

FDA Briefing Document

Vaccines & Related Biological Products Advisory Committee Meeting

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RotaTeq™ (rotavirus vaccine, live, oral, pentavalent)

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1.0 GENERAL INFORMATION

Product name

Proper name: Rotavirus Vaccine, Live, Oral, Pentavalent
Proposed trade name: RotaTeq™

Product composition (from the Applicant's proposed label):

RotaTeq™ is a live, oral pentavalent vaccine for use in the prevention of rotavirus gastroenteritis. The vaccine contains 5 live reassortant rotaviruses. The rotavirus 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 reassortant virus expresses the attachment protein, P1 (genotype P[8]), from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain (see Table 1).

Table 1. Components of RotaTeq™

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)
G1	WI79 – G1, P1[8]	WC3 - G6, P7[5]	G1 , P7[5]
G2	SC2 – G2, P2[6]		G2 , P7[5]
G3	WI78 – G3, P1[8]		G3 , P7[5]
G4	BrB – G4, P2[6]		G4 , P7[5]
P1	WI79 – G1, P1[8]		G6, P1[8]

Each 2-mL dose contains the following human-bovine rotavirus reassortants: G1, G2, G3, G4, and P1. The minimum dose levels of the reassortants are as follows:

G1 2.2 X 10⁶ infectious units
G2 2.8 X 10⁶ infectious units
G3 2.2 X 10⁶ infectious units
G4 2.0 X 10⁶ infectious units
P1 2.3 X 10⁶ infectious units

The reassortants are propagated in Vero cells using standard tissue 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 and also tissue culture media. There are no preservatives or thimerosal present.

Manufacturer Merck & Co., Inc.

Proposed indication Prevention of rotavirus gastroenteritis in infants and children.

RotaTeq™ is an oral pentavalent vaccine indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1 (e.g., G9). RotaTeq™ may be administered as early as six weeks of age.

Dosing regimen	3 doses with the first dose given at 6-10 weeks of age, followed by two additional doses, the interval between doses is 4-10 weeks
Route of administration	Oral, 3 doses

EXECUTIVE SUMMARY

This briefing document 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 to be separated by 4-10 week intervals.

The Biologics Licensing Application (BLA) contains five phase 1 and 2 trials and 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 with administration of this live oral rotavirus vaccine, the Applicant enrolled over 70,000 infants in the pivotal phase 3 trials 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). Exact efficacy estimates from study 006 (REST) have not yet been finalized, pending resolution of discrepancies in counts of follow-up time. 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. Regarding study 007, the statistical primary null hypothesis was that the efficacy of RotaTeq™ at expiry potency against all G1-, G2-, G3-, or G4-specific cases of rotavirus gastroenteritis occurring at least 14 days post-dose 3 through one rotavirus season would be $\leq 0\%$.

The numbers of the Applicant and the FDA statistical reviewer are different for the total follow-up time and numbers of gastroenteritis cases in study 007. This issue is currently under review and being discussed by FDA and the Applicant. The FDA statistical reviewer's conclusion regarding study 007 was that it was highly likely that RotaTeq™ had achieved the primary objective in this trial. Please see the FDA statistical review for additional information.

Immunogenicity

The Applicant states that an immunologic surrogate of efficacy has not yet been identified in the clinical trials of RotaTeq™. The use of immunogenicity data from RotaTeq™ has been used to demonstrate manufacturing consistency 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) for RotaTeq™ or in assessing protection against rotaviral disease.

SafetyIntussusception

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 at 42 and 60 days post vaccination. There was also no evidence of a clustering of intussusception cases within a 7-day or 14-day window post-vaccination.

In study 006 (REST), for the pre-specified 42-day post-vaccination endpoint, the results demonstrated 6 cases of intussusception 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.

However, regarding the risk for intussusception, it is important to keep in mind some of the characteristics of the population that was enrolled in these phase 3 trials, i.e., the first dose was administered to healthy infants at an age of 6-12 weeks who had no underlying gastrointestinal disease and no history of immunodeficiency and concomitant administration of live, oral poliovirus vaccine was an exclusion criteria.

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. There is 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 34 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 Applicant states that the incidence of fever (temperature greater than 100.5°F) was comparable in the vaccine and placebo groups during the week after any dose.

The Applicant states that 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%).

The Applicant states that 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.

However, 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.

Responses to diphtheria, tetanus, pertussis and pneumococcal conjugate vaccine were measured after 3 doses at approximately age 7 to 8 months; responses to Hib, Hepatitis B and polio were measured after 2 doses at approximately age 5 to 6 months. Subjects were required to have received a neonatal dose of hepatitis B vaccine.

