product approval is recommended by the FDA product reviewer.

Formulation

The Applicant states that the vaccine evaluated in the Phase 2 studies differed from that evaluated in the Phase 3 studies with regard to formulation (un-buffered versus buffered in the final formulation), scale of process (laboratory scale versus manufacturing scale), and potency assay (plaque assay versus multivalent quantitative polymerase chain reaction assay [M-QPA]) and addition of serotypes.

Vaccine dose selection:

In study 005, the Applicant evaluated doses of 5×10^6 PFU, 1×10^6 PFU and 5×10^5 PFU with efficacy estimates of 68%, 74% and 58%, respectively. Efficacy

after dose #1 ranged 23-37%, after dose #2 efficacy was 57-61% and after dose #3 it was 70-84%. The Applicant elected to use the $1x10^6$ PFU dose for further clinical development.

(From the Applicant)
The immunogenicity results among the vaccine regimens were compared to assist with the selection of expiry potency for the vaccine intended for licensure. The results of this analysis indicated that neither the middle-dose nor the low-dose pentavalent vaccine was similar to the high-dose pentavalent vaccine with respect to the proportion of subjects who had a ≥3-fold rise in SNA against G1. Also, the proportion of subjects who had a ≥3-fold rise increased with potency among the pentavalent vaccines for each immunologic assay, with the exception of fecal total IgA. The percentage of infants who had a significant response (i.e., ≥3-fold rise in antibody titer from baseline to Postdose 3 to the VP7 and VP4 rotavirus serotypes in the vaccine increased with increasing vaccine potency and was >80%, for the G1 SNA, G3 (Ohio State University) SNA, and serum anti-rotavirus IgA assays among subjects who received the high-dose pentavalent vaccine. It was concluded that the high-dose pentavalent vaccine induced significant G1 SNA responses in the greatest proportion of subjects, followed by the middle-dose pentavalent vaccine, and then followed by the low-dose pentavalent vaccine. The efficacy of the high-dose, middle-dose, and low-dose pentavalent vaccines was generally similar despite the differences in the magnitude of the antibody responses observed with these 3 vaccine regimens. Thus, the assigned expiry potency for RotaTeq™ was based on efficacy results, not on immunogenicity results.

The decision to administer a 3-dose regimen was based on astudy conducted at Children's Hospital of Philadelphia and the University of Rochester in 1992-1993. This study demonstrated that 3 doses induce a significant immune response (i.e., a ≥3-fold rise in antibody titer between the Predose 1 and Postdose 3 time periods) in a larger proportion of infants than a 2-dose regimen. This study was completed before the Applicant began the clinical development program for RotaTeq™; therefore, all subsequent studies utilized a 3-dose regimen.

Medical Officer comments:
The dose regimen for the phase 3 program was selected considering several different criteria including efficacy and immunogenictiy results from the phase 2 trials. The magnitude of the antibody response was greater with increasing vaccine potency. However, antibody response has not been shown to be a surrogate for protection. Despite differences in antibody response, the efficacy was similar across the different dose ranges in study 005 and the Applicant ultimately chose the middle pentavalent dose.

Description of the product

RotaTeq™ is a live, oral pentavalent vaccine that contains 5 live reassortant rotaviruses. The parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7) from the bovine rotavirus parent strain. The fifth reassorant virus expresses the attachment protein, P1A (genotype P[8]), referred to as P1[8], from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain (see Table 4).

Table 4 RotaTeq™ Parent Vaccine strains and Reassortants

Name of Reassortant	Human Rotavirus Parent Strains and Outer Surface Protein Compositions	Bovine Rotavirus Parent Strain and Outer Surface Protein Composition	Reassortant Outer Surface Protein Composition (Human Rotavirus Component in Bold)	Minimum Dose Levels (10^6 infectious units)
G1	WI79 – G1, P1[8]	WC3 - G6, P7[5]	**G1,** P7[5]	2.2
G2	SC2 – G2, P2[6]		**G2,** P7[5]	2.8
G3	WI78 – G3, P1[8]		**G3**, P7[5]	2.2
G4	BrB – G4, P2[6]		**G4,** P7[5]	2.0
P1[8]	WI79 – G1, P1[8]		G6, **P1[8]**	2.3

The reassortants are propagated in Vero cells using standard cell culture techniques in the absence of antifungal agents. The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts fo fetal bovine serum. There are no preservatives or thimerosal present. RotaTeq™ is a pale yellow clear liquid that may have a pink tint. The product must be stored and transported under refrigeration at 2-8^{o}C (36-46^{o}F)

Medical Officer comments:

The FDA product review states that the 24-month shelf life was determined taking into account the total time from filling to administration of the vaccine. Factored into this consideration is up to -------- for time that the product may spend at ambient room temperature during manufacturing (sealing, inspection, and packaging), distribution (from pharmacy to customer), and administration. Also factored into this consideration is a maximum of ------- for shipping at -------. Recommended storage after shipping is 2-8 °C until the vaccine is administered.

Bioassay validation

Statistical reasoning and calculations supporting bioassay validations in this submission were reviewed in the Biostatistics Division. There were no major bioassay-related statistical issues preventing this submission from being approved.

Medical Officer comments:
Please see Dr. Lev Sirota's review for additional information on bioassay validation. Dr. Sirota's review discusses the ----- quantitation of Vero Cell DNA which was an assay developed and validated for the determination of residual Vero cell genomic DNA present in rotavirus ---------- and the Rotavirus Multivalent-Quantitative, Polymerase Chain Reaction-Based, Potency Assay (M-QPA). Please also see Dr. Keith Peden's review which discusses cell substrate issues related to the Vero cell line that was used in production of this vaccine.

Extent of Exposure
Study 006 evaluated the safety of RotaTeq™ when administered at a range of potencies from 67.2 x 10^6 to 124 x 10^6 IU/dose (aggregate of the 5 serotypes). This range of potencies is within the range at which the vaccine intended for market was to be released. The maximum potency tested in this study, 124 x 10^6 IU/dose, was anticipated to be the maximum release dose in the final, formulation of RotaTeq™ intended for market.

Medical Officer comments:
Protocol amendment 006-04 included changing the unit of measurement for the doses of the 5 serotypes of rotavirus in RotaTeq™ from PFU to Infectious Units (IU).

The FDA product review states that Merck developed the M-QPA as an alternative to the standard plaque assay for several reasons.
1) Plaque assay provides aggregate potency (in terms of PFU), but it does not specifically identify the potency of each reassortant virus of the pentavalent vaccine.
2) Neutralizing Antibodies against one G serotype cross-reacts with other G types. Therefore complete neutralization of each reassortant in the presence of other serotypes of the pentavalent vaccine is not practical in a plaque assay.
3) The RT-PCR based M-QPA is highly sensitive, and use of reassortant-specific PCR primers makes it possible to evaluate the potency of an individual reassortant in a pentavalent mixture of viruses. The M-QPA methodology as proposed for potency and identity testing was found acceptable.

Specifications using the potency assay (M-QPA) include the following:
---------- and ---------- IU/reassortant dose and
---------- IU/aggregate dose

Table 5 Potency Specifications for Lot Release*

DOSE (potency/dose)
Reassortant Type G1: Specification: ---------- IU/dose
Reassortant Type G2: Specification: ---------- IU/dose
Reassortant Type G3: Specification: ---------- IU/dose
Reassortant Type G4: Specification: ---------- IU/dose
Reassortant Type P1: Specification: ---------- IU/dose
AGGREGATE (G1+G2+G3+G4+P1) Specification: ---------- IU/dose

*Submitted by the Applicant in BLA Amendment 004 (30 August 2005).

4.2 Animal Pharmacology and Toxicology

The Applicant states that animal model studies have shown that rhesus rotavirus may have a different tissue tropism than bovine or human rotavirus. After receiving oral rhesus rotavirus, young adult (severe combined immunodeficiency) SCID mice and immunologically competent BALB/c mice have developed hepatitis. Nearly all of the rhesus-rotavirus-infected SCID mice died; the BALB/c mice recovered in 2 to 4 weeks. Rhesus rotavirus was detected in liver tissue in 100% of SCID and 85% of BALB/c mice tested. In contrast, SCID and BALB/c mice who received oral bovine rotavirus (WC3) and human rotavirus were asymptomatic, and had no hepatitis, detectable extramucosal spread of virus, or death during the study.

Medical Officer comments:
In the earlier phase 1 and 2 clinical studies, subjects had liver function tests performed and hepatitis was not identified as a safety concern. Neurovirulence testing was not required because rotavirus is not considered to be a neurotropic virus. Please see Dr. Atreya's review for a full discussion of this product.

Immunologic Mechanism of Action
The exact immunologic mechanism by which RotaTeq™ protects against rotavirus gastroenteritis is unknown. RotaTeq™ is a live viral vaccine that replicates in the small intestine and induces immunity.

Immunity With wild-Type Rotavirus Infection (from the Applicant):
The basis for developing a rotavirus vaccine rested on the observation that wild-type rotavirus infection immunized children against subsequent disease. The immunity from wild-type infection does not prevent all subsequent infections; however, it provides nearly complete protection against severe disease and substantial protection against mild disease. The mechanism(s) by which wild-type rotavirus infection induces immunity is not well defined. Children typically have repeated infections and develop high titers of anti-rotavirus IgA and IgG in

serum and duodenal fluid over the first 24 to 36 months of life. G-serotype-specific neutralizing antibody is observed with the primary rotavirus infection; broader, heterotypic responses to multiple G serotypes appear only after repeated infections. Although some longitudinal studies have shown that high titers of these antibodies appear to correlate with protection against subsequent disease and/or infection, a single, definitive immunological surrogate of efficacy has not yet been identified.[2] The immunogenicity data to support licensure of RotaTeq™ was obtained from 3 Phase III clinical trials (Protocol 006 [REST]), (Protocol 007), and (Protocol 009). The use of immunogenicity data for RotaTeq™ has been limited to the demonstration of manufacturing consistency for observational comparisons between populations and in studies of the concomitant use of RotaTeq™ with other childhood vaccines. Immunogenicity was not used in making decisions about dose (viral titer). A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not been established. In phase 3 studies, 92.9% to 100% of 439 recipients of RotaTeq achieved a 3-fold or more rise in serum anti-rotavirus IgA (ELISA) after a three-dose regimen when compared to 12.3%-20.0% of 397 placebo recipients.

Immunogenicity assays

In the clinical trials, serum samples were collected from subjects Predose 1 and Postdose 3 in order to detect and quantify serotype-specific (G1, G2, G3, G4, P1, G6, and P7 [the WC3 parent bovine rotavirus strain has G6 and P7 serotypes]) serum neutralizing antibody (SNA) and serum anti-rotavirus IgA (not serotype specific: the rotavirus strain used to capture antibody is vaccine strain WC3). The absolute titers and fold-rise in titer of these assays were evaluated. In the past, in order to show seroconversion postvaccination, a 4-fold rise criterion was used for doubling dilution assays. Regarding the assays in these clinical trials, the Applicant provided data to support using a 3-fold rise in titer as a significant immune response. The assays were able to detect a 3-fold difference with 90% power at the 5% significance level.

Medical Officer comments:

There is no immune correlate of protection against infection with rotavirus. The clinical relevance of a 3 fold rise in titer has not been established. FDA has not endorsed the use of specific laboratory methodology or assay parameters/thresholds to either assess immunogenicity or to compare immune responses between rotavirus vaccines.

Rotavirus Serum Neutralization Assay (from the Applicant)

This assay was used to detect and quantify rotavirus neutralizing antibody from serum. The assay was performed by ---
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Serum Anti-Rotavirus IgA Assay (from the Applicant)

The rotavirus serum IgA assay was used to detect and quantify antirotavirus IgA from serum. ---

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Detection of Rotavirus Antigen in Stool Specimen (from the Applicant):

The Rotavirus Antigen Detection assay was used to determine the presence of rotavirus in Acute Gastrointestinal Episode (AGE) stools. ---

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Plaque Identification (from the Applicant):
If vaccine virus is demonstrated in stool, it is important to fully characterize the reassortant(s) shed and the presence of possible recombinants. Some reassortants are shed more frequently than others, the implications of which are still being evaluated. Because of their segmented genome, rotaviruses frequently recombine in nature. The Applicant reports that a recombination event involving wild type and vaccine type rotavirus had not been documented prior to the phase 3 clinical studies. The electropherotype assay is used to type any vaccine reassortants that may have been isolated from the plaque titration assay. ---
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Medical Officer comments:
The original protocol was amended in order to use PCR as the primary assay for serotyping. Plaque assay (electropherotyping) was utilized in order to identify vaccine virus strains. (See protocol amendment 006-01). The Applicant did not provide information regarding whether recombination events had occurred in the phase 3 clinical trials.

Regarding rotavirus, RNA recombination and reassortment are different events and are not interchangeable terms. A recombination event refers to recombination of one part of RNA with another within a given RNA segment and reassortment refers to swapping of an RNA segment in its entirety from one strain/serotype with another. Unless one detects two different RNA lineages within an RNA segment by nucleotide sequencing, a recombination event can not be confirmed. Differences in migration pattern assessed by electropherotyping only indicate that the RNA segment is relatively shorter or longer compared to the standard, it does not indicate recombination.

Pre-clinical pharmacology studies
Pharmacokinetic studies, genetic toxicity and reproductive toxicity studies were not required for this product. Studies of the oncogenic potential of this product and local tolerance studies were also not required.

Medical Officer comments:
Non-clinical studies supporting the safety of this vaccine included a 10-week subacute oral toxicity study in mice, and --- Vero cell DNA uptake studies in rats. Please refer to the FDA product reviews on RotaTeq™. Which were done by Dr. C.D. Atreya and Dr. Keith Peden.

5.0 Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions

Rotaviruses have 2 outer capsid proteins, the glycoprotein VP7 (G) and the protease susceptible hemagglutinin VP4 (P). The viruses are classified according to their G serotype and P serotype or genotype. In the United States, the most prevalent rotavirus serotypes are:

G1 also depicted as P1A[8] G1
G2 also depicted as P1B[4] G2
G3 also depicted as P1A[8] G3
G4 also depicted as P1A[8] G4
G9 also depicted as P1A[8] G9, and P2A[6] G9 [16].

Medical Officer comments:
In study 006, the most prevalent serotype that caused rotavirus gastroenteritis was G1 followed by G2, G4, G3 and G9. RotaTeq™ does not include serotype G9 but the Applicant states that P1 may provide some protection against G9.

The seasonality of rotavirus varies by country. In the U.S., the season is late winter and early spring. No seasonal association has yet been established for the occurrence of cases of intussusception in the United States. Surveys of antibody prevalence in children's sera throughout the world indicate that almost all children are infected with rotavirus within the first few years of life. Although, the maximum incidence of rotavirus gastroenteritis is usually between 6 and 24 months of age; severe clinical disease leading to hospitalization can occur at younger ages and 25% of disease leading to hospitalization occurs in children older than 24 months of age.[1]

A natural history study of wild-type rotavirus infection showed that 1, 2 and 3 previous rotavirus infections were 77%, 83% and 92% efficacious against any rotavirus diarrhea and that 1 and 2 rotavirus infections were 87% and 100% efficacious against severe rotavirus diarrhea. [2]

Parashar et al reviewed studies from 1986 to 2000 and estimated that on a global scale, each year, rotavirus causes 352,000–592,000 deaths (median, 440,000 deaths) in children less than 5 years of age. Children in the poorest countries account for 82% of rotavirus deaths.[3]

In the United States, rotavirus infection is responsible for approximately 50,000 hospitalizations and 20 deaths annually.[4] Treatment measures are supportive such as hydration. At the time of the BLA submission, there was no antiviral drug available for treatment and there was no U.S. licensed vaccine to prevent rotavirus gastroenteritis.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products.

Rotashield® (rotavirus vaccine [live, oral tetravalent], Wyeth Ayerst) was a live, rotavirus vaccine composed of 3 human -rhesus reassortant rotavirus strains and 1 rhesus rotavirus strain that was licensed in August l998. Intussusception was listed in the package insert as an adverse event that occurred in the pre-licensure trials. During the pre-licensure trials of Rotashield® there were 5 intussusception events among approximately 10,000 vaccinees—4 of these events occurred within 3 weeks after administration of the second or third dose. Three of the 4 events occurred in a subset of less than 2000 infants who were given experimental vaccine formulations that were never marketed.[5] The range of RotaShield® doses studied in the clinical trials included 10^4 to 4×10^6 PFU.

Distribution began in October l998 after the Advisory Committee on Immunization Practices (ACIP) of the U.S. CDC recommended routine immunization of all U.S. infants following a 3 dose schedule, preferably at 2, 4 and 6 months of age. In July l999, the CDC recommended that physicians immediately suspend use of RotaShield® after CDC-FDA Vaccine Adverse Event Reporting System (VAERS) revealed a higher-than expected number of intussusception reporting events among vaccinated infants. Wyeth –Ayerst, the manufacturer, recalled all unused vaccine doses and withdrew the product from the market and ACIP withdrew its recommendation.

During the 9 months that RotaShield® was in use, approximately 1.2 million doses were given to approximately 600,000 infants. In October l999, preliminary estimates suggested that a fully implemented program of RotaShield® use would have led to up to 1600 excess intussusception cases corresponding to a population-attributable risk (PAR) of 1 excess case per 2500 vaccine recipients.[6] The results of a multi-state, case-control study of vaccinated infants that was conducted by the CDC later confirmed a strong association between receipt of an initial dose of RotaShield® and the occurrence of intussusception during the 2 weeks immediately following vaccination, but a lower PAR value (i.e., 1 excess case of intussusception per 4670 to 9474 infants vaccinated).[6]

Of note, in the pre-licensure trials the few intussusception events among vaccinated infants occurred after receipt of the second or third dose. However, in the 9 month period of RotaShield® use, the first dose was temporally associated

with intussusception far more strongly than was the second dose, and the third dose of RotaShield® could not be shown to be temporally associated with intussuception.

5.3 Previous Human Experience with the Product including Foreign Experience

There is no previous human experience with RotaTeq™ in the U.S. or overseas.

5.4 Regulatory Background Information (FDA-Sponsor meetings, Advisory Committee Meetings, Commitments)

The basis for licensure of this new rotavirus vaccine was a pre-clinical program to develop a multivalent live, oral rotavirus vaccine and a clinical development program to test the safety and efficacy in subjects that would adequately represent the U.S. population. Addressing the intussusception issue was critical in this development program.

One phase 1 and four phase 2 studies were conducted to evaluate the efficacy, immunogenicity and safety of the research formulations and compositions of the vaccine, to select the final formulation, and to provide a basis for assigning the end-expiry dose. In addition, as a result of the reported association between Rotashield® and intussusception, the demonstration of the safety of RotaTeq™ with respect to intussusception became an important goal of the clinical development program. This posed quite a challenge because intussusception is uncommon with a reported background rate of one case per 2000 infants annually.

The development strategy followed by Merck to support the licensure of RotaTeq™ was based upon the following:
-Demonstration of efficacy in U.S. infants compared to placebo.
-Demonstration of efficacy at end-expiry.
-Demonstration of safety in a large multi-national population with adequate inclusion of infants who represent the demographics of the U.S. population.
-Demonstration of clinical lot-to-lot consistency in the immune responses utilizing serum neutralizing antibody

Regulatory Milestones/Timeline

June 1993	Phase 1 study initiated
Aug 1998	RotaShield® approved
July 1999	RotaShield® withdrawn
May 2000	Open and Closed Session Advisory Committee meeting to discuss REST design
Jan 2001	Study 006 (Rotavirus Efficacy and Safety Trial/REST) initiated
Nov 2003	60,000th subject randomized (REST)

Sept 2004 70,000th subject enrolled (REST)
Nov 2004 DSMB recommends stopping REST enrollment
April 2005 BLA submitted to FDA
Dec 2005 Vaccines and Related Biological Advisory Committee Meeting (VRBPAC) to discuss safety and efficacy of RotaTeq™

Regulatory Guidance and Advice Regarding Study 006 (REST)
Regulatory guidance and advice was provided by the Center for Biologics Evaluation and Research (CBER) and the Vaccine and Related Biologics Product Advisory Committee (VRBPAC) regarding the approval of the study design of protocol 006 (REST), including the acceptability of the statistical criteria to support the primary safety hypothesis regarding intussusception. CBER approved the study design recommending some modifications to the interim safety monitoring plan to decrease the Type 2 error (decrease the probability of declaring a safe vaccine unsafe) and a modification to decrease the chance of an ambiguous outcome. Advice on the consent form was also provided.

The instruments and endpoints were considered acceptable to FDA for use in evaluating the efficacy of RotaTeq™ to prevent rotavirus disease and included definitions for rotavirus gastroenteritis, rotavirus season, a scoring system for grading the severity of acute rotavirus gastroenteritis and serologic and diagnostic tests used to detect antibody to rotavirus (IgA and G serotypes) and rotavirus antigen. FDA and the Applicant agreed upon the parameters that would be used to evaluate whether RotaTeq™ interfered with the immune responses to concomitantly administered U.S. licensed vaccines.

The instruments and endpoints were considered acceptable to evaluate the safety of RotaTeq™ in relation to intussusception. Rotashield®, the simian rotavirus vaccine, was withdrawn from the market in July l999 because of concerns related to an increase in the number of infants who had developed intussusception after receiving this vaccine. The Applicant was in the process of developing their human bovine re-assortant rotavirus vaccine when RotaShield® was voluntarily withdrawn from the U.S. market. In May 2000, the Applicant presented their development plans to the Vaccines and Related Biological Products Advisory Committee in relation to how they would rule out an increased risk for intussusception with their product. A development plan was agreed upon including a clinical trial that might necessitate enrollment of 60,000 to 100,000 infants in order to rule an increased risk for the vaccine to cause intussusception which was felt to occur at a background rate of 1/2000 infant years. Details regarding the statistical plan related to intussusception and descriptions of how the adjudication committee and data safety monitoring board functioned are included on page 55 of this BLA review. The Applicant states that the case definition of intussusception used in this study was identical to that later developed by the Brighton Collaboration* Intussusception Working Group (Level 1 of Diagnostic Certainty) with one difference in that the Brighton Collaboration case definition calls for confirmation of an ultrasound diagnosis of

intussusception by demonstrating resolution of ultrasound findings after intussusception reduction; whereas, an ultrasound diagnosis of intussusception was accepted to define cases in Protocol 006 (REST) without this confirmation. Cases diagnosed by ultrasound alone were included to avoid missing cases that may have spontaneously reduced.
*(http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

Medical Officer comments:

The strengths of Study 006 include that it was a large, multi-center, international, randomized, placebo- controlled trial using a Data Safety Monitoring Board (DSMB) and a Safety Endpoint Adjudication Committee (SEAC). The majority of the study was done under U.S. IND. The Applicant had complete follow-up data to 42 days after the third vaccine dose on approximately 91% of the subjects in both the RotaTeq™ and placebo arms of the study. The study enrolled infants from the U.S. and foreign countries such as Finland. Consequently, different immunization schedules were used including the 2, 4, 6 month U.S. schedule and 2, 3, 4 month and 2, 3, 5 month schedules which may be utilized in other countries. Consequently, at 42 days post vaccine dose #1, some of the infants had not yet received their second vaccine dose while others, who were on a schedule using a 30 day interval between doses, would have actually already been 12 days post vaccine dose #2. This impacted the period post vaccine doses #1 and #2. Therefore, safety ascertainment was lower but balanced between the treatment arms at 50% (approximately 17,538 infants per study arm) post-dose #1 and 46% (approximately 15847 infants per study arm) post-dose #2. This difference in safety ascertainment and follow-up days, which resulted because of differences in the immunization schedules, was taken into account for the statistical calculation of relative risk (see p. 102 of this BLA review). Safety ascertainment was not affected for earlier time points such as 7 days, and 14 days after vaccine dose. Thus, when assessing the primary endpoint within 42 days post any vaccine dose, the relative risk did not include all 35,000 children per each study arm at this time. However, all cases of intussusception in the study were captured and plotted in relation to the time after their most recent vaccination.

Limitations of the study included that hematochezia was not a solicited adverse event on the vaccine report card or in the AGE workbook and thus, there may be under-reporting of this adverse event. Hematochezia has been reported in cases of intussusception. In addition, the AGE score that was used to define different grades of severity of gastroenteritis, did not include the parameter of dehydration.

The Applicant used criteria similar to the Brighton level 1 diagnostic certainty that were later developed (surgical, radiographic or autopsy confirmation of intussusception). If a case of intussusception was diagnosed using ultrasound, it was not necessary to perform a follow-up

ultrasound to document reduction. FDA agreed to the Applicant's case definition for intussusception.

CBER Advice Regarding Other Phase III Studies
From the Pre-Phase III/Phase III Meeting, CBER advised that the safety database for all adverse experiences should include approximately 10,000 subjects (5000 vaccine recipients). CBER advised Merck to conduct a study confirming the efficacy of the final vaccine intended for licensure at expiry potency (Protocol 007). CBER agreed with demonstration of the consistency of the manufacture of 3 distinct lots of RotaTeq™ for each reassortant using the serum neutralizing antibody (SNA) assays (EIA) to G1, G2, G3, G4, P1, and serum anti-rotavirus IgA despite the fact that these antibody titers have not definitively been demonstrated to correlate with efficacy (Protocol 009). CBER agreed with the study design to assess the immunogenicity and safety of concomitant administration of RotaTeq™ and licensed vaccines for 2- to 6-month-old infants. CBER agreed that the multivalent quantitative PCR-based potency assay (M-QPA) appeared to be effective over the range of potencies evaluated during the Phase III trials of RotaTeq and requested that the sensitivity be assessed in the context of the pentavalent formulation.

6.0 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material reviewed. Data sources for review included the electronic BLA.

6.1.1 BLA Volume Numbers which served as a Basis for the Clinical Review-Original Application submitted April 6, 2005.

-Vol. 2.5 Clinical Overview
-Vol. 2. 73 Clinical Summary of Efficacy
-Vol. 2. 74 Clinical Summary of Safety
-Vol. 5.2. which includes the following:
-Clinical Study Reports (CSR) in Legacy format and the accompanying ------- datasets for studies 001,002, 003, 004, 005, 006, 007 and 009 were reviewed.
-A random sample of case report forms (CRFs) were reviewed for the phase 3 clinical studies 006, 007 and 009. CRF's were reviewed for earlier studies 001,002, 003 and 004 depending on whether a specific type of adverse event/serious adverse event was a concern, e.g., cases of seizure were reviewed in the earlier studies.
-Narrative summaries that were provided on the deaths and cases of negatively and positively adjudicated cases of intussusception were reviewed.
-At the end of the electronic BLA there is a section termed "Other study reports" that was reviewed. This section includes 4 submissions, R1, R2, R3 and R4 which cover the topics of immune correlates for protection, safety in older infants ($\geq$ 6 months) who received their first dose of RotaTeq® , health economic

information regarding office visits, hospitalizations and ER visits and pharmacovigilance plans.

-The Safety Update which was submitted and dated July 25, 2005 by the Applicant and entered into the FDA electronic document room on August 11, 2005 was reviewed.
-All Efficacy Information Amendments were reviewed including those received on August 30th, October 31st, November 3rd and 7th of 2005.

6.1.2 Literature

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7. Bresee JS, Hummelmen E, Nelson EAS, Glass RI. Rotavirus in Asia: The value of surveillance for Informing Decisions about the Introduction of New Vaccines. J Infect Dis 2005: 192: S1-5.
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13. Newman RD, Grupp-Phalen J, Shay DK, Davis RL. Perinatal Risk Factors for Infant Hospitalization With Viral Gastroenteritis. Pediatrics 1999;103: 3-11.
14. Haber P, Chen RT, Zanardi LR, Mootrey GT, English R, Braun, MM and the VAERS Working Group. An analysis of rotavirus vaccine reports to the Vaccine Adverse Event Reporting System: More than intussusception alone? Pediatrics 2004; 113(4): 353-359.
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6.1.3 Post-marketing experience

No post-marketing experience is available on this product.

6.2 Tables of Clinical Studies

Brief summaries of the phase 1 and phase 2 clinical trials for RotaTeq™ are included below. Please also see Tables 6 and 7 which depict, respectively, the five phase 1 and 2 clinical studies 001, 002, 003, 004 and 005 which utilized a different vaccine (lower valency, not buffered, required pre-feed) than what was used in the phase 3 studies 006, 007, 009.

Summary of Phase I and Phase II Clinical Trials (From the Applicant)

Protocol 001 (Adult Safety Trial): “Safety, Tolerability, and Immunogenicity of Quadrivalent Rotavirus Vaccine in Healthy Adults” (1993). This Phase I, placebo-controlled safety study conducted with 31 adults showed that a quadrivalent (G1, G2, G3, and P1) formulation of the vaccine given at 10^7 plaque-forming units (PFU)/reassortant was not associated with systemic or gastrointestinal adverse experiences.

Protocol 002 (Proof-of-Concept Trial): “Safety, Immunogenicity, and Efficacy of a Live, Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine in Healthy Infants” (1993 to 1994). This Phase II “Proof-of-Concept” study was a multicenter efficacy trial in 439 infants, which showed that quadrivalent (G1, G2, G3, and P1) vaccine was generally well tolerated and efficacious in this study population. The regimen consisted of 3 oral doses of ~5.9×10^7 PFU/dose (aggregate). The proportions of subjects with fever, diarrhea, and vomiting were similar in the vaccine and placebo groups. The vaccine prevented 74.6% of all confirmed

rotavirus gastroenteritis (primarily G1), and 100% of severe rotavirus gastroenteritis.

Protocol 003 (Immunogenicity Clinical Trial of Buffered Formulations): “Safety, Immunogenicity, and Efficacy in Healthy Infants of G1 and G2 Human-Bovine Rotavirus Reassortant Vaccine in a New Buffer/Stabilizer Liquid Formulation” (1997 to 1998). One of the goals of Merck’s Rotavirus Vaccine Program was to have a liquid, buffered formulation that would protect the vaccine from gastric acid and would not require prefeeding or an antacid before administration, as well as to be stable for refrigeration. Several candidate formulations were developed and studied at a potency of ~1 x 10^7 PFU (aggregate) in Protocol 003. This was a multicenter safety, immunogenicity, and efficacy study in 731 infants in which 4 different buffered formulations of bivalent vaccine (G1, G2) were evaluated. The proportions of subjects with fever, vomiting, diarrhea, and irritability were similar in the vaccine and placebo groups. No severe systemic or gastrointestinal vaccine-related adverse experiences were reported. The primary endpoint of this study was immunogenicity; however, estimates of efficacy were also obtained. All formulations of the bivalent vaccine were generally similar with respect to the serum neutralizing antibody (SNA) response to G1, and efficacy estimates ranged from 73.0 to 87.8% against any G1- or G2-confirmed (primarily G1-confirmed) rotavirus gastroenteritis. However, the small study size limited the power to declare efficacy. In addition, the SNA responses to G1 in this study were generally similar to those seen in previous studies of the unbuffered vaccine formulation. These results led to identification of the final vaccine formulation that would be later used in the Phase III clinical trials. In addition, the Applicant notes that earlier Phase I and Phase II clinical trials utilized a different assay for measuring the vaccine potency than that used for the Phase III clinical trials. The plaque assay, which measures potency in plaque-forming units (PFU), was used in the Phase I and Phase II trials. The multivalent quantitative polymerase chain reaction (PCR)-based assay (M-QPA) was used to measure vaccine potency for the Phase III studies. The potency as measured by M-QPA is expressed as infectious units (IU). The terms PFU or IU/reassortant describe the potency of each individual reassortant of the vaccine (i.e., G1, G2, etc.). The term “aggregate” is used to refer to the potency of each of the reassortants added into a single aggregate potency, expressed in PFU or IU (aggregate).

Protocol 004 (G4 Monovalent Safety Trial): “Safety and Tolerability of Oral, Live G4 Human-Bovine Reassortant Rotavirus Vaccine in Healthy Adults and Healthy Infants” (1998). Because rotavirus serotype G4 has also been commonly associated with human gastroenteritis, a placebo-controlled safety trial of a G4 reassortant vaccine at a dose of 1 x 10^7 PFU was done so that this serotype could be added to the vaccine. The monovalent vaccine was not associated with serious systemic or gastrointestinal vaccine-related adverse experiences in the 15 adults and 70 children enrolled in the study

Protocol 005 (Dose-Ranging Efficacy Trial): “Safety, Immunogenicity, and Efficacy in Healthy Infants of G1, G2, G3, G4, and P1 Human-Bovine Rotavirus Reassortant Vaccine” (1998 to 2001). This study was conducted among 1946 subjects in Finland to determine the reassortant composition and to evaluate the

range of potencies across which the vaccine is efficacious. Subjects were randomized to 1 of the following 6 groups evaluating different vaccine potencies and reassortant compositions:

• Groups 1, 2, and 3 received pentavalent (G1, G2, G3, G4, and P1) vaccine at Potencies of ~5 x 10^6 PFU, ~1.6 x 10^6 PFU, and ~5 x 10^5 PFU per reassortant per dose, respectively.

• Group 4 received quadrivalent (G1, G2, G3, and G4) vaccine at ~5 x 10^6 PFU per reassortant per dose.

• Group 5 received monovalent P1 vaccine at ~5 x 10^6 PFU per dose.

• Group 6 received placebo.

Diarrhea, fever, irritability, and vomiting incidences were generally similar across all treatment groups, including placebo. Point estimates of efficacy (95% multiplicity-adjusted confidence interval [CI]) against rotavirus acute gastroenteritis caused by G1-, G2-, G3-, and G4-serotypes were: Group 1, 68.0% (31.1%, 86.4%); Group 2, 74.3% (37.9%, 91.0%); Group 3, 57.6% (11.8%, 80.9%); Group 4, 74.0% (40.3%, 90.3%); and Group 5, 43.4% (-1.7%, 69.2%). Efficacy against severe rotavirus acute gastroenteritis was 100% among Groups 1 to 4; and 88.1% among Group 5. Although the P1 monovalent vaccine did not demonstrate efficacy with statistical significance against rotavirus gastroenteritis of any severity caused by the G1, G2, G3, and G4 serotypes, it was efficacious against moderate-and-severe rotavirus gastroenteritis caused by these serotypes. It was also efficacious against rotavirus gastroenteritis of any severity when evaluated against all (any serotype) rotavirus gastroenteritis. In summary, these results indicated that all vaccine potencies and reassortant compositions studied were generally tolerated and efficacious against rotavirus acute gastroenteritis. Based on these results a pentavalent (G1, G2, G3, G4, and P1) reassortant composition was selected for further development. This study was also used to assign the expiry potency of the final vaccine, RotaTeq™, the efficacy of which was confirmed in one of the Phase III clinical trials (Protocol 007).

Table 6 Overview of Phase 1 and 2 Clinical Studies Contained in the BLA*

study	Study Design	Study Population Entered -Age -Sex	Number Vaccinated		Dose & Formulation of RotaTeq™	Objectives		
			RotaTeq™	Placebo		Safety	Immuno-genicity	Efficacy
#001	Single U.S. center, double- blind, randomized, placebo-controlled	Healthy adults -19 yrs. to 47 yrs. -M and F	20	11	Single dose G1, G2, G3, P1 Quadrivalent human-bovine reassortant 1 x 10^7 PFU	yes	yes	Not an objective
#002	Multi-center, double-blind randomized, and placebo-controlled	Healthy infants 1-7 months -M and F	218	221	3 doses spaced 6 to 8 weeks apart Quadrivalent human-bovine reassortant G1, G2, G3, P1 4 x 10^7 PFU	yes	yes	yes
#003	Multi-center, partially double blind, randomized, placebo-controlled	Healthy infants 6-21 weeks -M and F	142 (1 mL) No buffer 150 (1mL) 1x buffer 147 (2.5 mL) 1 x buffer 142 (1.0mL) Conc. Buffer	150	3 doses spaced 6 to 8 weeks apart G1 and G2 human reassortant in new stabilizer/ buffer 5 x 10^6 PFU	yes	yes	yes
#004	Multi-center, double-blind, randomized, placebo-controlled	Healthy adults (23-54 years) Healthy infants (8-21 weeks) -M and F	Adults 10 Infants 47	Adults 5 Infants 23	Single dose with 42 day follow-up G4 human bovine reassortant 10^7 PFU	yes	yes	no
#005	Single center, Double-blind, randomized, placebo-controlled	Infants 2 to 8 months -M and F	375 Group 1 328 Group 2 324 Group 3 270 Group 4 327 Group 5	322	Three doses at 1.0 mL each and given 4 to 8 weeks apart Group 1-3 pentavalent G1, G2, G3, G4 and P1 At 5 x $l0^6$, 1.6 x 10^6 and 5 x 10^5 PFU Group 4 quadrivalent G1, G2, G3 G4 at 5 x $l0^6$ PFU Group 5 monovalent P1 at 5 x $l0^6$ PFU	yes	yes	yes

*FDA summary

Table 7 Phase 3 Safety Cohort Studies 006, 007 and 009*

	Study 006**		Study 007		Study 009	
	RotaTeq™	Placebo	RotaTeq™	Placebo	RotaTeq™	Placebo
Randomized	35094	35052	651	661	680 (3 lots 226, 225, 229)	113
Vaccinated	35027 (67 not vaccinated)	34978 (74 not vaccinated)	650	660 (1 not vaccinated)	679 -226 -224 -229	112
Cross--treated or fourth dose	73**		1 (fourth dose of RotaTeq)	0	1	1
Excluded sites *** (included in randomized number above)	191	191	0	0	0	0
Total	35027	34978	650	660	679	112

*FDA analysis

**Total randomized for study 006 was 73 cross-treated + 35094 RotaTeq™ + 35052 placebo = 70,219 which includes subjects who were cross-treated and also those from the excluded sites. There are 73 cross-treated subjects in study 006, 1 cross-treated in 007, 2 cross-treated in 009 so a total of 76 cross-treated in the pivotal phase 3 studies and 4 additional excluded patients in study 006. Adding 382 subjects from the excluded sites to the 76 cross-treated and the 4 additional excluded subjects produces a total of 462 cross-treated and excluded subjects.

***The excluded sites (sites 034, 113 and 064) had 382 subjects that are included in the randomized totals for RotaTeq™ and Placebo groups in study 006 but delineated in the table for accounting purposes.

Total number for the pivotal phase 3 safety cohort denominator i.e. received at least one dose of vaccine and this includes the excluded sites but not the 76 cross-treated subjects:

RotaTeq™ = 35027 + 650 + 679 = 36,356
Placebo 34978 + 660 + 112 = 35,750
Total = 72,106

6.3 Review Strategy

The ------- program was used to subset data. The BLA contained a substantial amount of safety data on over 70,000 infants. Efficacy was also assessed using the "analysis" --- datasets. The AGE scoring system which was used to determine whether a case of acute rotavirus gastroenteritis (AGE) was defined as severe was also verified. The --- serology datasets were used for analyses on shedding and immunogenicity and concomitant vaccination studies. The --- healthcare utilization database (HUI) was used to corrorborate data relating to hospitalizations, emergency department and office visits for gastroenteritis and other adverse events.

The approach taken involved initially reading the clinical overviews and summaries of efficacy and safety. Study synopses were read for studies 001 through 005, realizing that the formulation in the phase 3 clinical studies 006, 007 and 009 was different than what had been studied in the earlier phase 1 and phase 2 trials. Global safety focused on studies 006, 007 and 009. However, for specific AEs such as seizures and intussusception the earlier phase clinical trial safety databases were reviewed. The minutes from the DSMB meetings for study 006 were also requested and reviewed. Questions arose during the safety and efficacy review related to issues such as how many subjects received oral polio vaccine, clarification on the number of non-IND sites that enrolled subjects, questions regarding efficacy in children who were breast fed and vaccine strain shedding in the medically compromised subjects and other requests for information that were made to the Applicant. The data submitted in answer to these queries can be found as "Information Amendments" in the electronic BLA and also in CBER secure e-mail.