The antibody responses to these vaccines were compared between recipients of RotaTeq™ and placebo recipients with non-inferiority criteria based on: 1) the proportion of subjects achieving the standard seroprotection criteria established for poliovirus types 1, 2, and 3, hepatitis B, *Haemophilus influenza* type b (as measured by polyribosylribitol phosphate [PRP]), diphtheria, and tetanus; and 2) the geometric mean titers (GMTs) to pertussis toxin (PT), pertussis filamentous hemagglutinin (FHA), and pertussis pertactin and to pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

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. Assay validation data for the tetanus and diphtheria assays is under review.

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. The ratio of GMT's (RotaTeq™ ÷ Placebo) was 0.6 and the 95% CI on the ratio of RotaTeq™ to placebo was 0.4 to 0.8, leading to the conclusion that the results were not similar between the placebo and RotaTeq™ arm. 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 and diphtheria/tetanus.

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). 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 Applicant states that 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 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 and also at scheduled sample times of 4 to 6 days post vaccine dose. The Applicant states that 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 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.

2.0 INTRODUCTION AND BACKGROUND

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. The four G serotypes responsible for most cases, i.e. greater than 80% of rotavirus cases worldwide and greater than 90% of U.S. cases are G1, G2, G3 and G4. The most common P serotype associated with these strains is P1 (genotype 8).

The Applicant states that in study 006, the most prevalent serotype that caused rotavirus gastroenteritis was G1 followed by G2, G4, G3 and G9.

Newly emerging serotypes in Asia include serotype 9 (G9) and this has accounted for approximately 30% of all strains detected in Asia during the past 2 years. This vaccine does not include this serotype but P1 may provide some protection. The Applicant states that in studies 006 and 007 there were 5 cases of gastroenteritis due to G9 in the per protocol group with 1 vaccine to 4 placebo cases.

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.

2.1 EPIDEMIOLOGY OF ROTAVIRUS INFECTION

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

On a global scale, each year, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations, and 352,000–592,000 deaths (median, 440,000 deaths) in children less than 5 years of age. By age 5, nearly every child will have an episode of rotavirus gastroenteritis, 1 in 5 will visit a clinic, 1 in 65 will be hospitalized, and approximately 1 in 293 will die. 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

2.2 REGULATORY BACKGROUND

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.

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

RotaShield® (rotavirus vaccine [live, oral tetravalent], Wyeth Ayerst) was licensed in August 1998. Intussusception was listed in the package insert as an adverse event that occurred in the pre-licensure trials. Distribution began in October 1998 after the 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 1999, 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 1999, 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. 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 intussusception.

2.3 BASIS FOR LICENSURE

The proposed basis for licensure of this new rotavirus vaccine is 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® (rotavirus vaccine [live, oral tetravalent], Wyeth Ayerst), 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 i.e., 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.

3.0 CLINICAL OVERVIEW

The Biologics License Application (BLA) contains three pivotal phase 3 studies. For each of these studies, full study reports and datasets were submitted for FDA review.

The overall safety database for RotaTeq™ comprised 36,356 infants who received the final formulation of RotaTeq™ used in phase 3 and 2470 infants and 30 adult subjects who received earlier formulations in phase 1 and phase 2. 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.

Please see Table 2 below for a listing of the phase 1 and 2 studies contained in the BLA

Data from two phase 3 studies 006 and 007 will be the basis for establishing the efficacy of the final formulation of RotaTeq™ and the safety of this vaccine will be supported by the three phase 3 trials studies 006, 007 and 009.

Table 2 Overview of Phase 1 and 2 Clinical Studies Contained in the License Application

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 10 ⁶ , 1.6 x 10 ⁶ and 5 x 10 ⁵ PFU Group 4 quadrivalent G1, G2, G3 G4 at 5 x 10 ⁶ PFU Group 5 monovalent P1 at 5 x 10 ⁶ PFU	yes	yes	yes

3.1 EFFICACY

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). Please refer to the FDA statistical review for additional information regarding the efficacy of RotaTeq™. The efficacy data is still under final FDA review.

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.**

Efficacy was 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 3 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 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 3 below.

Table 3 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.

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 was 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.

Efficacy (FDA analysis):

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. Regarding study 007, the statistical primary null hypothesis was that the efficacy of RotaTeq™ at expiry potency against all G1-, G2-, G3-, or G4-specific cases of rotavirus gastroenteritis occurring at least 14 days post-dose 3 through one rotavirus season would be $\leq 0\%$.

The following were results obtained by the FDA statistical reviewer as well as those provided by the Applicant in the original BLA submission for study 007 (See Table 4 below).

Table 4. Efficacy results for 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
Gastroenteritis cases	15	15	52	54
Efficacy estimate (%) and 95% confidence interval	71.0 (48.4, 85.0)	72.5 (50.5, 85.6)		

FDA analysis*

The numbers of the Applicant and the FDA statistical reviewer are different for the total follow-up time and for the numbers of gastroenteritis cases in study 007. This issue is currently under discussion by FDA and the Applicant. The FDA statistical reviewer's conclusion regarding study 007 was that it was highly likely that RotaTeq™ had achieved the primary objective in this trial. Please see the FDA statistical review for additional information.