6.4 Good Clinical Practices (GCP) and Data Integrity Informed Consent, Site specific Issues, Protocol Violators (OPV and the "Cross-treated") and site specific issues

The CSR (Clinical Study Report) and Data Analysis Plan (DAP) for each protocol were available for the preparation of this review. The clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of clinical trials. The studies were conducted following appropriate Good Clinical Practice (GCP) guidelines and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed. Data presented in this BLA were subject to audit by Merck Research Laboratories (MRL) Quality Assurance organizations based on approved standard operating procedures in effect at the time of the audit. Information presented in this document was audited against the supporting documentation provided herein in accordance with Merck Worldwide Quality Assurance Resources Standard Operating Procedures. The design, power, and number of subjects for the studies were chosen to provide sufficient data to assess the efficacy, immunogenicity, and safety of RotaTeq™ compared with placebo.

Subjects Not Included in the Planned Analyses Due to Unreliable Data
Three (3) study sites were deemed to have unreliable data, as a result of concerns raised during routine monitoring visits. These concerns led to an investigation of study conduct by a cross-functional team, which included members of Merck's Worldwide Clinical Quality Assurance Resources. Findings of these investigations were submitted to the U.S. Food and Drug Administration. A total of 253 subjects were randomized at Study Site Number 006-113, 33 subjects were randomized at Study Site Number 006-164; 95 subjects were randomized at Study Site Number 006-034 and the data from the study sites were not included in any of the Applicant's data displays or analysis due to the unreliability of the data.

Inspections of 2 study sites that were disqualified:
Site 164 was disqualified by CBER and a Notice of Disqualification Proceeding and Opportunity to Explain letter was issued on 4/22/04. Among the issues included in the letter is the falsification of information submitted to the sponsor regarding follow-up safety contacts that were reported as completed, but were not performed. Site 113 was issued a Notice of Disqualification Proceeding and Opportunity to Explain letter on 6/23/2003 and a Notice of Opportunity for Hearing on 2/4/04. Among the issues encountered with conduct of the clinical trial at site 113 were falsification of doses of study vaccine/placebo administered, false information regarding follow-up safety contacts, and false information regarding concomitant vaccinations. This is a just a brief synopsis regarding falsification of data at two study sites. Additional violations were noted. Please note: excluded sites were site 113 (253 + 1 = 254 subjects), site 164 (33 subjects), and site 034 (95 subjects) = 382 excluded subjects

Medical Officer comments:
The efficacy data for study 006 (REST) excludes sites 113 and site 164 and site 034 and 4 additional subjects --- allocation numbers 02642, 38102, 81399 and 81908 comprising a total of 386 excluded subjects. The subjects at these sites were included in the FDA safety evaluation, however.

IND and Non-IND data
In study 006 (REST) 61,985 subjects were enrolled under IND and 7,778 subjects were enrolled at study sites that were non-IND. There were 173 IND sites utilized in the U.S. Other countries with IND sites in study 006 included: 20 sites in Finland, 10 sites in Costa Rica, 2 sites in Guatemala and 2 sites in Taiwan.

In study 006, the countries listed below had sites where subjects were not enrolled under US IND:

Belgium	37 sites
Germany	154 sites
Italy	2 sites

Mexico	3 sites
Sweden	4 sites

Medical Officer comments:
The non-IND sites in study 006 (REST) did not contribute subjects to the efficacy analyses.

Protocol 007 enrolled 1312 subjects and Protocol 009 enrolled 793 subjects and these two pivotal studies were done completely under US IND i.e. BB-IND-----.

OPV administration
There were 69,696 subjects enrolled in Protocol 006 (REST) across 11 countries that received at least one dose of vaccine or placebo. Among these subjects, there were 17 that received live oral poliovirus vaccine, despite this being an exclusion criterion as outlined in the protocol Fifteen of seventeen subjects received either RotaTeq or placebo and live oral poliovirus vaccine during the National Vaccination Program in Mexico and all of these subjects were considered Protocol violators and were not included in the primary efficacy or immunogenicity analyses although they were evaluated for safety. None of these subjects developed intussusception.

Medical Officer comments:
None of the subjects who developed intussusception in the phase 3 trials had received live oral poliovirus vaccine.

Protocol Violators
"Cross-treated" subjects who received treatments other than what they were randomized to receive were evaluated in the data analysis differently by the Applicant and the FDA reviewer.

Medical Officer comments:
This reviewer analyzed the "cross treated" subjects separately. These subjects received 3 dose regimens such as "placebo, placebo, RotaTeq™". It was logistically easier to handle the 76 subjects separately when using the ------- datasets. Separate analysis facilitated examination of adverse events associated with a "late" first dose of RotaTeq™.

6.5 Financial Disclosures

From the BLA submission, the Applicant provided information regarding the list of investigators with financial interests in Merck. Investigators at the following sites had substantial financial interests in Merck: sites 006-018, 006-144, 006-190, 006-062 and 006-212.

Medical Officer comments:
No major issues regarding the integrity of clinical data from the above sites has been identified.

7 Human Pharmacology (Immunogenicity)

The immunogenicity data to support licensure of RotaTeq™ was obtained from 3 Phase III clinical trials (Protocol 006 [REST]), (Protocol 007), and (Protocol 009). The use of immunogenicity data for RotaTeq™ has been limited to the demonstration of manufacturing consistency for observational comparisons between populations and in studies of the concomitant use of RotaTeq™ with other childhood vaccines. Immunogenicity has not been used in making decisions about dose (viral titer). A relationship between antibody responses to RotaTeq and protection against rotavirus gastroenteritis has not been established. In phase 3 studies, 92.9% to 100% of 439 recipients of RotaTeq achieved a 3-fold or more rise in serum anti-rotavirus IgA (EIA) after a three-dose regimen when compared to 12.3%-20.0% of 397 placebo recipients.

Medical Officer comments:
See section 4.2 (Animal Pharmacology/Toxicology) for information regarding the immunogenicity assays used in the clinical trials for RotaTeq™

8 Clinical Studies

The phase 3 trials (006, 007 and 009) are the main focus of the clinical review that follows.

8.1 Indication: Prevention of rotavirus gastroenteritis in healthy children

8.1.1 Trial #1 Rotavirus Efficacy and Safety Trial (REST)

8.1.1.1 Protocol 006: Safety and Efficacy of Pentavalent (G1, G2, G3, G4 and P1) Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants (REST)

8.1.1.1.1 Objective/Rationale

Primary Objectives

1. To evaluate the efficacy of a 3-dose regimen of oral RotaTeq™ against rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
2. To assess the safety of RotaTeq™ with respect to intussusception within 42 days of any dose of vaccine/placebo.

Secondary Objectives

1. To evaluate the effect of a 3-dose regimen of RotaTeq™ on health care resource utilization, including visits to emergency departments, physician's

office visits, and Finnish health care centers or equivalent in other countries, and hospital admissions.
2. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against moderate and- severe and severe rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
3. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against rotavirus disease regardless of serotype that occurs at least 14 days following the third dose.
4. To assess the safety of RotaTeq™ with respect to the incidence of intussusception occurring within 1 to 7 days, 1 to 14 days, and 1 to 365 days of any dose of vaccine/placebo.
5. To assess the safety of RotaTeq™ with respect to all adverse experiences in a subset of subjects.
6. To assess the immunogenicity of RotaTeq™ as measured by the serum neutralizing antibody (SNA) response to reassortants G1, G2, G3, G4, P1, WC3 [components G6 and P7 (P[5] genotype)], and serum rotavirus-specific IgA in a subset of subjects.
7. To evaluate the antibody responses to the recommended routine childhood immunizations, including COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ when given concomitantly with oral RotaTeq™ in a subset of subjects.
8. To evaluate the efficacy, safety, and immunogenicity of oral RotaTeq™ when administered concomitantly with COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ in a subset of subjects.
9. To assess the safety of RotaTeq™ when administered concomitantly with a combination hexavalent pediatric vaccine (HEXAVAC™ or INFANRIX HEXA™) in a subset of subjects in Germany.

Tertiary Objectives
1. To evaluate a polymerase chain reaction (PCR) assay for identification of rotavirus in stool samples obtained from subjects with acute gastroenteritis.
2. To examine whether RotaTeq™ will be associated with a shift in the patterns of care among subjects who seek care for rotavirus disease.
3. To examine whether RotaTeq™ will be associated with a reduction in the number of days of parental work loss that occurs to care for children with rotavirus disease.
4. To summarize the fecal shedding of vaccine-strain rotavirus in a subset of subjects who developed significant medical conditions after enrollment in the study.

8.1.1.1.2 Design Overview
This was a large, multi-center, international, randomized, double blind, placebo-controlled clinical trial. The study began in January 2001 and ended in November 2004.

8.1.1.1.3 Population
Population Demographics
The study was originally intended to be enrolled at approximately 150 study sites

in the United States and approximately 30 study sites in Finland, but was expanded to other countries to assist with enrollment of the large sample size and potentially to evaluate the efficacy of RotaTeq™ in regions where serotypes other than G1 are prevalent. These additional countries included Belgium, Costa Rica, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, and Taiwan. The Navajo and White Mountain Apache Nations in the western United States, where G3 has historically been predominant, were considered as a demographic entity and included among the study sites.

Medical Officer comments:
Industrialized nations contributed 77% of the study population. Although not directely relevant to U.S. licensure, it will be important to further characterize the safety and efficacy of this product in infants residing in developing countries where babies may be co-infected with intestinal parasites or receive live oral polio vaccine.

Demographics for study 006 (REST)
A total of 70,078 subjects received at least one dose of vaccine (RotaTeq™ or placebo or cross-treated) in study 006. Subjects from Finland contributed 33% of the data and subjects from the U.S. and Puerto Rico contributed 48% of the data.. The remaining 19% of the subjects were from the following countries: Costa Rica, Guatemala, Mexico, Jamaica, Taiwan, Belgium, Germany, Italy and Sweden.

The following **inclusion and exclusion criteria** are from Protocol Amendment 006-04, the last protocol amendment.

Inclusion Criteria
1. Healthy infants.
2. Age 6 weeks through exactly 12 weeks (≥42 to ≤84 days; Date of Birth = Age Day 1).
3. For the subset of subjects in the United States who were being evaluated for concomitant use vaccines, infants must have received a neonatal dose (within seven days following birth) of hepatitis B vaccine.

Medical Officer comments:
There were no restrictions on breast-feeding or the use of concomitant vaccines other than OPV. Immunization schedules differed for the subjects e.g. the U.S. schedule is given at 2, 4, 6 months of age and the Finnish schedule at 2, 3, 4 months of age and a 2, 3, 5 month schedule was also allowed.

Exclusion Criteria
1. History of congenital abdominal disorders, intussusception, or abdominal surgery.
2. Known or suspected impairment of immunological function.
3. Known hypersensitivity to any component of the rotavirus vaccine, e.g.,

trypsin.
4. Prior administration of any rotavirus vaccine.
5. Fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization.
6. History of known prior rotavirus disease, chronic diarrhea, or failure to thrive.
7. Clinical evidence of active gastrointestinal illness. Infants with gastro-esophageal reflux disease (GERD) could have participated in the study as long as the GERD was well controlled with or without medication.
8. Receipt of intramuscular, oral, or intravenous corticosteroid treatment. Infants on inhaled steroids may have participated in the study.
9. Infants residing in a household with an immunocompromised person, including individuals with congenital immunodeficiency, 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. Prior receipt of a blood transfusion or blood products, including immunoglobulins.
11. Any infant who could not have been adequately followed for safety by telephone or home visit.
12. Receipt of oral poliovirus vaccine (OPV) at any time during the course of the study or within 42 days prior to the first dose of vaccine/placebo.
13. Any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.
14. For the subset of subjects in the United States who were being evaluated for concomitant vaccines, infants who had previously received any diphtheria, tetanus and acellular pertussis (DtaP) or diphtheria, tetanus and pertussis (DTP) vaccine, any *H. influenzae* type b vaccine, any oral or injected polio vaccine, any pneumococcal conjugate vaccine, or hepatitis B vaccine except within 7 days following birth.

Protocol Violators the "Cross-treated" subjects
It should be noted that in the phase 3 clinical trials there were 76 cross -treated subjects who were infants whose actual treatment was different than the treatment arm to which they were randomized; or they may have received an incorrect series of study vaccinations. This cross-treated group could include subjects who received a mixed regimen such as two placebo doses and one dose of RotaTeq™ or any other incorrect combination of placebo and study vaccine or a fourth dose of RotaTeq™ or placebo. (Appendix 2.7.4:4 p. 244 of the Safety Update "SUR" , July 25, 2005 includes a line listing of these subjects).

There were 76 "cross-treated" subjects which included those infants who received the following combinations of vaccine:

Type of "Cross-treatment"	Number of subjects
Cross Lots (Lot 2, Lot 2, Lot 1 in study 009)	1
Cross Treated (Placebo arm received 3 doses RotaTeq)	1
Five Doses (Placebo, Placebo, RotaTeq, RotaTeq, RotaTeq)	6
Five Doses (Placebo, RotaTeq, Placebo, RotaTeq, RotaTeq)	1
Four Doses (Placebo, Placebo, Placebo, Placebo)	1
Four Doses (Placebo, Placebo, RotaTeq, RotaTeq)	1
Four Doses (Placebo, RotaTeq, Placebo, RotaTeq)	2
Four Doses (Placebo, RotaTeq, RotaTeq, RotaTeq)	12
Four Doses (RotaTeq, Placebo, RotaTeq, RotaTeq)	14
Four Doses (RotaTeq, RotaTeq, Placebo, RotaTeq)	7
Fourth Dose (RotaTeq, RotaTeq, RotaTeq, RotaTeq)	1
Three Doses (Placebo, Placebo, RotaTeq)	5
Three Doses (Placebo, RotaTeq, Placebo)	3
Three Doses (Placebo, RotaTeq, RotaTeq)	5
Three Doses (RotaTeq, Placebo, Placebo)	1
Three Doses (RotaTeq, Placebo, RotaTeq)	4
Three Doses (RotaTeq, RotaTeq, Placebo)	8
Two Doses (RotaTeq, RotaTeq)	1
Two Doses (Rotateq, Placebo)	2

8.1.1.1.4 Products mandated by the protocol

Placebo
The placebo was approximately 2.0 mL per dose that contained approximately
---

Placebo (Lot Numbers: ----------

Product
The Applicant states that the vaccine evaluated in the Phase 2 studies differed from that evaluated in the Phase 3 studies with regard to formulation (un-buffered versus buffered in the final formulation), scale of process (laboratory scale versus manufacturing scale), and potency assay (plaque assay versus multivalent quantitative polymerase chain reaction assay [M-QPA]) and addition of serotypes.

Human Bovine reassortants which include G1 2.2 x10^6 infectious units, G2 2.8 x 10^6 infectious units, G3 2.2 x 10^6 infectious units, G4 2.0 x 10^6 infectious units, P1 2.3 x 10^6 infectious units. Reassortants are propagated in Vero cells in the absence of antifungal agents and suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium monobasic monohydrate, sodium hydroxide, polysorbate 80 and also tissue culture media. There are no preservatives or thimerosal.

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each vaccination was 2.0 mL of vaccine or placebo. Vaccination 1 was to be administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ (Lot Numbers: V260 VAO005F001, V260 VAO005F002, V260VAO005F003, V260 VAO005F006, V260 VAO005F007,V260 VAO005F008, V260 VAO005F009,V260 VAO007F001, V260 VAO007F002, V260 VAO008G001, V260 VAO008G002, V260VAO010H001, V260 VAO010H002, V260 VAO011I001, V260 VAO011I002, V260 VAO012J001,V260 VAO012J002, V260 VAO012J003, V260 VAO013K001, V260 VAO013K002, V260VAO013K003, V260 VAO014L001, V260 VAO014L002, V260 VAO014L003, V260 VAO014L004, V260VAO016M001, V260 VAO016M002, V260 VAO016M003, V260 VAO016M004, V260VAO017N001,V260 VAO017N002, V260 VAO017N003, V260 VAO021R001), when fully characterized, contained approximately ----- mg of sucrose, approximately --- mg of sodium phosphate, approximately --- mL of tissue culture medium, and ---------- mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an aggregate potency ranging from 67.2x10^6 to 124x10^6 infectious units (IU)/dose in approximately 2 mL of buffer/stabilizer. Theoretical calculation of ---------- material (-------) was -- mg/dose. Trace components of fetal bovine serum may have also been present. The stability of RotaTeq™ was assessed at predefined evaluation points throughout the study.

Medical Officer comments:
Please see the FDA product review for additional information.

For a subset of subjects in the United States (U.S. Concomitant Use Cohort), Merck also provided the licensed pediatric vaccines that were administered concomitantly (same day) with RotaTeq™ or placebo, which included COMVAX™, INFANRIX™, IPOL™, and PREVNAR™. These vaccines were administered at a dose of 0.5 mL. COMVAX™ (Lot Number: 1076L) was supplied in 0.5-mL single dose vials. INFANRIX™ (Lot Numbers: DTPA524A2, DTPA572A2, DTPA575A2) was supplied in 0.5-mL single-dose vials. IPOL™ (Lot Numbers: T1153-2 and T1189-2) was supplied in prefilled syringes and/or

multidose vials, 0.5-mL per dose. PREVNAR™ (Lot Numbers: 491-171 and 491-178) was supplied in 0.5-mL single-dose vials. PREVNAR™ was in short supply over the course of the study. When not available for Merck to provide, the study sites were permitted to administer PREVNAR™ from their supply. If PREVNAR™ was provided locally by the physician, the single panel, open label was not used. The lot number and expiration date were to be recorded.

Medical Officer comments:
See additional analysis request ed by FDA of Merck regarding fever in subjects who concomitantly received RotaTeq and Prevnar™ in the concomitant vaccine section of this review (see page 139 of this BLA review).

8.1.1.1.5 Endpoints

The prospective primary and secondary endpoints included the following:

Primary Endpoint:
1. To evaluate the efficacy of a 3-dose regimen of oral RotaTeq™ against rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
2. To assess the safety of RotaTeq™ with respect to intussusception within 42 days of any dose of vaccine/placebo.

Secondary Endpoints:
1. To evaluate the effect of a 3-dose regimen of RotaTeq™ on health care resource utilization, including visits to emergency departments, physician's office visits, and Finnish health care centers or equivalent in other countries, and hospital admissions.
2. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against moderate and- severe and severe rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
3. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against rotavirus disease regardless of serotype that occurs at least 14 days following the third dose.
4. To assess the safety of RotaTeq™ with respect to the incidence of intussusception occurring within 1 to 7 days, 1 to 14 days, and 1 to 365 days of any dose of vaccine/placebo.
5. To assess the safety of RotaTeq™ with respect to all adverse experiences in a subset of subjects.
6. To assess the immunogenicity of RotaTeq™ as measured by the serum neutralizing antibody (SNA) response to reassortants G1, G2, G3, G4, P1, WC3 [components G6 and P7 (P[5] genotype)], and serum rotavirus-specific IgA in a subset of subjects.
7. To evaluate the antibody responses to the recommended routine childhood immunizations, including COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ when given concomitantly with oral RotaTeq™ in a subset of subjects.

8. To evaluate the efficacy, safety, and immunogenicity of oral RotaTeq™ when administered concomitantly with COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ in a subset of subjects.
9. To assess the safety of RotaTeq™ when administered concomitantly with a combination hexavalent pediatric vaccine (HEXAVAC™ or INFANRIX HEXA™) in a subset of subjects in Germany.