Efficacy (Applicant Analysis):

The efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity caused by the serotypes (G1, G2, G3 and G4) in the vaccine through the first rotavirus season post-vaccination was 74% (95% CI: 67%, 79%).

The efficacy of RotaTeq™ against severe rotavirus gastroenteritis (clinical score >16) was comparable between study 006 and 007. An analysis based on integrated data from the 2 studies showed that RotaTeq™ was 98% (95% CI: 90%, 100%) efficacious against severe rotavirus gastroenteritis caused by the serotypes in the vaccine through the first rotavirus season post-vaccination. See Table 5 below.

Table 5

Per protocol* Efficacy Analysis by Disease Severity (Efficacy Cohort Study 006 & 007)***

Disease Severity	Number of cases		% Efficacy	95% CI
	Vaccine (N=3484)	Placebo (N=3499)		
Any	97	369	74	67, 79
Severe**	1	57	98	90, 100
<p>*Per protocol population and per protocol case definition (includes only cases that occurred at least 14 days after Dose #3 through the first rotavirus season) **Severity score >16 N = number of subjects vaccinated.</p>				

Applicant Analysis***

3.2 THE PIVOTAL SAFETY STUDIES (STUDIES 006, 007 AND 009)

The Study Population

Inclusion Criteria

The study population in the phase 3 trials included healthy infants age 6 weeks through 12 weeks. 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 7 days following birth) of hepatitis B vaccine. Infants born prematurely (gestational age \leq 36 weeks) were eligible for enrollment according to their chronological age if they were healthy. There were no restrictions on breast-feeding or the use of concomitant vaccines other than OPV.

Exclusion Criteria

Important exclusion criteria for the pivotal safety studies were the following: children with a history of congenital abdominal disorders, intussusception, or abdominal surgery, known or suspected impairment of immunological function., prior administration of any rotavirus vaccine, fever, with a rectal temperature \geq 38.1°C (\geq 100.5°F) at the time of immunization, history of known prior rotavirus disease, chronic diarrhea, or failure to thrive, clinical evidence of active gastrointestinal illness, receipt of intramuscular, oral, or

intravenous corticosteroid treatment, 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, prior receipt of a blood transfusion or blood products, including immunoglobulins and 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.

Infants on inhaled steroids may have participated in the study. Infants with gastroesophageal reflux disease (GERD) could have participated in the study as long as the GERD was well controlled with or without medication.

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.

Please see Table 6 below which outlines the subject numbers in the treatment arms for the individual phase 3 studies. 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.

Table 6 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)	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 again this includes cross-treated and also 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 already included in the randomized totals for RotaTeq™ and Placebo 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:

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

Organization of Safety Cohorts for Phase 3 Studies 006, 007 and 009:

1) Safety Cohort

72,106 infants including 70,005 subjects from study 006, 1310 subjects from study 007 and 791 subjects from study 009 received at least one dose of RotaTeq™ or placebo. Please see Table 6 (above) for the distribution of subjects across the three pivotal phase 3 studies. It should be noted that in the clinical trials there were 76 cross-treated subjects who were infants whose actual treatment was different than what treatment arm they were randomized to 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.

Subset of Safety Cohort- Fecal Shedding

Fecal shedding of vaccine virus strains for rotavirus positive samples was evaluated in 2515 infants in study 006 and study 007. They were evaluated for fecal shedding at post-dose 1 (647 subjects), post-dose 2 (521 subjects) and post-dose 3 (1347 subjects).

2) Detailed Safety Cohort (DSC)

11,742 infants are in this cohort and this includes a subset of infants from study 006 (9640 subjects), and all of the infants in study 007 (1311 subjects) and in study 009 (791 subjects) and these were subjects who received at least one dose of RotaTeq™ or placebo and were not cross treated.*

*There were 11753 subjects in the Detailed Safety cohort and 11 subjects were cross-treated (11753-11= 11,742). There were 8 subjects in the RotaTeq™ arm and 12 subjects in the placebo arm who did not have follow-up.

Detailed Safety Cohort subjects in studies 006, 007 and 009 were from Germany (636 infants), Taiwan (188 infants), Finland (3380 infants) and the United States (7538 infants). The detailed safety cohort contained children who were mainly from developed/industrialized countries. Therefore, the detailed safety experience of RotaTeq™ may not capture certain types of adverse events and safety concerns specific to infants in the developing world. Please see Table 7 below.

Table 7. Demographics of the Detailed Safety Cohort (studies 006, 007 and 009)

Detailed Safety Cohort	RotaTeq™	Placebo	Cross-treated
Randomized (N)	6153	5589	11
Gender			
Male	3184	2896	5
Female	2969	2693	6
Age (weeks)			
Under 6 weeks	1 (3 wks.)	1 (4 wks.)	-
6-12 weeks	6138	5568	-
Over 12 weeks*	14	20	-
Race			
White	4003	3638	5
Hispanic American	736	589	2
Black	259	265	1
Native American	515	491	2
Asian	236	243	1
Multi-racial	359	325	-
Indian	24	27	-
European	8	4	-
Polynesian	9	5	-
African	4	2	-
Total randomized	11,753 subjects this includes a subset of subjects from study 006 (9648 subjects) and all of the subjects from studies 007 (1312 subjects) and 009 (793 subjects).		

* 34 infants were age >12 weeks: 33 infants randomized at age 13 weeks and 1 at age 14 weeks.

Subset of the Detailed Safety Cohort- U.S. Concomitant Use Cohort

1358 infants in the DSC study 006 group who received doses of RotaTeq™ or placebo on the same day as pre-specified pediatric vaccines administered according to the U.S. licensed schedule.

Subset of the Detailed Safety Cohort- German Detailed Safety Cohort

638 infants in the Detailed Safety study 006 group who received concomitant doses of a hexavalent vaccine that is not licensed in the U.S.

Subset of the Detailed Safety Cohort- Fecal Shedding

658 subjects in the Detailed Safety study 006 group who were evaluated for fecal shedding of vaccine virus strains evaluated at 4-6 days post-dose 1 (240 subjects), post-dose 2 (210 subjects) and post-dose 3 (208 subjects).

3.2.1 IMPORTANT ASPECTS OF THE STUDY DESIGN AND RESULTS OF STUDY 006 (REST).

This was a phase 3 double-blinded placebo-controlled, randomized, international, multi-center study to evaluate the efficacy, immunogenicity, and safety of RotaTeq™. Subjects who met the eligibility criteria for enrollment were randomized in a ratio of 1:1 to receive either RotaTeq™ at potency within the release range intended for the licensed product or placebo.

The two primary objectives were:

1. 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; and
2. To evaluate the safety of RotaTeq™ with respect to intussusception within 42 days following any vaccination.

Secondary Objectives included:

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 included:

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. (There may be no significant reduction overall in the number of health care contacts among the children who receive RotaTeq™ as compared to those who receive placebo; however, there may still be a shift from inpatient care to outpatient care for rotavirus disease because of a reduction in the severity of cases.)
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.

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 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.

IND and non-IND data in the BLA

The majority of the subjects enrolled in this trial (90%) were studied under U.S. IND except for 7779 subjects at clinical sites in Belgium, Germany, Italy, Mexico and Sweden (3868 in the placebo arm and 3901 in the RotaTeq™ arm and 10 subjects cross-treated.). The non-IND subjects contributed to the safety analyses but not to the efficacy analyses.

Strengths and Limitations of the Data

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 each vaccine dose on approximately 91% of the subjects in both the RotaTeq™ and placebo arms of the study.

Limitations of the study include 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.

SAFETY

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.

The Detailed Safety Cohort recorded these same parameters for a 42 day period post vaccination. Infants in the Detailed Safety Cohort 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”.

Please note that information regarding hematochezia was not solicited on the Pediatric Vaccine Report Card or in the AGE workbook.

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.

Table 8 Summary of Study Procedures for Patients in the 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	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	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	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 Clinical Study Report (CSR) Protocol 006.

3.2.2 INTUSSUSCEPTION

Intussusception (IT) is the most frequent cause of intestinal obstruction in the first 2 years of life, and occurs when a portion of the intestinal tract telescopes into a segment just caudal to it. Intussusception is an uncommon illness, with an estimated annual incidence of 1 out of 2000 among infants <2 years of age. Typical clinical symptoms are irritability, colicky abdominal pain, vomiting, lethargy, and bloody, mucous containing fecal matter known as ‘currant-jelly stools’. Physical examination may reveal a tender, sausage-shaped mass in the right upper or lower quadrant. The diagnosis is confirmed by contrast enema (air or barium), ultrasound, surgery, or at autopsy. Rarely, a case of intussusception will spontaneously reduce; however, if left untreated, the condition is often fatal. Although the etiology of intussusception is not well defined, infectious agents and abnormal immunologic or neurologic responses may be contributing factors.

The design for study 006 included 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. The diagnosis of intussusception had to be made radiographically, surgically or at autopsy.

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: 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)

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 trials. 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 (MSMC).

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 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.

Group-Sequential Statistical Design and Evaluation

Primary Hypothesis:

The primary safety hypothesis for REST was that the oral pentavalent human-bovine reassortant vaccine would not increase the risk of intussusception relative to placebo within 42 days of any dose. [The statistical criteria correspond to (1) The distribution of intussusception cases between vaccine and placebo groups (case split) would not reach the predefined safety boundary for any of the two overlapping day ranges (1 to 7 and 1 to 42 days following any dose) being monitored by the DSMB at any time during the trial; and (2) The upper bound of the exact 95% confidence interval estimate of the relative risk of intussusception at the end of the study had to be < 10 .] The primary analysis of intussusception included all cases positively adjudicated by the blinded SEAC, regardless of whether they were judged to be vaccine related. As a separate analysis, cases associated with an anatomic lead point would be excluded but there were no such cases.