The instruments and endpoints were considered acceptable to FDA for use in evaluating the safety and efficacy of RotaTeq™ to prevent rotavirus disease. FDA and the Applicant agreed upon the parameters that would be used to evaluate whether RotaTeq™ interfered with the immune responses to concomitantly administered U.S. licensed vaccines.

Medical Officer comments:
Usual acceptance criteria for concomitant administration of RotaTeq™ with pertussis vaccines includes utilizing an endpoint where no greater than a 1.5 fold difference in geometric meant titers (GMTs) for pertussis antigens is demonstrated between treatment arms rather than allowing a less conservative 2-fold difference.

The 4 Protocol Amendments for study 006 (REST) may be found in the clinical study report (CSR 006) beginning on page 1468.

Summary of Changes to Study Protocol:
Protocol Amendment 006-01
An amendment was made to V260 Protocol 006, “Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants.” Enrollment in this trial began in mid-Jan-2001. As of 23-Jan-2002 with ~12,453 subjects enrolled, no cases of intussusception had been reported to date. The additions and clarifications were described in this document as follows:
-Secondary hypotheses and objectives were added to evaluate the concomitant use of RotaTeq™ with other routine childhood immunizations.
-The laboratory case definition for rotavirus gastroenteritis was clarified to indicate that PCR would be the primary assay for typing, pending validation.
-The health care utilization endpoints for safety and efficacy subjects were clarified. Efficacy subjects would be followed for all health care contacts for gastroenteritis; safety subjects would be followed only for health care contacts for gastroenteritis at hospitals, emergency departments, Finnish health care centers, and equivalent centers in other countries.
-The laboratory work-up for cases of intussusception was clarified to include testing of stools, blood, and tissue (if applicable) for pathogens that the Applicant believed might be associated with natural intussusception.
-The trademark, RotaTeq™, was registered for Merck’s pentavalent (G1, G2, G3, G4, and P1) human-bovine reassortant rotavirus vaccine. This trademark has been incorporated throughout the document.

-The interval between doses of RotaTeq™/placebo was lengthened from 28 to 56 days to 28 to 70 days to be more consistent with the routine childhood immunization visits in the United States.
-The exclusion criteria were revised such that infants with gastroesophageal reflux disease (GERD) may participate in the study as long as the GERD is well controlled with or without medication. In addition, it has been added that infants who could not be adequately followed for safety should be excluded from the study.
-The potential for expansion of the trial to other countries was discussed.
-The data about the association of intussusception and rhesus rotavirus tetravalent vaccine (RRV-TV) and the statistical calculations based on those data were updated according to the CDC publication in the New England Journal of Medicine, 22-Feb-2001.
-An update about current enrollment in the study was provided.
-The Sponsor Contact information for U.S. and Non-U.S. Sites was updated.

Medical Officer comments:
Two of the infants in the placebo group who had hematochezia but were negatively adjudicated cases of intussusception had Salmonella cultured from their stool.

Protocol Amendment 006-02
An amendment was made to V260 Protocol 006-01, "Safety and Efficacy of Pentavalent (G1, G2, G3, and P1) Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants." This amendment was generated solely to change 006-01 from Worldwide/U.S. IND study into a Worldwide/U.S. IND/Non-U.S. IND study. Therefore, the only change made was to add in boilerplate text associated with Non IND studies. The countries with sites which could potentially enroll non-IND subjects included: Germany, Belgium, Sweden, and Chile.

Medical Officer comments:
The countries that had non-IND clinical study sites were Germany, Belgium, Mexico, Sweden and Italy. The Applicant needed to increase enrollment and was concerned that international sites might not be able to expeditiously enroll if it required that subjects be followed under US IND.

Protocol Amendment 006-03
An amendment was made to V260 Protocol 006-02, "Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants. This amendment changed 006-02 to add concomitant testing of HEXAVAC™ at specific subsites in selected countries.
-Secondary hypotheses and objectives were added to evaluate the concomitant use of RotaTeq™2 with HEXAVAC™ which is not a U.S.-licensed vaccine.
-Minor alterations were made to hypotheses and objectives for accuracy and to reflect finalized results on earlier studies.

-The exclusion criteria were revised for the concomitant use subsites in selected countries only, such that these children must be excluded if they have already received any dose of HEXAVAC™ or any of the individual components which make up HEXAVAC™.
-Blinding and emergency unblinding language had been added.
-International expansion plans wereclarified.
-Minor alterations were made in the Adverse Experience Reporting Paragraph for accuracy.
-Becton-Dickinson syringe requirement for vaccine administration was removed.
-Dose package description was added.
-Selected paragraphs were rearranged for organizational clarity.

Protocol Amendment 006-04
An amendment was made to V260 Protocol 006-03, “Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Reassortant Rotavirus Vaccine in Healthy Infants.” This amendment changed 006-03 to remove the HEXAVAC concomitant use subset, add the detailed safety subset, clarify the definition of the end of study, and to incorporate the sample reduction plan for the assessment of immunogenicity.
Other changes made in this amendment included:
• The unit of measurement for the doses of the 5 serotypes of rotavirus in RotaTeq™ was changed to Infectious Units (IU).
• The definition of the end of study was clarified throughout the document.
• The immunogenicity analysis of the concomitant use of RotaTeq™ and HEXAVAC™ was removed from the protocol. However, a safety analysis of the concomitant use of RotaTeq™ and combination hexavalent pediatric vaccines was added to the protocol.
• Detailed safety subset was added to the protocol.
• Minor changes were made to the flow charts for the study.
• The sponsor contact information for U.S. sites was updated.
• “Epidemiology, Clinical Characteristics, and Public Health Significance of Rotavirus Disease” section was updated with most recent information available in the Clinical Investigator Brochure CIB) dated 03-Jan-2003.
• “Merck’s Rotavirus Vaccine Program” section was updated with most recent data available in CIB dated 03-Jan-2003.
• The expansion to other countries was discussed.
• Secondary objectives were changed to eliminate immunogenicity testing of fecal rotavirus-specific and total IgA. A secondary objective and hypothesis was added to assess the safety of RotaTeq™ when administered concomitantly with combination hexavalent pediatric vaccines.
• A tertiary objective was added to summarize fecal-shedding of vaccine-strain rotavirus in medically compromised subjects.
• Documentation requirement for Prevnar™ expiration date (if supplied by site) was added.
• The number of subjects in whom stool samples for vaccine shedding was collected was changed.

• Evaluation of stool samples for Immunogenicity was removed.
• “Serum Samples for “Efficacy” Subjects” section was clarified.
• Clinical material accountability was clarified.
• Definition of rotavirus season was clarified.
• Evaluation of antibody responses to concomitant vaccines was clarified.
• Overdose was defined as an excess of 1 dose per 12 days.

Medical Officer comments:
FDA was appropriately informed of changes to protocol 006. The change to utilize PCR for serotyping of rotavirus in stool specimens may enhance the diagnostic precision in defining the endpoint. Please see the FDA product review.

8.1.1.1.6 Surveillance and Monitoring

Active and passive efficacy and safety monitoring was utilized during study 006. The parent had to record parameters related to temperature, vomiting, diarrhea and irritability and whether an adverse event or acute gastroenteritis had occurred. However, this passive monitoring was supplemented with active monitoring that included contacting the subjects by phone or letter at day 7 and day 43 post vaccination. Regarding whether intussusception had occurred, the subject was contacted every 42 days until day 365 after vaccine dose #1 or the study site’s end-of-study date. **Case report forms were completed on subjects but only those with discontinuations or serious adverse events were included in the submission.** For each case of acute gastroenteritis, the study monitor completed a workbook which had additional information regarding stool specimen testing, health care utilization and whether the subject was dehydrated and re-hydrated**.** Efficacy and safety endpoints/parameters will be discussed briefly in order to demonstrate what types of monitoring was required during the phase 3 clinical studies.

Monitoring for Efficacy (taken from the Applicant’s BLA)

Primary Efficacy Endpoint
The biologic efficacy of the vaccine against any rotavirus disease regardless of severity was evaluated in a subset of subjects. These subjects were enrolled at pre-selected sites. In this subset, efficacy was evaluated among subjects who were receiving RotaTeq™ on at least 2 different schedules (e.g., 2, 3, 4 months in Finland and 2, 4, 6 months in the U. S.), and among subjects who were concomitantly receiving other childhood vaccinations. The efficacy of the vaccine when given concomitantly with prescribed childhood vaccines was evaluated in the U.S. efficacy subset. The efficacy of RotaTeq™ when given alone was not evaluated because of ethical concerns about delaying administration of childhood vaccinations in these young infants, and the preference to initiate RotaTeq™ by 6 to 12 weeks of age before they are old enough to be in the window (5-9 months of age) when an infant is more likely to develop natural intussusception.

Case Definition for Rotavirus Disease
For the subset of subjects evaluated for the primary efficacy endpoint, the full case definition for rotavirus disease was that a subject must meet both of the following clinical and laboratory criteria:
(1) 3 or more watery or looser-than normal stools within a 24-hour period and/or forceful vomiting (Acute Gastroenteritis Episode [AGE]);
(2) Rotavirus must be detected in a stool specimen taken within 14 days after the onset of symptoms. (Only G1, G2, G3, G4 specific rotavirus cases occurring ≥14 days after the third dose of RotaTeq™/placebo would be included in the primary efficacy analysis.)

The clinical criteria that were used to determine whether a stool specimen should be collected for rotavirus testing were: the occurrence of 3 or more watery or looser-than-normal stools, or one watery stool, within a 24-hour period and/or forceful vomiting. Stool samples were collected for all AGEs occurring anytime after the receipt of the first dose until the end of the trial.

In this subset of subjects, if an AGE occurred at any time after receipt of Dose 1, the following steps should have been taken:
a) The parent/guardian should contact the study coordinator immediately.
b) Two stool samples should be obtained as soon as possible after onset of gastrointestinal symptoms. Optimally, the first sample should be obtained within 24 hours of onset of symptoms and the second should be obtained 24 hours later. At the latest, all samples should have been obtained within 14 days after the onset of symptoms. c) The parent/guardian should complete the Pediatric Acute Gastroenteritis Episode Report Card (AGRC), recording the subject's symptoms daily until symptoms have completely resolved. Symptoms and signs to be recorded by the parent included temperature, vomiting, diararhea and behavior (irritability). AGEs were expected to occur naturally during the course of this study. The AGEs could be the result of rotavirus natural infection or of another enteric pathogen.

An **Efficacy Endpoint Adjudication Committee** reviewed episodes of vomiting and/or diarrhea to determine if they met the clinical definition of an AGE as defined in the protocol. They assigned a clinical score for the severity of the episode using the system outlined in Table 10. This blinded committee was comprised of 3 physicians with expertise in rotavirus disease and pediatric gastroenterology, none of whom were otherwise involved in the conduct of the protocol. A standard operating procedure (SOP) was developed to guide the Efficacy Endpoint Adjudication Committee. This SOP included information about: the rationale for the adjudication activities; the adjudication rules and clinical classification criteria; the conflict resolution procedures; and the procedures for data flow from the onset of the event to adjudication.

Defining the Rotavirus Season
The rotavirus season varied according to the location of the site. For those study sites which were located in the Northern United States and Finland, the onset and end of the rotavirus season was designated as 01-Dec and 30-Jun of each year of the study, respectively. For other sites and countries, the rotavirus season may begin earlier and that date would be prospectively determined using historical epidemiologic data about
rotavirus in that area. Subjects were followed for efficacy beginning immediately after the first dose through all rotavirus seasons until the end of the trial. The primary efficacy analysis considered only those cases that occur after the 14 days of follow-up Postdose 3 and through the first rotavirus season that begins after the 14 days of follow-up Postdose 3. Intent-to-treat cases, which included cases that occured at any time during the study, were also evaluated.

Stool Sample Collection/Testing for Evaluation Primary Efficacy Endpoint
Two stool samples were collected, one immediately after onset of symptoms and another 24 hours later. All samples were collected within 14 days after onset of symptoms. Stools were sent to ---------- laboratory in ----------
and screened for rotavirus antigen by EIA. If a sample was rotavirus-positive by EIA, the sample was divided into 2 aliquots. One aliquot was sent to the Merck Research Laboratories for serotyping by PCR. PCR was used for serotyping after the assay was validated.

Medical Officer comments:
Please see the product review regarding validation of assays used.

The second aliquot was sent to ---------- laboratory in ----------
---------- and tested for vaccine virus by plaque assay and electropherotyping. If the electropherotyping result suggested a recombinant, the strain was sequenced for further characterization. For the primary efficacy analysis, the AGE was considered a “case” of rotavirus only when wild-type viruses of the same serotype contained in the vaccine were detected in 1 of the 2 acute samples. An aliquot of stool was also sent from ---------- to ----------
laboratory in ------- where PCR was used to help determine/identify other causal agents of the AGE such as Norwalk-like viruses, Sapporo-like viruses, astroviruses and enteric adenoviruses**.** In addition, health care providers were encouraged to evaluate stools for other enteric pathogens based on their clinical judgment as per routine standard of care.

Safety monitoring and Adverse Event Reporting
All parents were given a Pediatric Vaccination Report Card that was utilized by the parent to record temperatures, diarrhea, vomiting and “other complaints or illnesses” for 7 days post vaccination. See Table 8 below regarding the study procedures followed for the large safety cohort of over 70,000 children in the phase 3 studies. Table 9 outlines the procedures followed for the Detailed Safety Cohort . Concomitant vaccinations and medications were captured on the report

card as well. The Detailed Safety Cohort recorded these same parameters post-vaccination but were followed for all adverse events during the 42 days after each dose of vaccine.

Solicited adverse events included diarrhea, vomiting and other complaints or illnesses. Parents were asked to grade adverse events as mild (awareness of symptom but easily tolerated) moderate (definitely acting like something is wrong) or severe (extremely distressed or unable to do the usual activities).

For each case of gastroenteritis the following data were collected in the Acute Gastroenteritis Case Evaluation (AGE) Workbook: temperature and method used, number of stools (normal, loose, watery), number of vomiting episodes, behavior (normal, irritable/less playful , lethargic listless) and “other symptoms”.

Medical Officer comments:
Information regarding hematochezia was not solicited on the Pediatric Vaccine Report Card or in the Acute Gastroenteritis (AGE) workbook.

Table 8 Study Procedures for Patients in Safety Cohort*

Dose	Time Relative to Each Dose	Clinical Procedures	Samples
Dose 1 (Day 1)	Day 1	Determined eligibility/obtained consent. Dosed with RotaTeq™ or placebo. Reviewed instructions with parent/legal guardian.	Stool sample for health outcomes†(if applicable) For intussusception, special instructions were provided (if applicable)
	Day 7 Day 14 Day 42	Contacted parent/legal guardian to inquire about the following: 1. Health outcomes for rotavirus gastroenteritis 2. Intussusception 3. Serious adverse experiences	
Dose 2 (Days 28 to 70 PD1)	Day 1	Dosed with RotaTeq™ or placebo. Reviewed instructions with parent/legal guardian.	Stool sample for health outcomes†(if applicable) For intussusception, special instructions were provided (if applicable)
	Day 7 Day 14 Day 42	Contacted parent/legal guardian to inquire about the following: 1. Health outcomes for rotavirus gastroenteritis 2. Intussusception 3. Serious adverse experiences	
Dose 3 (Days 28 to 70 PD2)	Day 1	Dosed with RotaTeq™ or placebo. Reviewed instructions with parent/legal guardian.	Stool sample for health outcomes†(if applicable) For intussusception, special instructions were provided (if applicable)
	Day 7 Day 14 Day 42	Contacted parent/legal guardian to inquire about the following: 1. Health outcomes for rotavirus gastroenteritis 2. Intussusception 3. Serious adverse experiences	

Day 43 following the final vaccination to 365 days PD1 or until the study site's end-of-study date, whichever came first.	Contacted parent/legal guardian approximately every 6 weeks for intussusception and health outcomes for rotavirus gastroenteritis.	Stool sample for health outcomes†(if applicable) For intussusception, special instructions were provided (if applicable)
Day 366 PD1 to the end of study.	Letters may have been sent to parent/legal guardian approximately every 6 months for updates about the study.	
†For the Safety Cohort, evaluation of health outcomes included evaluation of hospitalizations and emergency department visits (or equivalent in countries outside the United States). PD = Postdose.		

*From the Applicant p.2437 Clinical Study Report (CSR) Protocol 006

Table 9 Study Procedures for Patients in Detailed Safety Cohort*

Dose	Time Relative to Each Dose	Clinical Procedures1	Samples
Dose 1 (Day 1)	Day 1	Determine eligibility/obtain consent. Dose with RotaTeq™/placebo.2 Review instructions with parents. Hand out Vaccination Report Card (VRC), thermometer, and instructions for use.	Blood sample ~2 to 3 mL **(Taiwan sites only)**. 3
	Day 7 Day 14 Day 42	Contact parent/guardian to inquire about the following: 1. Health Care Contact1for gastroenteritis (stomach illness with vomiting and/or diarrhea) 2. Intussusception 3. SAEs	For health care contacts for gastroenteritis, a stool sample is requested. For intussusception, specific instructions will be provided.
Day 14	DDay/d 14		
Day 42			
Dose 2 (Days 28 to 70 PD1)	Day 1	Dose with RotaTeq™/placebo.2 Review instructions with parents. Obtain and review VRC from Visit 1. Hand out new VRC.	
	Day 7 Day 14 Day 42	Contact parent/guardian to inquire about the following: 1. Health Care Contact1for gastroenteritis (stomach illness with vomiting and/or diarrhea) 2. Intussusception 3. SAEs	For health care contacts for gastroenteritis, a stool sample is requested. For intussusception, specific instructions will be provided.
Day 14	Day 14		
Day 42	Da		

Dose 3 (Days 28 to 70 PD2)	Day 1	Dose with RotaTeq™/placebo.2 Review instructions with parents. Obtain and review VRC from Visit 2. Hand out new VRC	
	Day 7 Day 14 Day 21	Contact parent/guardian to inquire about the following: 1. Health Care Contact1for gastroenteritis (stomach illness with vomiting and/or diarrhea) 2. Intussusception 3. SAEs On Day 42 (+1), obtain VRC and review with parent.	For health care contacts for gastroenteritis, a stool sample is requested. IT instructions provided.
Day 14	Day Day 42(+1) 14		
	Day 42(+1)		On approximately Day 42, collect blood sample ~2 to 3 mL **(Taiwan sites only)**. 3
Day 43 PD3 to 365 days PD1 or until the site's end-of-study date, whichever comes first.		Contact parent/guardian approximately every 6 weeks and ask about intussusception and Health Care Contacts1for gastroenteritis. Parent/guardian to contact study personnel immediately if subject has intussusception and/or Health Care Contacts1for gastroenteritis.	For health care contacts for gastroenteritis, a stool sample is requested. For intussusception, specific instructions will be provided.
Day 366 PD1 to the end of study.		Letters may be sent to parent/guardian approximately every 6 months to update them about the study.	
1 For "Detailed Safety Subjects," evaluation of health care contacts will include evaluation of hospital admission or outpatient treatment in an emergency department, Finnish health care center, or equivalent center in other countries. 2 Among detailed safety subjects in Germany, RotaTeq™/placebo will be given concomitantly with either HEXAVAC™ or INFANRIX HEXA™ on the routine childhood immunization schedule. 3 For sites in Taiwan. PD = Postdose.			

From the Applicant pl. 2438 CSR 006.

After the subject's final vaccination and 42 days of safety follow-up, the parent or legal guardian was contacted at 6-week intervals until Day 365 from vaccination Visit 1 or until the study site's end-of-study date, whichever came first.

The study design included rigorous active safety surveillance for intussusception. The parents/legal guardians of all subjects were contacted by telephone or home visit on approximately Days 7, 14, and 42 after each vaccination with RotaTeq™ or placebo and asked about all serious adverse experiences including intussusception. After the subject's final vaccination and 42 days of safety follow-up, the parent/legal guardian was contacted at 6-week intervals until Day 365 from vaccination Visit 1 or until the study site's end-of study date, whichever came first. Because each study site was given a pre-specified end-of-study date, not all subjects were followed for 365 days after vaccination Visit 1. All subjects needed to be followed for at least 42 days after each vaccination and a study site's end-of-study date could not be prior to this time. If a subject was lost to follow-up, all attempts were made by the study site to contact the parent/legal guardian.