REST employed a group-sequential design. Initially, 60,000 subjects were enrolled. If a decision regarding vaccine safety with respect to intussusception according to predefined statistical criteria could not be made after these first 60,000 subjects, then additional subjects were enrolled. The predefined statistical criteria discussed above referred to the acceptance region, which consisted of all case splits such that the upper bound on the exact 95% confidence interval for relative risk is ≤ 10 , and such that no safety monitoring boundary was reached. Thus, assuming the study was not stopped early by the DSMB for safety concerns, the DSMB biostatisticians and the Merck un-blinded statistician determined whether the case split fell into the acceptance region after the safety follow-up had been completed on the first 60,000 subjects. In May 2004 the DSMB recommended that an additional 10,000 subjects should be enrolled. No safety risk had been identified but the primary safety hypothesis with respect to intussusception had not been met. Safety monitoring by the DSMB continued until November 2004 when the DSMB stopped the study because the primary safety hypothesis had been satisfied. Subjects completed the dosing phase of their regimen and 42 days of safety follow-up.

The DSMB biostatisticians and the Merck unblinded statistician were responsible for evaluating the cases of intussusception with respect to group-sequential acceptance region criteria. The Applicant stated that the analysis was kept strictly confidential among

the DSMB biostatisticians, and appropriate reporting of the results followed in order to preserve the blinding of this study.

There were no cases of positively adjudicated intussusception (IT) in the smaller phase 3 studies 007 and 009.

There were 35 investigator-diagnosed cases of IT in study 006. Thirty-two of the 35 investigator-diagnosed cases were positively adjudicated by the SEAC and are presented as case splits in Table 9 below.

Table 9 depicts the study 006 (REST) intussusception case splits at intervals of 0-7 days, 0-14 days, 0-42 days, 0-60 days, 0-365 days and at 0-462 days post vaccine dose. For the intervals at 60 days or less, the table outlines where the IT cases occurred in relation to the particular dose of vaccine that the child had most recently received i.e. vaccine dose #1, vaccine dose #2 or vaccine dose #3.

The primary safety endpoint interval was pre-specified as the 0-42 day window.

Table 9 Intussusception Case Split for Study 006 with Interval Post –Vaccine Dose

Interval Post Vaccine Dose	All Cases of Intussusception		Vaccine Dose #1		Vaccine Dose #2		Vaccine Dose #3	
	RotaTeq™	Placebo	RotaTeq™	Placebo	RotaTeq™	Placebo	RotaTeq™	Placebo
Days								
0-7	1	0			1			
0-14	1	1			1			1
0-42	6	5		1	4	1	2	3
0-60	8	6	1	1	5	2	2	3
0-365	13	15						
0-462	13	19						

FDA Analysis*

The 0-7 day and 0-14 day evaluation window for intussusception (IT):

No clustering of IT within a 7-day or 14-day window is evident.

The 0-42 day IT evaluation window:

In the 42-day window results, there were 6 cases of IT in the RotaTeq™ group versus 5 cases of IT 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 by the FDA statistician. The upper bound of the 95% confidence interval is less than 10, which satisfies the prospectively specified primary safety objective of REST.

The 0-60 day IT evaluation window:

Although a 42-day window was pre-specified, the size of the window could be considered arbitrary. Thus, it is also reasonable to use a 60-day window since the time between any two doses was 4-10 weeks (28-70 days). The number of IT cases within a 60-day window post-dose was 8 cases of IT in the RotaTeq™ group and 6 cases in the placebo group, a relative risk estimate of 1.3 with a 95% confidence interval of (0.4, 4.7) as obtained by the FDA statistician.

The FDA statistical analysis also demonstrated the following:

After dose 2, 4 cases of IT were observed for the RotaTeq™ group compared to 1 case in the placebo group. [RR = 4.0 with a 95% CI of (0.4, 197.0)]. When the window size is expanded to 60 days, the number of IT cases in the RotaTeq™ group is 5, versus 2 in the placebo group [RR = 2.5 with 95% CI of (0.4, 26.3)].

No pattern emerges for when the IT cases occurred after each dose, for either the RotaTeq™ group or the placebo group when examined with a 60-day window.

When evaluating all of the IT cases confirmed for all subjects completing the follow-up period (see Table 9 at 0-462 days), the total number of IT cases is much greater in the placebo group (19) than in the vaccine group (13). The relative risk estimate is 0.68 with a 95% CI of (0.3, 1.5).

Intussusception in Phase 2 (Study 005-Dose ranging study)

In addition, there was a case of intussusception in the phase 2 study 005. This case occurred in a 7 month old Caucasian male who received a low-dose pentavalent vaccine formulation. At day 8 post-dose #1, he developed vomiting, hematochezia and on day 9 post-dose #1 he underwent surgery with reduction of an ileocecal invagination. The subject recovered and was subsequently given additional study vaccine doses #2 and #3. A stool sample was collected from the subject 3 days after the Dose 1 was given and no vaccine virus was identified in the sample. A pathology report of the resected tissue revealed benign lymphoid hyperplasia. The subject subsequently recovered and went on to receive Doses 2 and 3 of the study vaccine/placebo. This event occurred before the association of intussusception and the RotaShield™ vaccine had been reported.

Although this case was investigator-diagnosed and not adjudicated, it was confirmed at surgery. The Applicant was asked to perform an analysis adding this case, which had occurred in a recipient of an earlier formulation of RotaTeq™ within the 42 day window, to the cases of IT identified in study 006. The Applicant's analysis demonstrated that if

this case from study 005 is now counted, the overall relative risk estimate for IT is 1.4% with a 95% CI of (0.4 to 5.6).

Intussusception and Death in Study 006 (REST)

One death occurred in a subject reported to have a positively-adjudicated (confirmed) case of intussusception and septicemia. The death occurred outside of the 42 day post vaccine dose window. This subject was a 2-month old white male, entered into the study and randomized to receive RotaTeq™. On Day 96 post-dose 3, the subject developed abdominal pain and vomiting and was seen in a physician's office. The subject had passed 2 normal stools that day. On the afternoon of Day 98 post-dose 3, the subject was still vomiting, was lethargic, and passed 2 bloody stools. That same day he went to the emergency room, where he had 1 to 2 currant jelly-type stools. A barium enema was performed that revealed a profound ileocolic or ileoileal intussusception. The subject was taken to the operating room where the intussusception was surgically reduced, with a portion of necrotic bowel removed. However, the post-operative course was complicated by septicemia and the subject died on day 99 post-dose 3.

3.2.3 DEATHS

There were no deaths in the phase 1 and 2 trials.

There were 52 deaths in the phase 3 clinical trials. The number of deaths was balanced between the two treatment arms with 25 deaths in the RotaTeq™ arm and 27 deaths in the placebo arm. There were no deaths in the cross-treated subjects.

The most common cause of death in each treatment arm was SIDS (17 deaths) with eight deaths in the RotaTeq™ arm and nine deaths in the placebo arm.

Deaths in the RotaTeq™ Arm

For the RotaTeq™ arm, there were 7 SIDS deaths in study 006 and 1 SIDS death in study 007. Autopsies were obtained for all SIDS deaths except one SIDS death in study 007.

Regarding the timing of these deaths, fifteen of 25 deaths in the RotaTeq™ arm occurred within 42 days of vaccination. There were 15 males and 10 female infants who died. Overall, in an analysis of the deaths, there were no unusual trends related to the subject demographics. Causes of death were varied and included SIDS, infections such as meningitis, bronchopneumonia and pyelonephritis, motor vehicle accidents, injuries. The child who had intussusception and died at day 99 post-dose 3 has already been discussed above. A complete listing of the study deaths in the RotaTeq™ treatment arm is provided below:

Causes of Death in the RotaTeq™ arm in the Phase 3 studies

AN*	Age (wks.)	Sex	Race	Treatment	Relday	Cause of death	Onset	Vaccine#
10859	12	male	white	RotaTeq	3	SIDS	3	1
71865	10	female	white	RotaTeq	3	SIDS	3	1
51464	8	male	black	RotaTeq	14	Pyelonephritis acute	14	1
36545	9	male	Hispa	RotaTeq	19	SIDS	19	1
35522	11	male	white	RotaTeq	20	SIDS	20	1
89236	10	male	multi	RotaTeq	21	Meningitis bacterial	21	1
39911	10	male	Hispa	RotaTeq	31	SIDS	31	1
67540	8	female	Hispa	RotaTeq	35	Neoplasm malignant	35	1
81747	9	female	white	RotaTeq	40	Asphyxiation	40	1
49807	10	male	multi	RotaTeq	47	SIDS	47	1
53660	8	male	white	RotaTeq	79	Non-accidental injury to child	79	1
26340	8	male	white	RotaTeq	118	Road traffic accident	118	1
89222	10	female	multi	RotaTeq	189	Bronchopneumonia	189	1
75312	9	male	Hispa	RotaTeq	48	SIDS	15	2
65570	8	male	multi	RotaTeq	52	Sudden death unexplained	21	2
46518	12	female	white	RotaTeq	68	Motor vehicle accident	33	2
72212	8	female	black	RotaTeq	69	Bronchopneumonia	6	2
42327	7	male	black	RotaTeq	144	Motor vehicle accident	81	3
81410	10	female	black	RotaTeq	144	Death	16	3
3810	7	female	NatAm	RotaTeq	218	Motor vehicle accident	154	3
43717	9	male	white	RotaTeq	218	Intussusception	96	3
71064	7	female	NatAm	RotaTeq	312	Cardio-respiratory arrest	210	3
10084	12	male	white	RotaTeq	318	Pineal neoplasm malignant	248	3
11535	9	female	white	RotaTeq	512	Asphyxiation	441	3
1946**	10	male	Hispa	RotaTeq	84	SIDS	41	2