Medical Officer comments:
At 42 days post vaccine dose # 3, the Applicant had follow-up data on 91% of the subjects in the placebo and 91% of subjects in the RotaTeq™ arm (see Table 10 below). The follow-up time at 42 days post vaccine dose #1 and #2 was 46 to 50% because some of the subjects were on a 2,3,4 month immunization schedule with 30 days between doses and thus they would have received a second dose already at 42 days. Please see Section 8.1.1.2.3 for additional discussion regarding follow-up for Intussusception.

Table 10 Number of Subjects in REST with follow-up for Intussusception*

Number of Subjects Vaccinated (n = 34788)		Follow-up Time for Intussusception in relationship to vaccine dose number and time (days) post vaccine dose	Number of Subjects Vaccinated (n = 34837)	
Placebo (n)	Placebo %		RotaTeq™(n)	RotaTeq %
34768	99.9	7 days post dose #1	34821	>99.9
34740	99.9	14 days post dose #1	34794	99.9
17502	50.3	42 days post dose #1	17573	50.4
32745	94.1	7 days post dose #2	32773	94.1
32733	94.1	14 days post dose #2	32757	94.0
15856	45.6	42 days post dose #2	15838	45.5
31810	91.4	7 days post dose #3	31911	91.6
31802	91.4	14 days post dose #3	31903	91.6
31555	90.7	42 days post dose #3	31631	90.8

*Based on safety update (July 25, 2005) and excludes cross treated subjects. Follow-up for a time period ends when a subject is vaccinated with a subsequent dose and follow-up then begins for the next period post that subsequent vaccine dose. This was the Applicant's analysis.

The phase 3 trials used a **data safety monitoring board (DSMB)** which was composed of individuals who are experts in operational, medical, and biostatistical aspects of clinical trial. No member of the DSMB could participate in this study as an investigator or be involved in any way in the conduct of the study. The DSMB considered all serious adverse events, but specifically determined the relevance of each case of intussusception as it accrued for the overall safety of the vaccine, using both clinical judgment and pre-specified statistical criteria as guidelines, and it was responsible for reporting to the Merck Senior Management Committee.

The Data and Safety Monitoring Board (DSMB) unblinded the treatment arm of positively-adjudicated (confirmed) cases and made recommendations for continuing the study based on predefined safety boundaries as well as clinical judgment. These safety boundaries were designed such that the study would be stopped early if the relative risk of intussusception (IT) in any of the 2 overlapping day ranges (1 to 7 and 1 to 42 days after any vaccination) was statistically significantly increased among recipients of RotaTeq™ versus placebo recipients.

Safety Endpoint Adjudication Committee (SEAC)

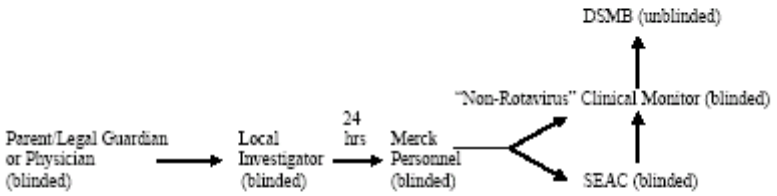
A Safety Endpoint Adjudication Committee (SEAC) was employed which was composed of three physicians with expertise in pediatric surgery, pediatric radiology and the clinical diagnosis of intussusception. Adjudication of suspected cases of intussusception was performed in a blinded manner using a pre-specified case definition and adjudication guidelines described in a standard operating procedure (SOP). Each member of the committee performed an individual adjudication of each case of intussusception as it occurred during the trial. The full committee convened to perform the final adjudication for each case. In the event of a disagreement, the members voted and a majority ruling was made as to whether the case fulfilled the pre-specified criteria for a diagnosis of intussusception. All adjudications by the committee were final.

Investigators blinded to treatment assignment performed surveillance for intussusception cases as described in the protocols. In the event the investigator identified a potential intussusception case, he/she reported the case to Merck and Co., Inc. as a Serious Adverse Experience (SAE) within 24 hours. The investigator assembled specific documentation including medical records, radiographic films, and any other supporting documents and submitted them to the blinded Merck Rotavirus Vaccine Program Clinical Monitor. The Clinical Monitor or a designated Medical Program Clinical Specialist (MPCS) reviewed the documentation for completeness, requested any missing documentation, and resolved with the investigator any clinical questions concerning the case. Following review, the Clinical Monitor or MPCS assembled an intussusception package for adjudication with information about the case, made a copy for his/her files, and sent the package to the members of the blinded SEAC. Simultaneously, the Rotavirus Vaccine Program Clinical Monitor or MPCS notified a designated, blinded Merck Clinical Monitor (BCM) who was not involved with the Rotavirus Vaccine Program. This designated BCM alerted the independent, unblinded Data and Safety Monitoring Board (DSMB) about the potential intussusception case. The SEAC adjudicated all cases of intussusception and determined whether or not, in their clinical judgment, the cases were vaccine-related. For a case of intussusception caused by an obvious anatomic lead point, the SEAC could decide that it was, or was not vaccine-related. Regardless of the decision about vaccine-relatedness, all cases of intussusception were reported to the DSMB. The SEAC adjudicated the potential cases of intussusception and the results were communicated to the DSMB.

The sequence of decision-making is illustrated in the following figure (Figure 2.7.4: 2) which was taken from the Applicant’s Summary of Clinical Safety.

Figure 2.7.4: 2

Reporting Process for Potential Cases of Intussusception



SEAC = Safety Endpoint Adjudication Committee.
DSMB = Data and Safety Monitoring Board.
Note: For the parent/legal guardian, investigator, and Merck personnel, blinding refers to treatment arm assignment and the final adjudication results. For the SEAC and the Non-Rotavirus Clinical Monitor, blinding refers to treatment arm assignment.

[Ref. 5.3.5.1: P006]

8.1.1.1.6 Statistical Considerations

Statistical Considerations: Efficacy

The Applicant combines the data from studies 006 and 007 for their efficacy analyses. However, the FDA statistician analyzed the study 006 and study 007 results separately, in part, because the primary null hypothesis for each study was different.

Efficacy analyses include a factor of time, i.e. person-days of follow-up. The FDA statistician and clinical reviewer sought additional details regarding differences in the definition of "episode" versus "acute gastroenteritis episode" (AGE). The choice regarding whether to use the "episode" or "AGE" for the "initial day of illness" impacted the calculation of follow-up time.

The Applicant performed efficacy analyses and counted follow-up time using the first day of the "episode" and the FDA used the first day that a child actually met the definition of an acute gastroenteritis episode "AGE". The comments below will outline the hierarchy of definitions that were used to describe different aspects of illness due to rotavirus, i.e. "episode" vs "AGE" vs "case". In the protocol, the FDA statistical reviewer was unable to find the definition of "episode" and therefore FDA efficacy analyses utilized the date of an "acute gastroenteritis episode" for the follow-up time efficacy calculations.

Medical Officer comments:
Please refer to the FDA statistical review for additional details.

The following hypothetical scenario may help to explain the issues related to differences in calculating follow-up time in the efficacy analysis. A child may initially begin their rotavirus gastroenteritis illness on day 1 with one

loose stool. On day 2 the symptoms progress and the child has 2 loose stools that would fulfill the Applicant's definition of an "episode" (see definition below) but it is not yet an "acute gastroenteritis episode" or "AGE") see definition below. By day 3 the illness progresses and the child now has 3 loose stools or has forceful vomiting and now meets the specific definition of an"AGE" but, to be classified as a "case", the child must have an "AGE" corrorborated with laboratory data confirming that the symptom complex was due to strains of rotavirus for which the vaccine should have been protective.

The Applicant states that rotavirus gastroenteritis cases consist of all subjects with one or more "episodes" classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case. The word "episode" was not defined either in the protocol or in the data analysis plan submitted prior to the BLA submission. Through several telephone communications with the Applicant, the FDA statistical reviewer learned that an "episode" was defined as one of the following criteria: (1) 2 watery or loose stools, (2) vomiting, (3) rectal temperature ≥ 38.1 C, (4) irritable or lethargic behavior, or (5) seizure in a 24-hour period. Again, the aforesaid description of an "episode" is different than the definition of an "acute gastroenteritis episode" (AGE) which is also different than a "case" (see definition below).

The case definition for rotavirus disease that was used for the efficacy analysis required that a subject must meet both the following clinical and laboratory criteria:
(1) 3 or more watery or looser-than normal stools within a 24-hour period and/or forceful vomiting (Acute Gastroenteritis Episode [AGE]);
(2) Rotavirus must be detected in a stool specimen taken within 14 days after the onset of symptoms. (Only G1, G2, G3, G4 specific rotavirus cases occurring ≥14 days after the third dose of RotaTeq™/placebo would be included in the primary efficacy analysis.)

The following is the Applicant's explanation regarding the difference between an "episode" and an "acute gastroenteritis episode" or AGE.
-The determination of an episode start date is not explicitly defined in any study documentation**,** but it is based on the AGE Clinical Scoring System that was documented in the protocols.
-The definition of a symptomatic episode corresponds to the minimum criteria of the AGE Clinical Scoring System (see Table 11 below). Specifically, if a subject has at least 2 watery or looser-than-normal stools OR at least one vomiting event OR at least one temperature of at least 38.1 OR is irritable, lethargic/listless, OR has a seizure on a given day, then that subject has a symptomatic episode. If there is a 3-day absence of these symptoms and they re-occur, then the episodes are considered different from each other (this is documented in the Data Analysis Plan).

-The definition of an acute gastroenteritis episode “AGE” is at least 3 watery or looser-than-normal stools OR at least one vomiting event on a given day. Therefore, a symptomatic episode can either be an AGE or not. In the case of the former, the episode does not necessarily start on the day the AGE starts. For example, if 39^0C and irritability are reported on Day 1 of an episode, and 2 bouts of vomiting and temperature of 38.5^0C, and irritability are reported on Day 2 , then the episode starts on Day 1 and the AGE starts on Day 2. But, the symptoms that occurred on Day 1 are considered to be associated with those on Day 2. Therefore, when considering this case, the episode starts on Day 1. Furthermore, when scoring the episode, it is important to incorporate the symptoms that occurred on Day 1, not just those that occurred on Day 2 and beyond. With any illness, it is uncommon for all symptoms to start simultaneously. Typically an illness begins with a prodrome followed by a full manifestation. For example, rotavirus gastroenteritis typically begins with low grade fever followed by onset of vomiting and then diarrhea. If these symptoms manifest on separate days, a clinician would not consider them to be separate illnesses, but rather manifestations of the same illness.

Table 11 Clinical Scoring for Acute Gastroenteritis (AGE) *

Score to be Summed According to Evaluation of Symptoms and Durations (See Below)	1	2	3
Diarrhea No. of stools/day† Duration in days‡	 2 to 4 1 to 4	 5 to 7 5 to 7	 ≥ 8 ≥ 8
Vomiting No. of emeses/day§ Duration in days‡	 1 to 3 2	 4 to 6 3 to 5	 ≥ 7 ≥ 6
Rectal Temperature Degrees in Celsius% Duration in days‡	 38.1 to 38.2 1 to 2	 38.3 to 38.7 3 to 4	 ≥ 38.8 ≥ 5
Behavioral Symptoms Description¶ Duration in days‡	 Irritable/less playful 1 to 2	 Lethargic/listless 3 to 4	 Seizure ≥ 5

† Maximum number of watery or looser-than-normal stools/day on any given day over the course of the episode.

‡ Number of days on which child had a symptom of any score. **Days do not have to be consecutive.**

§ Maximum number of times child vomited on any given day over the course of the episode.

% Highest temperature over the course of the episode which is equal or **greater than 38°C (100.4°F), rectal.**

¶ If a child is reported to have two or more symptoms, only the one with the highest score is counted.

*From the Applicant CSR 006.

The Applicant based the primary efficacy estimate on the definition of 'episodes' instead of the AGE. The FDA reviewer performed a separate analysis by using the date of the first clinical case (AGE) as the true date of a case in calculating the follow-up time. The results are presented in Table 12 below. There were 43 subjects with slightly different onset dates based on the initial date of AGE compared to those using the initial date of 'episode' definition. However, the difference in the two efficacy estimates occurs after the third decimal place. Therefore, the FDA statistical reviewer considered it acceptable to use the 'episode' definition for the efficacy estimate. When comparing Table 1 (see Executive Summary and it is also depicted below) and Table 12**,** the number of rotavirus gastroenteritis cases in each study arm is the same, the person days of follow-up in each study arm is different but the efficacy estimates are similar.

Table 12. Efficacy in the Per Protocol (PP) Population for Study 006(REST)*

Study 006 (REST)	RotaTeq™	Placebo
Subjects vaccinated	2834	2839
Subjects in efficacy analysis	2207	2305
Person Days of follow-up	**623885**	**622333**
Rotavirus gastroenteritis cases caused by G1, G2, G3 or -G4 serotype	82	315
Efficacy estimate (%) and 95% confidence interval	74.0 (66.8, 79.9)	

*FDA analysis with efficacy estimate based on the first day of a confirmed rotavirus gastroenteritis case instead of 'episode'.

Study 006 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 serotypes 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 serotypes in the vaccine through the first rotavirus season post-vaccination was 74% (95% CI: 67%, 79%) (see Table 1 below which was taken from the Executive Summary):

Table 1. Efficacy in the Per Protocol (PP) Population for Study 006 (REST)*

Study 006 (REST)	**RotaTeq™**	**Placebo**
Subjects vaccinated	2834	2839
Subjects in efficacy analysis	2207	2305
Person Days of follow-up	**623880**	**622388**
Rotavirus gastroenteritis cases caused by G1, G2, G3 or -G4 serotype	82	315
Efficacy estimate (%) and 95% confidence interval	74.0 (66.8, 79.9)	

FDA analysis*

Additional Efficacy Analyses for Study 006 (REST):
Intent-to-treat analyses (ITT) were performed in order to assess the impact of RotaTeq™ on rotavirus antigen-positive diarrheal disease due to vaccine and non-vaccine rotavirus serotypes in all subjects who received at least one dose of vaccine. In these intent-to-treat analyses, the per protocol case definition was also used except that cases were counted starting with the day of the first vaccination rather than counting 14 days after the third vaccination as was done for the per protocol (PP) analyses.

Table 13 below shows 49.7% efficacy for RotaTeq™ in the intent-to-treat population (ITT). Table 12 includes only subjects with no vaccine-strain in the stool sample.

Table 13. Efficacy in the Intent-to-Treat Population (ITT)* in Study 006 (REST), Rotavirus Antigen positive disease, all serotypes**

Study 006 (REST)	RotaTeq™		Placebo	
Subjects vaccinated	2834		2839	
EIA positive, vaccine-strain negative, all serotypes	Merck 202	FDA **198**	Merck 400	FDA 395
Efficacy estimate (%) and 95% confidence interval	49.7 (40.3, 57.7)			

*Intent-to-treat includes rotavirus disease cases occurring after the first dose.
**This FDA analysis does not include cases due to the vaccine strains.

In Study 006 (REST), efficacy was also evaluated in the intent-to-treat (ITT) population which included all rotavirus disease cases occurring after the first dose. The term “all rotavirus disease” includes rotavirus EIA antigen positive disease using both vaccine strain negative and vaccine strain positive cases of all serotypes. Results of the FDA analysis for “all rotavirus disease” demonstrated there were 207 cases in 2834 subjects vaccinated with RotaTeq® when compared to 395 cases in 2839 subjectst who received placebo. This FDA analysis that includes “all rotavirus serotypes” regardless of whether the case was due to a vaccine strain or not demonstrated that 9 additional cases of rotavirus disease (198 + 9 = 207) were identified and these cases all occurred in the RotaTeq™ recipients.

Statistical Considerations: Safety
The statistical analysis for intussusception in the BLA for did not differ from the statistical analysis described in the clinical protocol. The following sections are directly taken or paraphrased from the BLA.

Study 006 (REST) employed a group-sequential design. Initially, 60,000 subjects were to be enrolled, receive all 3 vaccinations of RotaTeq™ or placebo, and complete 42 days of safety follow-up after the final vaccination. After the first 60,000 subjects completed the safety follow-up after the final vaccination, the DSMB would unblind the treatment arm of positively-adjudicated intussusception cases (as determined by the SEAC) and assess whether the predefined

statistical criteria for the primary safety hypothesis were met. If the criteria were not met with 60,000 subjects, then an additional group of 10,000 subjects would be enrolled. This process of enrolling additional groups of 10,000 subjects would continue until the predefined statistical criteria were met or until 100,000 subjects would be enrolled.

Clinical Study Timeline

-On 12-Jan-2001, the study was initiated upon randomization of the first subject.
-On 27-Nov-2003, the 60,000th subject was randomized in the study.
-On 19-May- 2004 after the first 60,000 subjects had completed at least 42 days of safety follow-up after the final vaccination, the DSMB met to formally evaluate the statistical criteria for the primary safety hypothesis including the relative risk of intussusception and the corresponding 95% confidence interval (per the Data Analysis Plan (DAP) this was considered to be stage 1 review). The DSMB also reviewed all serious adverse experiences. At this meeting, the DSMB recommended that enrollment in the study continue to 70,000 subjects based on the fact that the pre-specified statistical criteria to satisfy the primary safety hypothesis with respect to intussusception was not met.
-On 30-Sep-2004, the enrollment of 70,000 subjects was completed. On 06-Oct-2004, enrollment was temporarily placed on hold until the DSMB could formally evaluate the current safety data.
-On 10-Nov-2004**,** the DSMB met again to formally evaluate the statistical criteria for the primary safety hypothesis including the relative risk of intussusception and the corresponding 95% confidence interval. The DSMB also reviewed all serious adverse experiences. After review of the most recent safety data, the DSMB recommended to the blinded Merck Senior Management Committee that enrollment in the study could be stopped and that the study had satisfied the criteria for the primary safety hypothesis with respect to intussusception. The DSMB also recommended that all subjects continue to receive the full vaccination regimen and the required safety follow-up. As of the DSMB meeting, new enrollment officially stopped and subjects who were in the dosing phase of the study continued to receive study vaccinations and at least 42 days of safety follow-up after the final vaccination. As of 06-Oct-2004, a total of 70,301 subjects were randomized in this study according to the Interactive Voice Response System (IVRS), the automated system used for randomizing subjects. However, the data included in the primary database and in this report reflect the data that the DSMB evaluated when they made their recommendation to stop enrollment (69,274 randomized subjects). The cutoff date for having all clinical and laboratory data from the worksheets in-house was 10-Nov-2004 (which coincided with the DSMB meetings as described above). The cutoff date for having all data discrepancies resolved was 13-Dec-2004.
-The clinical database was frozen on 23-Dec-2004. All clinical and laboratory data which included data, as of the 10-Nov-2004 DSMB meeting, were reviewed by the Clinical development team through 13-Dec-2004 and were included in the CSR. Data for study visits that were reviewed after 13-Dec-2004 were not included in the CSR. These study visits included data for vaccination Visit 1, Visit

2 and Visit 3 and/or the safety follow-up period. Study visits that were reviewed after 13-Dec-2004 were eligible to be included in the Safety Update Report (SUR) for all subjects in the study who had at least 42 days of safety follow-up following their last vaccination. In addition, there was another meeting with the DSMB, after the last subject had received safety follow-up in the study to review any additional positively-adjudicated intussusception cases, to review serious adverse experiences and to review other analyses from the study.

Study sites were closed to enrollment on a rolling basis because of the long duration of the study (>4 years) and logistics of managing a multiple study sites. All study sites were given a pre-specified end-of-study date. Some study sites may have reached their end-of-study date prior to the end of the extended safety follow-up period (Day 365 safety follow-up from vaccination Visit 1). However, all study sites were to complete safety follow-up for all subjects for at least 42 days following the final vaccination and the end-of-study date could not be prior to this time (see page 156 CSR 006).

<u>From the Applicant's Data Analysis Plan (P.4545) of Clinical Study 006 Report</u>
Developing the safety boundaries was challenging because of the extremely low background rate of intussusception that was expected. These trials had been planned assuming a rate of intussusception of 1 per 2000 person-years, which equaled approximately 1 per 100,000 person-weeks. This meant that if there was no increased risk of intussusception caused by the vaccine, then very few cases would be observed during the defined day ranges. The boundaries were determined so that the lower limit of the 95% confidence interval estimate of the relative risk at each boundary point was greater than 1, with appropriate adjustments for differential amounts of follow-up between the vaccine and placebo groups. This corresponds to a statistical test that rejects a null hypothesis of RR=1 against an alternative hypothesis that the RR is >1 at the one-sided 0.025 level. The boundaries are illustrated in Figures 1 and 2. Note that in Figure 1, which compares vaccine cases occurring within 7 days of vaccination to placebo cases occurring within the primary follow-up period of 42 days of vaccination, the boundary has been adjusted by a factor of k = 21/ (102 + 21) = 0.171. The 21 represents 7 days of follow-up after each of the 3 doses, and the 102 represents the total amount of primary follow-up as calculated by assuming 30 days of follow-up after doses 1 and 2, and 42 days of follow-up after dose 3. Section 8.1.1.2.3 discusses intussuception and includes a Timeline and Table 39 which help to illustrate why the adjustment factor "k" was needed.

Figure 1
Safety Monitoring

Critical Boundary for Stopping Study for Safety
Days 1 – 7 Postdose Vaccine Cases

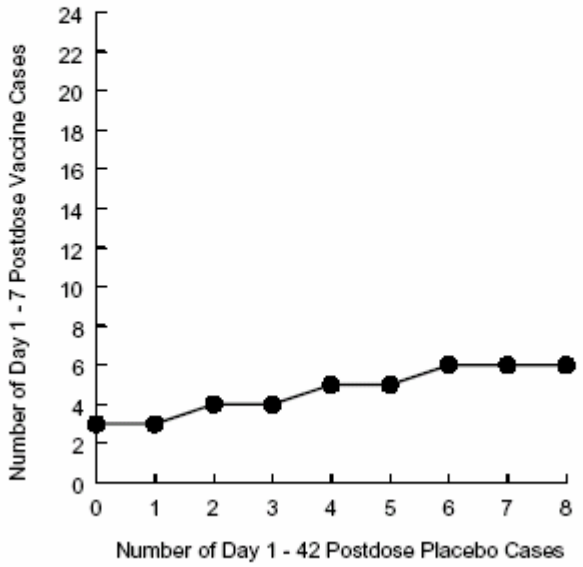
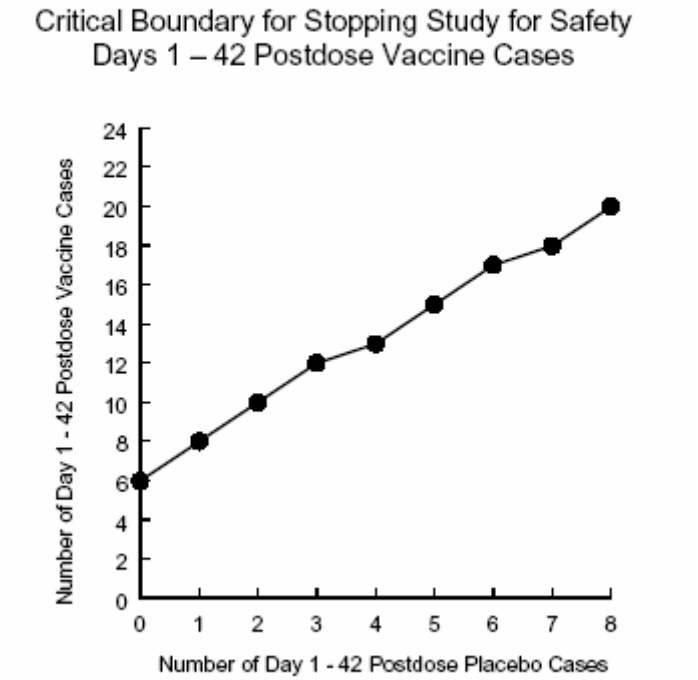


Figure 2
Safety Monitoring



End of Study Criterion (from p. 4604 of the study 006 CSR)
The trial employed a group-sequential design. Initially, 60,000 subjects were enrolled. If a decision regarding the safety of RotaTeq™ with respect to intussusception according to predefined statistical criteria could not be made after these 60,000 subjects, then additional subjects would be enrolled.
The predefined statistical criterion referred to an acceptance region, which consisted of all case splits, (Vaccine:Placebo), where V represented the number of cases in the group that received RotaTeq™ and P represented the number of cases in the group that received Placebo, such that the upper bound on the exact 95% confidence interval for relative risk within 42 days of any dose was ≤10, and such that no safety monitoring boundary was reached. Exact confidence intervals for this purpose were computed based on the procedure described above. Examples of case splits that satisfied the end-of-study criterion are given in Table 14 below. Immediately following Table 14 is the formula used to calculate the relative risk of intussusception.

Table 14 Case Split Examples that Satisfy the End-of-Study Criterion*

Total Number of Observed Cases	Satisfactory Case Splits (V:P)	Relative Risk (RR)	Upper Bound on RR
0	None	N/A	N/A
1	None	N/A	N/A
2	0:2	0.0	5.3
3	1:2	0.5	9.6
	0:3	0.0	2.4
4	1:3	0.3	4.2
	0:4	0.0	1.5
5	2:3	0.7	5.8
	1:4	0.3	2.5
	0:5	0.0	1.1
6	3:3	1.0	7.5
	2:4	0.5	3.5
	1:5	0.2	1.8
	0:6	0.0	0.8
7	4:3	1.3	9.1
	3:4	0.8	4.4
	2:5	0.4	2.4
	1:6	0.2	1.4
	0:7	0.0	0.7
8	4:4	1.0	5.4
	3:5	0.6	3.1
	2:6	0.3	1.9
	1:7	0.1	1.1
	0:8	0.0	0.6

*From the Applicant CSR 006 (REST)

End-of-Study Analysis: (From the Applicant, p. 4550 CSR 006)
The End-of-Study Analysis was performed by the Clinical Biostatistics Department of Merck Research Laboratories. If REST was not stopped for safety concerns, the primary safety hypothesis was tested. A one-sided test of the null hypothesis that the relative risk of intussusception is > 10 during 1 - 42 days postdose was used. A point estimate of the relative risk and the corresponding two-sided 95% confidence interval was calculated. The point estimate, confidence limits, and p-value was appropriately adjusted to account for the design of this trial. The vaccine was to be considered safe if the null hypothesis was rejected, or equivalently, if the upper bound of the confidence interval was less than or equal to 10. Due to the low background rate of intussusception, few cases were expected, which meant that observed relative risks much less than 10 would be required to satisfy the primary hypothesis. Monte Carlo simulation of this trial showed that the expected number of total cases for the primary study period of 1-42 days following any dose is 10, assuming that the true relative risk was 1. With this number of cases, the unadjusted maximum point estimate of relative risk that satisfied the primary safety hypothesis was 1.5.

Multiplicity:
For the primary safety hypothesis, the point estimate, confidence limits, and p-value for relative risk were appropriately adjusted for multiplicity due to the interim monitoring criteria and sequential design.

Power Calculations:
A Monte Carlo simulation was undertaken to estimate (1) the probability that REST would be stopped early based on the safety boundaries, and (2) the power of REST to satisfy the primary hypothesis, under various scenarios. The simulation was based on 10,000 randomly generated potential study results. For each study replication, cases of intussusception for placebo and vaccine recipients were assumed to be Poisson random variables. A random sequence of cases was generated and it was determined whether (1) the sequence caused the study to be stopped for safety according to the graphs, or (2) the study satisfied the primary hypothesis. The following describes the power analysis. To allow for differential timing between doses 1 and 2, and between doses 2 and 3, it was conservatively assumed that there would be 30 days between doses and a 42 day follow up after the third dose. Therefore, the incidence of intussusception was estimated for a 102 day period, assuming a background rate of 1 per 2000 person-years. If there is no increase in the incidence of intussusception due to the vaccine (i.e., true relative risk = 1), then the probability of incorrectly stopping REST early due to a safety concern is approximately 0.06, and the probability of correctly concluding at the end of the study that the vaccine satisfies the primary safety hypothesis is 0.94. Thus, if the true relative risk is 1.0, there is approximately 94% power to satisfy the primary hypothesis, accounting for the possibility of incorrectly stopping the trial early because of a potential safety concern. On the other hand, if the true relative risk is similar to that observed with RRV-TV, then there is a high chance of stopping REST early. Specifically, based on the risk profiles in the CDC report referenced in the protocol, the probability of stopping this study early is ~91% using the case-control profile, and ~85% using the case-series profile.

End of Study Analysis (from the Applicant CSR 006 p. 4607)
The appropriate analysis of relative risk must account for the group-sequential design. Because the group-sequential design provided multiple opportunities for the study to end due to a favorable safety outcome, the p-value, point estimate, and confidence limits were adjusted accordingly. These adjustments were calculated based on an ordering of the sample space. Given a particular ordering of the sample space, the p-value was defined as the probability of observing results that were at least as extreme (in favor of the alternative hypothesis) as the observed results, under the null hypothesis. The ordering that was used for this study was the ordering proposed by Tsiatis, Rosner, and Mehta. This ordering defined outcomes as more extreme if they resulted in stopping on a favorable note prior to the terminal stage of the study or if they resulted in a test statistic that is more favorable for the alternative hypothesis at the terminal stage of the study. Notationally, let (V:P) be the case split of

recipients of RotaTeq™ and placebo and M be the stage of the study where M = 1, …, 5, corresponding to sample sizes of 60000, 70000, 80000, 90000, and 100000, respectively. Then, the ordering was defined by:

[(V:P)*, M*] was as extreme as [(V:P)**, M**] if:
(1) M* < M** and (V:P)* was such that the end-of-study criterion was satisfied, or (2) M* = M** and V* ≤ V**.

For this ordering, if the trial stops at M=1 (i.e., 60,000 subjects), the p-value was identical to the conventional fixed sample size p-value. If the trial stopped at any M > 1, the p-value was adjusted accordingly. Based on Jennison and Turnbull , the p-value function was defined as:

$$F(p) = \sum_{j=0}^{V_{\tilde{M}}} C_{\tilde{M}}(j,p) + \sum_{M=1}^{\tilde{M}-1} L_M(p),$$

where

$\tilde{M}$ represents the observed terminal stage;

V_M is the observed cumulative number of cases in the group that received RotaTeq at stage M;

$C_M(j,p)$ represents the probability of reaching stage M with $V_M = j$, which is equal to

$$\sum_{l \in A_{M-1}} C_{M-1}(l,p) \binom{T_M}{j-l} p^{j-l} (1-p)^{T_M-(j-l)},$$

where

A_M consists of all numbers of cases in the group that received RotaTeq within stage M such that the end-of-study criterion would not be satisfied,

T_M is the observed number of total cases within stage M, and

$$C_1(j,p) = \binom{T_1}{j} p^j (1-p)^{T_1-j}; \text{ and}$$

$L_M(p)$ represents the probability of stopping due to satisfying the end-of-study criterion at stage M, which is equal to

$$\sum_{l \in A_M} C_M(l,p).$$

The p-value was given by F (10/11).
The point estimate ($\hat{\pi}$), or median unbiased estimator (Birnbaum), of relative risk π was found using the mid p-value function

$$G(p) = \sum_{j=0}^{V_{\tilde{M}}-1} C_{\tilde{M}}(j,p) + \frac{1}{2} C_{\tilde{M}}(V_{\tilde{M}},p) + \sum_{M=1}^{\tilde{M}-1} L_M(p),$$

and solving $G(p_m) = 0.5$, and then calculating $\hat{\pi} = \frac{p_m}{1-p_m}$.

The lower 95% confidence limit (π_l) is found by solving

$$\sum_{j=0}^{V_{\tilde{M}}-1} C_{\tilde{M}}(j,p_l) + \sum_{M=1}^{\tilde{M}-1} L_M(p_l) = 0.975,$$

and then calculating $\pi_l = \frac{p_l}{1-p_l}$.

The upper 95% confidence limit (π_u) is found by solving

$$\sum_{j=0}^{V_{\tilde{M}}} C_{\tilde{M}}(j,p_u) + \sum_{M=1}^{\tilde{M}-1} L_M(p_u) = 0.025,$$

and then calculating $\pi_l = \frac{p_u}{1-p_u}$.

Without adjustments made for the group-sequential design, these confidence intervals were equivalent to Clopper-Pearson intervals.

Medical Officer comments:
Relative risk calculations for intussusception were performed by the FDA statistician; please refer to the FDA statistical review.

8.1.1.2 Results for Study 006

8.1.1.2.1 Populations Enrolled and Analyzed

Table 15 and Table 16 below include the subject accounting for study 006 through Day 42 and following the 3rd Study Vaccination and through day 365 following the 1st vaccination among all Study 006 Subjects.

Medical Officer comments:
There were no major imbalances detected in the treatment arms in regard to reasons for discontinuation. Please see the safety section of this review for additional details regarding reasons to discontinue from study 006. Numbers bolded in Table 15 below show the differences in FDA and Merck numbers.

Infants received their first dose of vaccine at 6 to 12 weeks of age and the two subsequent doses were given at 4 to 10 week intervals. Thus, the

earliest time for required follow-up to be completed for an infant (initial dose at 6 weeks with 4 week intervals between the subsequent two doses) would have been an infant completing the dosing schedule at 14 weeks (98 days) with 42 days of follow-up or minimum follow-up time of 140 days. The longest required period of follow-up would have been an infant who received the first dose at 12 weeks with 10 week intervals between the two subsequent doses thus completing the dosing schedule at 32 weeks (224 days) with 42 days of follow-up or maximum required follow-up time of 266 days.

Table 15 Subject Accounting for Protocol 006 (REST) Through Day 42 Following the 3rd Study Vaccination Among all Subjects in the Study (Safety Cohort)

Study 006	RotaTeq™		Placebo		Total	
	n	%	n	%	n	%
Screening Failures					943	
Randomized	**34940** **+191 excluded site subjects = 35131** **Difference of 37 (cross-treated) vs FDA numbers**		**34897** **+191 excluded site subjects = 35088** **Difference of 36 (cross-treated) vs FDA numbers**		**69837**	
Randomized not vaccinated	67	0.2	74	0.2	141	0.2
Vaccinated at visit 1	34873	99.8	34823	99.8	69696	99.8
Vaccinated at visit 2	32815	93.9	32792	94.0	65607	93.9
Vaccinated at visit 3	31946	91.4	31849	91.3	63795	91.3
Completed 3rd study vaccination and/or 42 day follow-up safety	31913	91.3	31827	91.2	63740	91.3
Discontinuations prior 3rd vaccination and /or before 42 day safety follow-up period:	3027	8.7	3070	8.8	6097	8.7
-Adverse event	225	0.6	206	0.6	431	0.6
-Protocol deviation	1075	3.1	1175	3.3	2220	3.2
-Refused further participation	189	0.5	220	0.6	409	0.6
-Lost to follow-up	69	0.2	92	0.3	161	0.2
-Moved	221	0.6	214	0.6	435	0.6
-Other	1248	3.6	1193	3.4	2441	3.5

† There were 3 study sites in the Safety Cohort deemed to potentially have unreliable data. All subjects from these 3 study sites are excluded from this table: 95 subjects from study site 006034, 253 subjects from study site 006113, and 33 subjects from study site 006164.
‡ Includes 41 subjects who were randomized to receive RotaTeq™ but received either placebo at vaccination Visit 1 or a mixed regimen of RotaTeq™ and placebo. A display of the actual treatment regimen received by these cross-treated subjects is shown in Appendix 2.7.4: 4.
§ Includes 39 subjects who were randomized to receive placebo but received either RotaTeq™ at vaccination Visit 1 or a mixed regimen of RotaTeq™ and placebo. A display of the actual treatment regimen received by these cross-treated subjects is shown in Appendix 2.7.4: 4.
‖ 'Randomized not vaccinated' subjects were randomized to a treatment group but did not receive a vaccination.
¶ These data are based on the subject status after the dosing phase and not on actual follow-up dates.
# 'Other' was used for all circumstances that did not apply to a prespecified reason for discontinuation. The most common reason reported was: 'parent refused further doses, but agreed to continue with safety follow-up'.
Calculation of percentage: The number of subjects in a given category divided by the number of subjects randomized.
N = Number of subjects randomized; n = Number of subjects in a given category; AN = Allocation number.
APP = Application data, which is data from original application; SUR = Safety Update Report data, which is all new visits that occurred after the original application; CUM = Cumulative data, which is all data including both new and updated data that occurred after the original application. It is important to note that APP data and SUR data are not additive to CUM data because SUR includes only new visits and does not include any updated data. For the extent of exposure tables, if data for a new visit was entered for a subject, the new visit data as well as data from all other existing visits for this subject will appear in the SUR data.

(Adapted from Applicant Safety Update, July 25, 2005, Appendix Table 2.7.4:1, p. 236)

Table 16 Subject Accounting Protocol 006 (REST) Through Day 365 After 1st Study Vaccination or Study Site's End-of Study Date Among all Randomized Subjects (Safety Cohort)

Study 006	RotaTeq™		Placebo		Total	
	n	%	n	%	n	%
Screening Failures					943	
Randomized	34940		34897		69837	
Randomized not vaccinated	67	0.2	74	0.2	141	0.2
Vaccinated at visit 1	34873	99.8	34823	99.8	69696	99.8
Completed safety follow-up for 365 days after visit 1 or until study site's end-of study date	33875	97.0	33778	96.8	67653	96.9
Subjects continuing safety f/u for 365 days post vaccination visit 1	132	0.4	122	0.3	254	0.4
Discontinued any time before 365 days of f/u or prior end-of-study date:	933	2.7	997	2.9	1930	2.8
-Adverse event	34	0.1	33	0.1	67	0.1
-Protocol deviation	57	0.2	68	0.2	125	0.2
-Refused	213	0.6	244	0.7	457	0.7
-Lost to follow-up	440	1.3	487	1.4	927	1.3
-Moved	89	0.3	78	0.2	167	0.2
-Other	100	0.3	87	0.2	187	0.3

† There were 3 study sites in the Safety Cohort deemed to potentially have unreliable data. All subjects from these 3 study sites are excluded from this table: 95 subjects from study site 006034, 254 subjects from study site 006113, and 33 subjects from study site 006164.
‡ Includes 41 subjects who were randomized to receive RotaTeq™ but received either placebo at vaccination Visit 1 or a mixed regimen of RotaTeq™ and placebo. A display of the actual treatment regimen received by these cross-treated subjects is shown in Appendix 2.7.4: 4.
§ Includes 39 subjects who were randomized to receive placebo but received either RotaTeq™ at vaccination Visit 1 or a mixed regimen of RotaTeq™ and placebo. A display of the actual treatment regimen received by these cross-treated subjects is shown in Appendix 2.7.4: 4.
‖.'Randomized not vaccinated' subjects were randomized to a treatment group but did not receive a vaccination.
¶ - - = no value.
# 'Other' was used for all circumstances that did not apply to a prespecified reason for discontinuation. The most common reason reported was: 'parent refused further doses, but agreed to continue with safety followup'.
Calculation of percentage: The number of subjects in a given category divided by the number of subjects randomized.
N = Number of subjects randomized; n = Number of subjects in a given category; AN = Allocation number.
APP = Application data, which is data from original application; SUR = Safety Update Report data, which is all new visits that occurred after the original application; CUM = Cumulative data, which is all data including both new and updated data that occurred after the original application. It is important to note that APP data and SUR data are not additive to CUM data because SUR includes only new visits and does not include any updated data. For the extent of exposure tables, if data for a new visit was entered for a subject, the new visit data as well as data from all other existing visits for this subject will appear in the SUR data.