*AN is allocation number

Relday is day in relation to vaccine dose #1

Onset is day in relation to most recent dose of study vaccine

**study 007 subject

Deaths in the Placebo Arm

For the Placebo arm, there were 9 SIDS deaths. Autopsies were obtained for all SIDS deaths. Regarding the timing of these deaths, 13 of 27 deaths occurred within 42 days of vaccination. There were 14 males and 13 female infants who died. There were no unusual trends related to the causes of death or regarding the demographics of the cases of these infants who died. The causes for death were varied including pneumonia, sepsis, neoplasm, malignancy, drowning. A complete listing of the study deaths in the placebo arm is provided below:

Causes of Death in the Placebo Arm in the Phase 3 studies:

AN*	Age (wks.)	Sex	Race	Treatment	Relday	Cause of death	Onset	Vacc #
41128	10	female	white	Placebo	30	Cardiac failure	30	1
47230	10	male	Hispa	Placebo	149	SIDS	149	1
52136	9	female	white	Placebo	19	SIDS	19	1
59465	10	male	Hispa	Placebo	115	Haemorrhage	115	1
61635	12	male	white	Placebo	11	SIDS	11	1
70753	9	female	Hispa	Placebo	26	SIDS	26	1
76644	8	female	black	Placebo	26	SIDS	26	1
1699	9	male	white	Placebo	75	SIDS	25	2
3148	12	male	Hispa	Placebo	131	Sepsis (E. coli)	89	2
33605	11	female	Hispa	Placebo	104	Unknown cause of death	38	2
35490	7	female	black	Placebo	59	SIDS	26	2
41576	7	male	Hispa	Placebo	162	Drowning	107	2
44454	7	male	Hispa	Placebo	41	Septic shock	13	2
73125	9	male	white	Placebo	332	Heat exhaustion	260	2
82679	10	male	black	Placebo	111	Death	55	2
89402	9	male	multi	Placebo	98	Pneumonia	37	2
96099	9	female	white	Placebo	86	SIDS	30	2
39442	12	male	white	Placebo	60	Neoplasm malignant	1	3
55579	10	female	white	Placebo	269	Cancer	152	3
63187	12	male	white	Placebo	181	Death unexplained	75	3
64659	10	male	white	Placebo	506	Interstitial lung disease	435	3
71412	7	female	NatAm	Placebo	123	Cardiopulmonary failure	46	3
74032	10	female	multi	Placebo	564	Anoxic brain damage	445	3
79119	7	male	black	Placebo	146	Status epilepticus	62	3
80862	7	female	black	Placebo	280	SIDS	199	3
93017	6	female	black	Placebo	329	Bilateral pneumonia	245	3
95794	10	female	Hispa	Placebo	71	Unknown cause of death	9	3

*AN is allocation number

Relday is day in relation to vaccine dose #1

Onset is day in relation to most recent dose of study vaccine

3.24 SERIOUS ADVERSE EVENTS and ADVERSE EVENTS

There were 2470 infants and 30 adults who participated in the phase 1 and 2 studies. The vaccine formulation used in these earlier trials was different than the product used in the phase 3 studies. There was one case of intussusception which occurred in a 7 month old child in study 005 at day 9 post-dose #1 which has already been discussed.

Serious Adverse Events (SAEs) for the Phase 3 Studies (006, 007 and 009)

In the phase 3 studies, safety monitoring was required for a period of 42 days after each vaccine dose. However, study 006 (REST), was also designed to capture intussusception cases and serious adverse events up to 365 days beyond the first vaccine dose.

Consequently, safety data for serious adverse events is presented for both ≤ 42 days and time periods from the first day after vaccination beyond 42 days designated “any time”. Safety data for time periods beyond 42 days was predominantly from study 006.

Table 10 below outlines the distribution of all serious adverse events for all subjects in the phase 3 studies 006, 007 and 009 using the two time periods “any time” and “less than or equal to 42 days”. The number of serious adverse events are presented by individual study and then summarized by treatment arm across the three trials.

Table 10. Serious Adverse Events (SAEs) Phase 3 Studies 006, 007 and 009*

SAEs	Study 006			Study 007			Study 009			Total		
	Rota N= 35027	Pla N= 34978	X-Tr N= 73	Rota N= 650	Pla N= 660	X-Tr N= 1	Rota N= 679	Pla N= 112	X-Tr N= 2	Rota N= 36356	Pla N= 35750	X-Tr N= 76
# SAEs at any time	1352	1464	8	24	34	1	14	5	0	1390	1503	9
# subjects with 1 or more SAE at any time	881	973	6	21	28	1	10	3	0	912 2.5%	1004 2.8%	7
# SAEs at ≤ 42 days	1108	1088	7	24	31	1	14	5	0	1146	1124	8
# subjects with 1 or more SAE at ≤ 42 days	730	751	5	21	25	1	10	3	0	761 2.1%	779 2.2%	6
# subjects discontinue for SAE at any time	87	75	0	1	5	0	1	1	0	89 0.24%	81 0.23%	0
# subjects discontinue for SAE at ≤ 42 days	80	63	0	1	5	0	1	1	0	82 0.23%	69 0.20%	0
# Deaths at any time	24	27	0	1	0	0	0	0	0	25	27	0
#Deaths at ≤ 42 days	14	13	0	1	0	0	0	0	0	15	13	0