(from Applicant Safety Update, July 25, 2005, Appendix Table 2.7.4:1, p. 238)

A total of 70,078 subjects received at least one dose of vaccine (RotaTeq™ or placebo or cross-treated) in study 006. Subjects from Finland contributed 33% of the data and subjects from the U.S. and Puerto Rico contributed 48% of the data. The U.S. data also includes the Navajo and White Mountain Apache Nations in

the western United States where G3 has historically been predominant. The remaining 19% of the subjects were from the following countries: Costa Rica, Guatemala, Mexico, Jamaica, Taiwan, Belgium, Germany, Italy and Sweden.

See Table 17, below, which includes the demographics on subjects in study 006.

Table 17 Demographics for Study 006 *

Study 006	**RotaTeq™**		**Placebo**	
Randomized (N):	34940		34897	
	n	%	n	%
Gender				
Male	17738	50.8	17675	50.6
Female	17202	49.2	17222	49.4
Age (weeks)				
5 and under	1	0.0	1	0.0
6 to 12	34847	99.7	34797	99.7
Over 12	92.0	0.3	99.0	0.3
Mean	9.8		9.8	
SD	1.42		1.42	
Median	10.0		10.0	
Range Male Female	3 to 13 3 to 13 6 to 13		4 to 16 6 to 13 4 to 16	
Race				
White	24014	68.7	24016	68.8
Hispanic-American	4977	14.2	4920	14.1
Black	2939	8.4	2957	8.5
Multiracial	1820	5.2	1828	5.2
Asian	538	1.5	554	1.6
Native-American	531	1.5	515	1.5
Other	121	0.3	107	0.3

*from Applicant's Appendix 2.7.4:5, p. 246, Cumulative Data

Medical Officer comments:
It should be noted that the subjects in Study 006 were mainly from industrialized countries. The demographic characteristics including race and gender were balanced across the treatment arms of the study. Regarding age, the treatment arms were balanced except for certain age strata by week for the group that was less than or equal to 36 weeks gestation. Please see Table 18 below.

When considering the demographic profile of the three pivotal safety studies, each treatment arm included approximately 50% male and 50% female subjects. The majority of the subjects were white (69%) and the remainder were Hispanic-American (14.2%), Black (8.2%), multi-racial

(5.2%), Asian (1.5%), Native-American (1.5%) and other (0.4%) and this was balanced between the treatment arms. Most subjects (99.7%) were age 6-12 weeks at randomization and this was balanced between the treatment arms and the mean age at randomization was 9.8 weeks.

Populations included in subset analyses for REST

Breast Feeding Status

Breast-feeding was permitted in all studies. In study 006, there were 15,634 infants in the placebo arm who were "breast fed only" at any time and there were 15,838 infants who were "breast fed only" in the RotaTeq™arm.

Medical Officer comments:

Overall, there was no major difference in the number of "breast fed only" infants "at any time" across the treatment arms. Section 8.1.1.2.2 includes an exploratory analysis of efficacy in breast fed infants. The Applicant did not provide this analysis in the original BLA submission but submitted data (--- transport files) and this subset analysis to the BLA upon FDA request.

Gestational Age Less than or equal to 36 weeks

In study 006, RotaTeq™ or placebo was administered to 2,070 pre-term infants ranging from 25 to 36 weeks gestational age (GA), median 34 weeks, according to their age in weeks since birth. Safety data were available on 2043 of these 2070 pre-term infants.

Table 18 Age strata of the pre-term infants in Study 006 (REST)*

Study 006 (REST)	Number of Subjects in each Treatment Arm in REST who were Gestational Age ≤ 36 weeks		
Gestational Age (weeks)	RotaTeq™ (n)	Placebo (n)	Cross-treated (n)
36	3	4	
35	426	457	1
34	260	270	1
33	123	131	2
32	102	98	
31	33	37	
30	13	27	
29	9	13	
28	13	7	
27	2	5	
26	2	1	
25	1	2	
Total	987	1052	4
Overal Cohort Size	2043		

*FDA

Medical Officer comments:

Overall, this is a substantial body of clinical study data for premature infants. Ninety five percent of the infants were between 31 to 36 weeks gestational age. In the gestational age strata of ≤ 28 weeks, there were only eighteen infants in the RotaTeq™ arm and fifteen infants in the placebo arm. In regard to gestational age in weeks, the age strata across the treatment arms was not evenly distributed at ages less than 31 weeks (see Table 18 above).

Breast Feeding in the Gestational Age(GA) less than or equal to 36 weeks.

The number of infants less than or equal to 36 weeks GA who were "breast fed only" included 240 infants in the placebo arm and 223 infants in the RotaTeq arm and 1 child who was cross-treated and received three doses (RotaTeq™, RotaTeq™, Placebo).

Distribution of premature infants (≤36 weeks GA) who were "breast fed only"per treatment group (total 464)

Treatment arm	Gest Age (weeks)	#subjects
Placebo	25	1
Placebo	29	3
Placebo	30	11
Placebo	31	9
Placebo	32	13
Placebo	33	25
Placebo	34	56
Placebo	**35**	**120**
Placebo	36	1
Placebo	41	1
RotaTeq	28	1
RotaTeq	29	3
RotaTeq	30	3
RotaTeq	31	7
RotaTeq	32	15
RotaTeq	33	22
RotaTeq	34	58
RotaTeq	**35**	**110**
RotaTeq	38	1
RotaTeq	39	1
RotaTeq	40	2
Three Doses (RotaTeq, RotaTeq, Placebo)	34	1

Medical Officer comments:

The percentage of premature infants who were "breast fed only" was similar across the treatment arms; 23% RotaTeq™ recipients compared to 23% placebo recipients.

Medically Compromised Infants in Study 006

Upon FDA request, on June 17, 2005 a dataset on 618 medically compromised infants (317 placebo and 301 RotaTeq™) was submitted to the BLA. The

Applicant describes the dataset as a convenience sample. Prior to unblinding the database on 29-Dec-2004, subjects who were potentially medically-compromised as identified by reports of serious clinical adverse experiences or who received potentially immunocompromising medications (i.e.at least one dose of systemic corticosteroids) as a concomitant therapy withRotaTeq™ or placebo, were identified to be evaluated for fecal shedding of vaccine-virus strains (n=619). The identification of these subjects was performed by the 3 clinical monitors assigned to the development program for RotaTeq™.

Medical Officer comments:
This is a convenience sample. One should not assume that this experience could be extrapolated to support the safe use of this live vaccine in an immunocompromised population.

Conditions deemed to be potentially "medically-compromising" included: abdominal distention, anal abscess, anaphylactic reaction, anemia, atopic eczema, bacteremia (including pneumococcal bacteremia), bacterial sepsis, carcinoma, cardiac failure congestive, circulatory collapse, coarctation of the aorta, cystic fibrosis, eczema, failure to thrive, groin abscess, haematochezia, hepatic steatosis, human herpesvirus 6 infection, hypersensitivity, inguinal abscess, intestinal function disorder, intestinal malrotation, Kawasaki's disease, lymphadenitis, meningitis (including meningitis bacterial), metabolic acidosis, neuroblastoma, neutropenia, oedema peripheral, oral candidiasis, perianal abscess, perineal abscess, primitive neuroectodermal tumor, psoriasis, rectal abscess, sepsis (including sepsis bacterial),subcutaneous abscess, urosepsis, urticaria, urticaria pigmentosa, and varices esophageal.

Among the subjects reported to have a potentially medically-compromising condition or reported to have received at least one dose of systemic corticosteroids and who submitted a stool specimen for testing, The Applicant states that there was no vaccine virus strain shedding detected in a stool sample that was collected when *t*he subject may have been medically-compromised.

Medical Officer comments:
"***Medically compromised" is not equivalent to immunocompromised. It is not safe to assume that experience regarding shedding of vaccine virus in this small subset analysis could be extrapolated to support the use of this live oral rotavirus vaccine in an immunocompromised population. See section 8.1.1.2.2 for more discussion of efficacy and shedding.***

Protocol Violations
In the Safety population, protocol violations were mainly due to "cross treatment" (cross-treated subjects are listed in Table 6.1 p. 171 CSR study 006) and also 17 children received OPV. Please see the following description of protocol violations for the Efficacy and Immunogenicity cohorts which is provided on p.4609 of the clinical study report for REST. Please also see the Subject

Accounting Tables for the individual phase 3 studies.

Description of Protocol Violations
Exclusion Criteria were listed in the protocol. Per-protocol analyses excluded subjects according to the Exclusion Criteria and the following:

Efficacy
a. Subjects who do not have 3 vaccinations with at least 28 days between each vaccination were excluded.
Immunogenicity
a. Subjects who did not have 3 vaccinations with at least 28 days between each vaccination were excluded.
b. Subjects who did not have valid serology results at scheduled bleeds (due to missing bleed, bleed off schedule, lost sample, insufficient quantity of sera for assay, etc.) were excluded at that time point (but eligible for inclusion at earlier and later time points).
c. Subjects with data obtained during or after a laboratory-confirmed rotaviral disease episode were excluded.
d. For analyses involving both prevalues and postvalues, e.g., 3-fold rise analyses and change-in-titer analyses, a subject was excluded if a Predose 1 or a Postdose 3 value is missing. The analysis did not plan to account for missing values through imputation or other statistical methods. In the subject accounting section of the clinical study report (CSR), all excluded subjects and the reason(s) for exclusion were listed (a subject may be counted more than once if he/she has multiple reasons for exclusion).

Discontinuations
There were 7 additional subjects who discontinued from their respective study due to a clinical adverse experience during the SUR reporting period. There were 6 subjects who discontinued due to a serious adverse experience and 1 subject who discontinued due to a non-serious clinical adverse experience.

Overall, there were 212 subjects in the Phase III studies who discontinued from their respective study due to either a serious clinical adverse experience or a non-serious clinical adverse experience. Of these subjects who discontinued, 115 received RotaTeq™ and 97 received placebo. Table 2.7.4: 51 in the Safety Update (p. 178-210) displays a listing ordered by treatment group and study site number of all subjects who discontinued due to a clinical adverse experience.

8.1.1.2.2 Efficacy Endpoints and Outcomes

Efficacy of the final formulation was evaluated using the Efficacy Cohort population which consisted of 5673 subjects from Protocol 006 (REST) and 1310 subjects from Protocol 007 (end-expiry). In REST the dose at release potency (range from 67.2×10^6 to 124×10^6 IU/dose) was used while in study 007, End-Expiry, the dose used was at the end of shelf-life (11×10^6 or 1.1×10^7 IU/dose).

Medical Officer comments:
The FDA statistician analyzed and reported the efficacy data for REST and study 007 separately because the doses utilized and the primary null hypotheses were different. Similar to REST, Study 009 (Lot consistency) utilized the dose of RotaTeq™ at release potency. When considering immunogenicity, keep in mind whether the dose utilized in the study was at release potency or end expiry. Overall, despite differences in dose, efficacy for RotaTeq™ was similar across REST and study 007. Immunogenicity results from the earlier dose-ranging study 005 demonstrated that the magnitude of the antibody response depended on the potency of RotaTeq™ used but that immunogenicity did not necessarily correlate with efficacy/protection.

The primary efficacy hypothesis was that RotaTeq™ would be efficacious against rotavirus disease caused by serotypes G1, G2, G3 and G4 that occurred at least 14 days after the third vaccination through one rotavirus season post-vaccination. The definition of acute rotavirus gastroenteritis (AGE) differed slightly from the WHO definition in that a subject could have vomiting alone without associated diarrhea (see the case definition below).

Case Definition of Rotavirus Gastroenteritis:
An acute gastroenteritis episode (AGE) was defined as the occurrence of 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. The per-protocol case definition for rotavirus-associated gastroenteritis that was used to determine vaccine efficacy was that a subject met both of the following clinical and laboratory criteria: (1) greater than or equal to 3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting (i.e., an AGE), and (2) rotavirus antigen was detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days of the onset of symptoms. Only G1-, G2-, G3-, or G4-specific rotavirus gastroenteritis cases naturally occurring through the first full rotavirus season that began at least 14 days after the third dose of RotaTeq™ or placebo were included in the primary efficacy analysis.

Secondary efficacy outcomes were evaluated with respect to: (1) severity of gastroenteritis based on scoring of clinical symptoms, (2) individual naturally-occurring G-serotype rotavirus gastroenteritis cases of the serotypes included in the vaccine (i.e., G1,G2, G3, and G4), (3) any naturally-occurring rotavirus (4) naturally-occurring G-serotypes not included in the vaccine (e.g., G9 and G10), and (5) naturally occurring G-serotype rotavirus gastroenteritis cases of the serotypes included in the vaccine occurring through the second rotavirus season.

In order to evaluate the severity of rotavirus gastroenteritis, a 24-point clinical scoring system was utilized (see Table 19 below). Please note that the Applicant uses a standard “rectal equivalent conversion factor” for temperature obtained by routes other than a rectal temperature. The temperature conversion factor used in the phase 3 studies studies included adding 1 degree Fahrenheit to otic and

oral temperatures and 2 degrees Fahrenheit to axillary temperatures.

A clinical score of ≤8 was considered mild gastroenteritis, a score of >8 but ≤16 was considered moderate disease and >16 was considered severe disease. Please see Table 19 below.

Table 19 Clinical Scoring for Acute Gastroenteritis (AGE) *

Score to be Summed According to Evaluation of Symptoms and Durations (See Below)	1	2	3
Diarrhea No. of stools/day† Duration in days‡	 2 to 4 1 to 4	 5 to 7 5 to 7	 ≥ 8 ≥ 8
Vomiting No. of emeses/day§ Duration in days‡	 1 to 3 2	 4 to 6 3 to 5	 ≥ 7 ≥ 6
Rectal Temperature Degrees in Celsius% Duration in days‡	 38.1 to 38.2 1 to 2	 38.3 to 38.7 3 to 4	 ≥ 38.8 ≥ 5
Behavioral Symptoms Description¶ Duration in days‡	 Irritable/less playful 1 to 2	 Lethargic/listless 3 to 4	 Seizure ≥ 5

† Maximum number of watery or looser-than-normal stools/day on any given day over the course of the episode.

‡ Number of days on which child had a symptom of any score. **Days do not have to be consecutive.**

§ Maximum number of times child vomited on any given day over the course of the episode.

% Highest temperature over the course of the episode which is equal or **greater than 38°C (100.4°F), rectal.**

¶ If a child is reported to have two or more symptoms, only the one with the highest score is counted.

*From the Applicant.

FDA requested that the Applicant perform an analysis of “severe disease” without adjusting the temperature using the “rectal equivalent”. For protocol 006, it was determined that 88% of all temperatures reported for the clinical scoring module were collected rectally. When looking at the severe cases, there were only 6 subjects who were classified as severe, that would not be classified as severe, if their temperatures were not “converted” to rectal equivalent. All of these subjects were in the placebo group, which would lead to a case split of 1 vaccine to 45 placebo instead of 1 vaccine to 51 placebo, for severe cases.

Medical Officer comments:

The clinical scoring system used by the Applicant to assign a level of severity to a case of acute gastroenteritis is not a standard definition but

was pre-specified. This definition does not capture the parameter of dehydration.

Definition of the Rotavirus Season (from the Applicant)
The rotavirus season varied according to the location of the study site. For those study sites which were located in the Northern United States and Finland, the onset and end of the rotavirus season were designated as 01-Dec and 30-Jun of each year of the study, respectively. For other sites and countries, the rotavirus season began earlier and that date was prospectively determined using historical epidemiologic data about rotavirus in that area. Subjects were followed for efficacy beginning immediately after the first dose through all rotavirus seasons until the end of the trial. The primary efficacy analysis considered only those cases that occurred after the 14 days of follow-up post-dose 3 and through the first rotavirus season that began after the 14 days of follow-up post-dose 3. Intent-to-treat cases, which included cases that occurred at any time during the study, were also evaluated.

The primary analyses of efficacy and immunogenicity were based on the per protocol subject populations.

The **per-protocol case definition** for rotavirus gastroenteritis is that a subject meet both of the following criteria: (1) ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) rotavirus must be detected in a stool specimen taken within 14 days of the onset of symptoms**.**

The **intent-to-treat case definition** counts cases that occur at any time after the first dose.

The prospective primary and secondary endpoints included the following:
Primary Endpoint:
1. To evaluate the efficacy of a 3-dose regimen of oral RotaTeq™ against rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
2. To assess the safety of RotaTeq™ with respect to intussusception within 42 days of any dose of vaccine/placebo.

Secondary Endpoints:
1. To evaluate the effect of a 3-dose regimen of RotaTeq™ on health care resource utilization, including visits to emergency departments, physician's office visits, and Finnish health care centers or equivalent in other countries, and hospital admissions.
2. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against moderate and- severe and severe rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.
3. To evaluate the efficacy of a 3-dose regimen of RotaTeq™ against rotavirus disease regardless of serotype that occurs at least 14 days following the third dose.

4. To assess the safety of RotaTeq™ with respect to the incidence of intussusception occurring within 1 to 7 days, 1 to 14 days, and 1 to 365 days of any dose of vaccine/placebo.
5. To assess the safety of RotaTeq™ with respect to all adverse experiences in a subset of subjects.
6. To assess the immunogenicity of RotaTeq™ as measured by the serum neutralizing antibody (SNA) response to reassortants G1, G2, G3, G4, P1, WC3 [components G6 and P7 (P[5] genotype)], and serum rotavirus-specific IgA in a subset of subjects.
7. To evaluate the antibody responses to the recommended routine childhood immunizations, including COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ when given concomitantly with oral RotaTeq™ in a subset of subjects.
8. To evaluate the efficacy, safety, and immunogenicity of oral RotaTeq™ when administered concomitantly with COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ in a subset of subjects.
9. To assess the safety of RotaTeq™ when administered concomitantly with a combination hexavalent pediatric vaccine (HEXAVAC™ or INFANRIX HEXA™) in a subset of subjects in Germany.

Medical Officer comments:
Endpoint #9 was not directly relevant to U.S. licensure.

Background

Efficacy (From p. 4594 Data Analysis Plan Study 006, Appendix 3.10)
For the primary hypothesis, a one-sided test of H0: $\pi \leq 0.35$ versus H1: $\pi > 0.35$, where π=1-RRotaTeq™/Rplacebo and RRotaTeq™ and Rplacebo represent the respective true disease incidences for RotaTeq™ and placebo, was performed. To test this hypothesis, an exact conditional procedure was used under the assumption that the number of subjects who met the case definition for rotavirus gastroenteritis in the group who received RotaTeq™, X, and the number of subjects who met the case definition for rotavirus gastroenteritis in the group who received placebo, Y, are distributed as independent Poisson random variables with parameters λRotaTeq™ and λplacebo, respectively. Given the total number of observed subjects who met the case definition for rotavirus gastroenteritis, T, X follows a binomial distribution with parameters T and p=λRotaTeq™ / (λRotaTeq™ + λplacebo). By conditioning in this manner, the hypothesis test above can be executed by an exact test of H0: $p \geq p0$ versus H1: $p < p0$, where p0= 0.65/(0.65+k), and k = total amount of follow-up in the placebo group/total amount of follow-up in the group who received RotaTeq. "Amount of follow-up" is the sum of the follow-up times (person-days) for all subjects in the respective group. Efficacy follow-up for the per protocol group begins 14 days after the final vaccination. For rotavirus cases, efficacy follow-up ends with the onset of symptoms for the first acute gastroenteritis episode meeting the rotavirus case definition. For non-cases, efficacy follow-up ends with the subject's

discontinuation date.

The point estimate (100 x $\hat{\pi}$) of the efficacy of RotaTeq™ (100 x π) and the corresponding exact two-sided confidence interval was calculated. This exact inference on π was made by making the corresponding exact inference on p and using the relationship $\pi = [1 - p(1+k)]/(1-p)$. Therefore, the lower bound on the confidence interval for π was $[1 - pu(1+k)]/(1-pu)$, and the upper bound was $[1 - pl(1+k)]/(1-pl)$, where pu and pl were the respective upper and lower bounds of the exact confidence interval for p. **RotaTeq™ was declared efficacious if the null hypothesis was rejected (or equivalently, if the lower bound of the confidence interval exceeds 35%).** These techniques were performed for the primary hypothesis, based on all degrees of severity of non-vaccine-related (naturally occurring) cases occurring at least 14 days Post-dose 3 and through the first rotavirus season that began at least 14 days Post-dose 3 caused by serotypes G1, G2, G3, and G4.

Efficacy was also evaluated by moderate-to-severe (severity score >8) and severe (severity score >16) rotaviral disease. The moderate-to-severe and severe efficacy analyses counted as cases only those subjects with severity scores >8 and >16, respectively. Because a subject may have multiple episodes of rotaviral disease, 2 analyses were carried out: the first used the severity score from the first episode, and the second used the severity score from the most severe episode. Severity scores were calculated according to Appendix 2 of the protocol. Analyses and hypothesis testing were carried out as described above, except a lower bound of 0 was used. Non-serotype-specific efficacy and individual serotype-specific efficacy was Also evaluated. These analyses counted as cases without regard to serotype and only those of specific serotypes, respectively. In addition, efficacy based on cases occurring through an additional rotavirus season beyond the primary season were evaluated. Both per-protocol (excluding subjects who were protocol violators) and intent-to-treat (all subjects with valid efficacy data) subject populations were evaluated in the analyses described above. All subjects from all pre-designated efficacy sites were used for the primary analysis. Efficacy was also evaluated by dose schedule (2, 3, 4 months versus 2, 4, 6 months) and separately for subjects in the United States concomitant use subset.

The per-protocol case definition for rotavirus gastroenteritis was that a subject meet both of the following criteria: (1) ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) rotavirus must be detected in a stool specimen taken within 14 days of the onset of symptoms. All episodes that occur at least 14 days Post-dose 3 were classified as negative, positive, or not evaluable according to the per-protocol case definition given in the Per-Protocol and Intent-to-Treat Case Definitions table below (Table 20). However, any subject with a positive rotavirus laboratory result based on symptoms occurring earlier than 14 days Post-dose 3, which was characterized

as naturally occurring (not vaccine related), was excluded from the analysis, and subsequent episodes were not evaluated. In the event of multiple episodes occurring at least 14 days Post-dose 3, a subject was classified as a rotavirus case if any episode was classified as positive, and as a non-case only if all episodes were classified as negative. Subjects with at least one “not evaluable” episode and no positive episodes were excluded from the analysis. Episodes were considered separate if there was at least a 3-day absence of symptoms between them.

From the Applicant (CSR 006 p. 4595)
Efficacy was also evaluated based on an intent-to-treat case definition for The intent-to-treat population. The intent-to-treat case definition counted cases that occurred at any time Postdose 1. The intent-to-treat case definition also used a different convention from the per-protocol case definition for handling missing and out-of-day-range data, regarding any possible case as a case. Details on how to apply the intent-to-treat and per-protocol case definitions to individual acute gastroenteritis episodes are given in the Per-Protocol and Intent-to-Treat Case Definitions table below (Table 19**).**

An **Efficacy Endpoint Adjudication Committee** was utilized to verify:
(1) that episodes met the clinical case definition, and (2) the clinical severity score of the episode.

Table 20 Per-Protocol and Intent-to-Treat Case Definitions*

Symptoms	Laboratory Result	Per-Protocol Case Definition†	Intent-to-Treat Case Definition‡
Missing - AGRC form not returned§	Missing	Negative	Negative
	Negative	Negative	Negative
	Positive	Not evaluable	Positive
Missing - AGRC form incomplete	Missing	Not evaluable	Positive
	Negative	Negative	Negative
	Positive	Not evaluable	Positive
	Late negative	Not evaluable	Positive
	Late positive	Not evaluable	Positive
Symptoms do not meet clinical case definition¶	Missing	Negative	Negative
	Negative	Negative	Negative
	Positive	Negative	Negative
	Late negative	Negative	Negative
	Late positive	Negative	Negative
Symptoms meet clinical case definition	Missing	Not evaluable	Positive
	Negative	Negative	Negative
	Positive	Positive	Positive
	Late negative	Not Evaluable	Positive
	Late positive	Not Evaluable	Positive

† According to the per-protocol case definition, any subject with one or more episodes classified as positive will be considered a rotavirus case. Any subject whose episodes are all classified as negative will be considered a noncase. Any subject with one or more "not evaluable" episodes and no positive episodes will be excluded from analyses. ‡ According to the intent-to-treat case definition, any subject with one or more episodes classified as positive will be considered a rotavirus case. All other subjects will be considered noncases. § When AGRC form not returned, then by definition laboratory result cannot be late, and missing laboratory result would indicate absence of sample. _ Late laboratory result refers to laboratory result test performed on stool sample collected more than 14 days after onset of symptoms. ¶ Clinical case definition refers to ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting.
AGE=Acute gastroenteritis episode.
AGRC = Acute gastroenteritis repord card.

*Adapted from the Applicant.

Handling of Dropouts or Missing Data and Approaches to Analyses (p. 143 CSR Study 006)

The primary analyses of efficacy and immunogenicity were based on per protocol subject populations. Subject populations comprised of all subjects with valid efficacy data (including protocol violators), referred to as modified "intention-to-treat" study populations, were also evaluated. Each efficacy estimate using the per-protocol case-definition was computed based on the per-protocol study population. The same estimates were also computed based on the modified intention-to-treat population, with the exception of estimates that were stratified by region of origin or subpopulation. An estimate using the intention-to-treat case definition was also computed based on the modified intention-to-treat study population (see Table 20 above for the per-protocol and intention-to-treat case definitions).

Subjects were excluded from the per-protocol Post-dose 3 efficacy analyses according to the following criteria:

1. Subjects who missed any of the 3 study vaccinations.

2. Subjects who received an insufficient amount of vaccination material.
3. Subjects who did not have at least 28 days between study vaccinations.
4. Subjects who received a mixed regimen of study materials (cross-treatment).
5. Subjects for whom the treatment arm was prematurely unblinded.
6. Subjects for whom there was a temperature excursion among administered vials.
7. Subjects classified as not evaluable by per-protocol case definition due to a rotavirus positive stool antigen EIA result (wild-type) prior to 14 days Postdose 3.
8.Subjects classified as not evaluable by the per-protocol case definition due to incomplete clinical and/or laboratory results and/or stool samples that were collected out of the pre-specified day range.

Subjects excluded from the primary per-protocol efficacy analyses for reasons 1 through 6 above were also excluded from the per-protocol immunogenicity analyses. In addition, data were excluded from the per-protocol immunogenicity analyses based on the following criteria:
1. Invalid assay data, including multiple values per sample date, based on laboratory determinations.
2. Samples obtained after a laboratory-confirmed rotavirus gastroenteritis episode.
3. Samples obtained outside the DAP-specified day ranges (9 to 33 days after the third dose for 14-day postvaccination assay samples, and 37 to 61 days after the third dose for the 42-day postvaccination assay samples).

Efficacy Populations Analyzed (From Applicant CSR 006 page 173)
Subjects randomized in the Efficacy Cohort, which includes the U.S. Concomitant Use Cohort, were evaluated for the primary and secondary efficacy hypotheses. The primary analysis of efficacy was based on the per-protocol subject population. Table 21 below provides an accounting of subjects excluded from the primary per-protocol efficacy analysis, and a listing of subjects excluded from this analysis is provided in the CSR. The main analysis of the secondary immunogenicity hypothesis regarding antibody responses to RotaTeq™ was also based on the per-protocol population, which excludes the same protocol violations listed in Table 21. As shown in Table 21, the most frequent reasons for exclusion were failure to receive 3 study vaccinations and incomplete clinical and/or laboratory results. Throughout the document, the text, “subjects who had a temperature excursion among administered vials”, refers to those subjects who received study material from vials or dosing tubes that were exposed to a temperature excursion outside theprotocol-specified temperature range during the refrigerator storage at the study site. There were observational differences in the number of subjects excluded between treatment groups. Among the subjects who were excluded due to a wild-type rotavirus positive stool prior to 14 days Postdose 3, the difference is largely due to more subjects that had missing PCR serotype results or were deemed to be non-typeable or negative by PCR serotyping in the group that received RotaTeq™ relative to placebo. In addition, these subjects were not shedding vaccine-virus strains according to plaque

assay results. Among the subjects who were excluded due to a wild-type rotavirus positive stool prior to 14 days Postdose 3, there was only one excluded subject who had a subsequent episode of acute rotavirus gastroenteritis that would have contributed to the per-protocol analysis. The study was not designed to address efficacy when less than 3 vaccinations of RotaTeq™ were provided. In addition, the majority of subjects who were excluded due to incomplete clinical and/or laboratory results or stool sample out of day range, did not have a laboratory result.

Table 21
Accounting of Subjects Excluded From Primary Efficacy Analysis

	RotaTeq™	Placebo
Subjects vaccinated in the Efficacy Cohort	2834	2839
Subjects included in primary efficacy analysis	2207	2305
Subjects excluded from primary efficacy analysis	627	534
Protocol violations†	295	271
Temperature excursion among administered vials	15	10
Less than 3 vaccinations or less than 28 days between vaccinations	276	256
Prematurely unblinded	0	1
Temperature excursion among administered vials and less than 3 vaccinations or less than 28 days between vaccinations	1	2
Cross-treated	0	1
Less than 3 vaccinations or less than 28 days between vaccinations and prematurely unblinded	2	0
Cross-treated and prematurely unblinded	1	1
No follow-up	11	6
Unevaluable according to per-protocol case definition:	321	257
Wild-type positive stool antigen EIA prior to 14 days Postdose 3	112	59
Incomplete clinical and/or laboratory results or stool sample out of day range	209	198

† Subjects may have more than one protocol violation. Subjects with multiple violations are included in the counts for each individual violation, but only once in the total number excluded due to protocol violations.
EIA = Enzyme immunoassay.

From Applicant Table 6.11 p. 175 (CSR 006 April 2005)

Subset Analyses
The Applicant included a subset analysis of efficacy according to whether the infant was breast fed “always”, “never” or “sometimes”. An analysis of efficacy in pre-term Infants was also provided.

The following is taken from the FDA statistical review:
Co-primary objective for Study 006:
The other co-primary objective besides intussusception concerns the issue of efficacy:

- To evaluate the efficacy of a 3-dose regimen of oral RotaTeq against rotavirus disease caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose.

The per-protocol case definition for rotavirus gastroenteritis is that a subject meet both of the following criteria: (1) ≥ 3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) rotavirus must be detected in a stool specimen taken within 14 days of the onset of symptoms.

The statistical hypothesis associated with this objective was that RotaTeq™ would be efficacious in protecting against naturally occurring rotavirus gastroenteritis caused by human rotavirus serotypes (G1, G2, G3, G4), which are intended targets of the vaccine, through the first full rotavirus season that began at least 14 days following vaccination when compared with placebo. In order to reject the null hypothesis of ≤ 35% efficacy, the lower bound of the two-sided 95% confidence interval had to be > 35%." (from the Applicant CSR 006, p. 212)

Table 22

Primary Efficacy Analysis of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases Occurring Through the First Rotavirus Season That Began at Least 14 Days Following Vaccination in the Per-Protocol Population Using Per-Protocol Case Definition*

	RotaTeq™	Placebo
Subjects vaccinated	2834	2839
Protocol violators †	295	271
Subjects with no follow-up	11	6
Subjects classified as unevaluable per per-protocol case definition ‡	321	257
Subjects contributing to efficacy analysis	2207	2305
Days of efficacy follow-up	623880	622399
Subjects classified as rotavirus gastroenteritis cases per-protocol definition	82	315
Efficacy estimate (%) and 95% confidence interval	74.0 (66.8, 79.9)	---
p-Value for efficacy >35%	<0.001	---
Conclusion §	Efficacious	---

†Subjects who had temperature excursions among administered vials, who had less than 3 vaccinations or less than 28 days between vaccinations, who were cross-treated, or who were prematurely unblinded. ‡Subjects were classified as unevaluable due to wild-type rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, incomplete clinical and/or laboratory results, or stool samples collected out of day range. §A conclusion of "efficacious" indicates that the criterion for efficacy was met, i.e., the lower bound of the confidence interval on the efficacy of RotaTeq™exceeds 35%. NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case. EIA = Enzyme immunoassay.

*Applicant Analysis

FDA Statistical Reviewer's Comments

1. The sponsor stated in the NOTE in Table 22 above: "Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case." The word "episode" was not defined either in the protocol or in the data analysis plan submitted prior to the BLA submission. Through several telephone communications with the sponsor, the reviewer learned that an "episode" was defined as one of the following criteria: (1) 2 watery or loose stools, (2) vomiting, (3) rectal temperature ≥ 38.1 C, (4) irritable or lethargic behavior, or (5) seizure in a 24-hour period.

2. Since the primary efficacy estimate is based on the definition of 'episodes' instead of the gastroenteritis cases, the reviewer performed a separate analysis by using the date of the first clinical case as the true date of a case in calculating the follow-up time. The results are presented in Table 23. There were 43 subjects with slightly different onset dates based on the rotavirus gastroenteritis compared to those with 'episode' definition. However, the difference in the two estimates occurs after the third decimal place. Therefore, it is considered acceptable to use the 'episode' definition.

Table 23 Efficacy estimate based on the first day of a confirmed rotavirus gastroenteritis case instead of 'episode' in REST*

	RotaTeq	Placebo
Subjects vaccinated	2834	2839
Subjects in efficacy analysis	2207	2305
Days of follow-up	623885	622333
G1, G2, G3, G4 serotype	82	315
Efficacy estimate (%) and 95% confidence interval	74.0 (66.8, 79.9)	

*FDA analysis

Analyses included in the Label:
The efficacy evaluations in these studies included: 1) Prevention of any grade of severity of rotavirus gastroenteritis; 2) Prevention of severe rotavirus gastroenteritis, as defined by a clinical scoring system; and 3) Reduction in hospitalizations due to rotavirus gastroenteritis.

The vaccine was given as a three-dose series to healthy infants with the first dose administered between 6 and 12 weeks of age and followed by two additional doses administered at 4- to 10-week intervals. The age of infants receiving the third dose was 32 weeks of age or less. Oral polio vaccine administration was not permitted; however, other childhood vaccines could be concomitantly administered. Breast-feeding was permitted in all studies.

The case definition for rotavirus gastroenteritis used to determine vaccine efficacy required that a subject meet both of the following clinical and laboratory criteria: (1) greater than or equal to 3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting; and (2) rotavirus antigen detection by enzyme immunoassay (EIA) in a stool specimen taken within 14 days of onset of symptoms. The severity of rotavirus acute gastroenteritis was determined by a clinical scoring system that took into account the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes.

The primary efficacy analyses included cases of rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 that occurred at least 14 days after the third dose through the first rotavirus season post vaccination.

Analyses were also done to evaluate the efficacy of RotaTeq against rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 at any time following the first dose through the first rotavirus season postvaccination among infants who received at least one vaccination (Intent-to-treat, ITT) in the Rotavirus Efficacy and Safety Trial (REST).

Primary efficacy against any grade of severity of rotavirus gastroenteritis caused by naturally occurring serotypes G1, G2, G3, or G4 through the first rotavirus season after vaccination was 74.0% (95% CI: 66.8, 79.9) and the ITT efficacy was 60.0% (95% CI: 51.5, 67.1). Primary efficacy against severe rotavirus gastroenteritis caused by naturally occurring serotypes G1, G2, G3, or G4 through the first rotavirus season after vaccination was 98.0% (95% CI: 88.3, 100.0), and ITT efficacy was 96.4%, (95% CI: 86.4, 99.6); see Table 24**.**

Table 24 Efficacy of RotaTeq against any grade of severity of and severe* G1-4 rotavirus gastroenteritis through the first rotavirus season post-vaccination in REST

	Per Protocol		Intent-to-Treat†	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	2,834	2,839	2,834	2,839
Gastroenteritis cases				
Any grade of severity	82	315	150	371
Severe*	1	51	2	55
Efficacy estimate % and (95% confidence interval)				
Any grade of severity	74.0 (66.8, 79.9)		60.0 (51.5, 67.1)	
Severe*	98.0 (88.3, 100.0)		96.4 (86.4, 99.6)	

*Severe gastroenteritis defined by a clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes
†ITT analysis includes all subjects in the efficacy cohort who received at least one dose of vaccine.

The efficacy of RotaTeq against severe disease was also demonstrated by a reduction in hospitalizations for rotavirus gastroenteritis among all subjects enrolled in REST. RotaTeq reduced hospitalizations for rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 through the first two years after the third dose by 95.8% (95% CI: 90.5, 98.2). The ITT efficacy in reducing hospitalizations was 94.7% (95% CI: 89.3, 97.3) as shown in Table 25.

Table 25 Efficacy of RotaTeq™ in reducing G1-G4 rotavirus-related hospitalizations in REST*

	Per Protocol		Intent-to-Treat*	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	34,035	34,003	34,035	34,003
Number of hospitalizations	6	144	10	187
Efficacy estimate % and (95% confidence interval)	95.8 (90.5, 98.2)		94.7 (89.3, 97.3)	

*Applicant's ITT analysis includes all subjects who received at least one dose of vaccine.

Medical Officer comments:

The *definition of severe disease was based on a grading score unique to this protocol which did not capture dehydration. Consequently, in the label, the Applicant was allowed to include hospitalization as another measure for disease severity. The efficacy cohort (Table 24) was a smaller subset of the overall REST population and the denominator for the health care utilization dataset was much larger (Table 25).*

Study 007

Primary efficacy against any grade of severity of rotavirus gastroenteritis caused by naturally occurring serotypes G1, G2, G3, or G4 through the first rotavirus season after vaccination was 72.5% (95% CI: 50.6, 85.6) and the ITT efficacy was 58.4% (95% CI: 33.8, 74.5). Primary efficacy against severe rotavirus gastroenteritis caused by naturally occurring serotypes G1, G2, G3, or G4 through the first rotavirus season after vaccination was 100% (95% CI: 13.0, 100.0) and ITT efficacy against severe rotavirus disease was 100%, (95% CI: 30.9, 100.0) as shown in Table 26.

Table 26**
Efficacy of RotaTeq against any grade of severity of and severe* G1-4 rotavirus gastroenteritis through the first rotavirus season postvaccination in Study 007

	Per Protocol		Intent-to-Treat†	
	RotaTeq	Placebo	RotaTeq	Placebo
Subjects vaccinated	650	660	650	660
Gastroenteritis cases				
Any grade of severity	15	54	27	64
Severe*	0	6	0	7
Efficacy estimate % and (95% confidence interval)				
Any grade of severity	72.5 (50.6, 85.6)		58.4. (33.8, 74.5)	
Severe*	100.0 (13.0, 100.0)		100.0 (30.9, 100.0)	

*Severe gastroenteritis defined by a clinical scoring system based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral change
†ITT analysis includes all subjects in the efficacy cohort who received at least one dose of vaccine.
** Applicant Analysis

Multiple Rotavirus Seasons

The efficacy of RotaTeq through a second rotavirus season was evaluated in a single study (REST). Efficacy against any grade of severity of rotavirus gastroenteritis caused by rotavirus serotypes G1, G2, G3, and G4 through the two rotavirus seasons after vaccination was 71.3% (95% CI: 64.7, 76.9). The efficacy of RotaTeq in preventing cases occurring only during the second rotavirus season postvaccination was 62.6% (95% CI: 44.3, 75.4). The efficacy of RotaTeq beyond the second season postvaccination was not evaluated.