*FDA analysis

In the phase 3 studies there were 65,901 adverse events reported at “any time” and 2902 (4.4 %) were serious adverse events. In the placebo arm, 1004 subjects (2.5%) had at least one or more serious adverse events at any time compared to 912 (2.8%) for RotaTeq™. Similar results were noted when the serious adverse events were considered at ≤42 days: 761 RotaTeq™ subjects (2.1%) with at least one or more SAEs compared to 779 Placebo subjects (2.2%).

The most frequent causes for serious adverse events in the three phase 3 studies at any time and also at ≤42 days were bronchiolitis, gastroenteritis, pneumonia, pyrexia and urinary tract infection. The data regarding the number of subjects who experienced the most frequent serious adverse events at any time are in Table 11 below. There were more subjects in the placebo arm who had serious adverse events due to bronchiolitis and gastroenteritis across the phase 3 studies “at any time”.

Table 11. Most Frequent Serious Adverse Events in the Phase 3 Studies*

Most frequent SAEs in Phase 3	RotaTeq™ (N=36356)	Placebo (N=35750)
Bronchiolitis	233 (0.64 %)	268 (0.75 %)
Gastroenteritis	76 (0.21 %)	129 (0.36 %)
Pneumonia	59 (0.16 %)	62 (0.17 %)
Pyrexia	50 (0.14 %)	50 (0.14 %)
Urinary Tract Infection	39 (0.11 %)	31 (0.08 %)

*FDA analysis

Serious Adverse Events Resulting in Discontinuation

The percentage of subjects in the RotaTeq™ arm who discontinued at “any time” and at ≤42 days for a serious adverse event was 0.25% and 0.23% respectively and this was similar to the number of placebo subjects who discontinued at “any time” (0.23%) and at ≤42 days (0.20%). The most frequent reasons to discontinue for a serious adverse event at any time are outlined in Table 12 below.

Table 12. Most Frequent Serious Adverse Events that led to Discontinuation in Phase 3*

Most frequent SAEs that led to discontinuation at any time post vaccine dose in Phase 3	RotaTeq™ (N= 36356)	Placebo (N= 35750)
Gastroenteritis	4 (0.010 %)	9 (0.025 %)
SIDS	7 (0.020 %)	7 (0.020 %)
Inguinal Hernia	6 (0.017 %)	7 (0.020%)
Bronchiolitis	5 (0.014 %)	7 (0.020 %)
Convulsion	6 (0.020 %)	2 (0.006 %)
Vomiting	3 (0.008 %)	0 (0.000 %)
Pyrexia	2 (0.006 %)	2 (0.006 %)

* FDA analysis

The numbers of subjects who discontinued at any time for the frequent serious adverse events in the table above are small and it is difficult to draw definitive conclusions regarding this data. However, more subjects discontinued for convulsion and vomiting in the RotaTeq™ arm while more subjects discontinued for gastroenteritis in the placebo group.

In studies 006, 007 and 009, at less than or equal to 42 days post-dose, it appeared that serious adverse events occurred in a similar distribution across the treatment arms: 43% of SAEs (placebo) and 46% of SAEs (RotaTeq™) occurred after dose 1, 34% of SAEs (placebo) and 31% of SAEs (RotaTeq™) occurred after dose 2 and 23% of SAEs (placebo) and 23% of SAEs (RotaTeq™) occurred after dose 3.

The Applicant also evaluated hematochezia across the phase 3 trials during 42 days after vaccination by treatment group and dose. The incidence of hematochezia appeared to be similar for the RotaTeq™ treatment arm when compared to placebo after dose 1, 2 or 3.

In the FDA analysis of hematochezia for the Detailed Safety Cohort, at 7 days and at ≤ 42 days post vaccine dose, the incidence of hematochezia was similar across the treatment arms, i.e., at 7 days RotaTeq™ (0.3%) compared to placebo (0.4%) and at ≤ 42 days RotaTeq™ (0.8%) compared to placebo (0.7%). It is important to keep in mind that hematochezia was not a solicited adverse event on the VRC or AGE workbook

Adverse Events

The Applicant states that within the 42 days after any dose, infants who received RotaTeq™ when compared to placebo experienced vomiting and diarrhea 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%). The Applicant states that 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%).

Overall, infants appeared to tolerate RotaTeq™ when compared to placebo.

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