Rotavirus Gastroenteritis Regardless of Serotype
The rotavirus serotypes identified in the efficacy subset of REST and Study 007 were G1, P1[8]; G2, P1[4]; G3, P1[8]; G4, P1[8]; and G9, P1[8].

In REST, the efficacy of RotaTeq against any grade of severity of naturally occurring rotavirus gastroenteritis regardless of serotype was 71.8% (95% CI: 64.5, 77.8) and efficacy against severe rotavirus disease was 98.0% (95% CI: 88.3, 99.9). The ITT efficacy starting at dose 1 was 51.0% (95% CI: 41.7, 58.9) for any grade of severity of rotavirus disease and was 96.4% (95% CI: 86.4, 99.6) for severe rotavirus disease.
In Study 007, the primary efficacy of RotaTeq against any grade of severity of rotavirus gastroenteritis regardless of serotype was 72.7% (95% CI: 51.9, 85.4) and efficacy against severe rotavirus disease was 100% (95% CI: 12.7, 100). The ITT efficacy starting at dose 1 was 48.0% (95% CI: 21.6, 66.1) for any grade of severity of rotavirus disease and was 100% (95% CI: 31.0, 100.0) for severe rotavirus disease.

Rotavirus Gastroenteritis By Serotype
The efficacy against any grade of severity of rotavirus gastroenteritis by serotype in REST is shown in Table 27.

Table 27
Serotype-specific efficacy of RotaTeq against any grade of severity of rotavirus gastroenteritis among infants in REST through first rotavirus season post-vaccination (Per Protocol)

Serotype identified by PCR	Number of cases RotaTeq (N=2,834)	Number of cases Placebo (N=2,839)	% Efficacy (95% Confidence Interval)
Serotypes present in RotaTeq			
G1, P1[8]	72	286	74.9 (67.3, 80.9)
G2, P1[4]	6	17	63.4 (2.6, 88.2)
G3, P1[8]	1	6	NS
G4, P1[8]	3	6	NS
Serotypes not present in RotaTeq			
G9, P1[8]	1	3	NS
Unidentified*	11	15	NS

N=number vaccinated
NS=not significant
*Includes rotavirus antigen-positive samples in which the specific serotype could not be identified by PCR

Medical Officer comments:
Serotype G1 is the most prevalent serotype in U.S. Efficacy was significant against G1 and G2 but not significant against serotypes that were less prevalent such as G3, G4 and G9.

Immunogenicity

From the Applicant:
Subsets of subjects in the Efficacy Cohort and the Taiwan Cohort were pre-selected from randomized subjects across all investigators participating in these cohorts to prevent selection bias, for the evaluation of the antibody responses to RotaTeq™, which included:

- The first 300 subjects randomized in Finland
- The first 300 subjects in the United States who were enrolled in the Efficacy Cohort, but were not within in the U.S. Concomitant Use Cohort (referred to as the U.S. Efficacy With Scheduled Serum Samples 14 DaysPostdose 3 subset)
- The first 300 subjects randomized in the U.S. Concomitant Use Cohort
- The first 300 subjects randomized from the Navajo and White Mountain Apache Nations
- The first 100 subjects randomized in the Taiwan Cohort.

The timing for the collection of scheduled serum samples varied in different subsets of subjects. For subjects participating in the Efficacy Cohort from Finland and the United States, not including the U.S. Concomitant Use Cohort, serum samples were collected before vaccination Visit 1 (Predose 1), vaccination Visit 3 (Postdose 2), and 14 days after vaccination Visit 3 (Postdose 3). For subjects participating in the U.S. Concomitant Use Cohort and the subjects enrolled from the Navajo and White Mountain Apache Nations, serum samples were collected before vaccination Visit 1 (Predose 1), before vaccination Visit 3 (Postdose 2), and 42 days after vaccination Visit 3 (Postdose 3). For subjects in the Taiwan Cohort, only 2 serum samples were collected, one before vaccination Visit 1 (Predose 1) and one 42 days after vaccination Visit 3 (Postdose 3). Initially, serum was collected 14 days Postdose 3 in the subset of subjects from Finland and the subjects referred to as the “U.S. Efficacy With Scheduled Serum Samples 14 Days Postdose 3” subset. When the U.S. Concomitant Use Cohort was added to the study, the Postdose 3 sample collection time was changed from 14 days to 42 days in order to permit appropriate evaluation of immunogenicity of the concomitantly administered vaccines**.** Subjects from the Navajo and White Mountain Apache Nations and from Taiwan also had the Postdose 3 sample collection at 42 days to correspond to the timing of the safety follow-up.

Comparison of Immunogenicity Results of All Studies serum neutralizing antibody (SNA) and serum IgA
Immunogenicity data were not integrated based on results observed from previous clinical trials showing that the magnitude of antibody responses vary with potency and that there is no definite immunologic surrogate marker of efficacy. Therefore, integrating immunogenicity data observed across clinical trials, which utilized a range of potencies, would have limited clinical significance. The Phase III clinical trials confirmed the observation that the magnitude of antibody responses varied with potency. Immunogenicity results from Protocol

007, which evaluated the expiry potency (end-of-shelf-life potency) of the pentavalent vaccine, showed generally lower antibody responses to the components of the vaccine than those achieved in Protocol 006 (REST) and Protocol 009 (release potency).

Observational comparison of antibody responses across clinical trials shows that the Postdose 3 GMTs of SNA to G1 and serum anti-rotavirus IgA were generally similar and as expected based on the potency being evaluated. The percentage of infants who had a significant response (i.e., ≥3-fold rise in antibody titer from baseline to Postdose 3 in serum anti-rotavirus IgA was >85% among subjects who received the human-bovine reassortant rotavirus vaccine across all the Phase II and Phase III clinical trials, which utilized various vaccine formulations and potencies. Low G2 and G3 SNA responses were observed in all Phase II and Phase III clinical trials with one exception. In Protocol 005, a Phase II clinical trial, a high Postdose 3 GMT of SNA against G3 using the Ohio State University (OSU) 78-8 assay had been demonstrated (the percentage of infants with a ≥3-fold rise was 84.8%). However, a much lower response was observed in the Phase III trials. Due to these unexpected results, an investigation was conducted to determine if a root cause could be identified. The investigation included possible clinical, formulation, manufacturing process, and assay causes for the finding; however, a definitive root cause could not be determined. The low Postdose 3 GMTs of SNA against G2 and G3 observed in the Phase III trials is not consistent with G2 and G3 efficacy data against naturally-occurring rotavirus gastroenteritis caused by the G2 and G3 serotypes. In Protocol 006 (REST), the efficacy estimates for the G2 and G3 serotypes were 63.4% and 82.7%, respectively. The vaccine utilized in the clinical trials of Protocol 006 (REST) and Protocol 009 was within the release range of potencies intended for the licensed product. An observational comparison between these 2 clinical trials with respect to Postdose 3 GMTs for rotavirus serotypes G1, G2, G3, G4, and P1 SNA and serum anti-rotavirus IgA and the proportions of subjects with a ≥3-fold rise in antibody level from baseline to Postdose 3 for rotavirus serotypes G1, G2, G3, G4, and P1 SNA showed that the antibody responses in Protocol 009 were generally similar to the antibody responses in Protocol 006 (REST), where efficacy against rotavirus gastroenteritis was demonstrated.

Regarding serum IgA and similar to SNA, 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 after a three-dose regimen when compared to 12.3%-20.0% of 397 placebo recipients (see Tables 28, 29 and 30 below).

Table 28 Immunogenicity Summary for Serum Anti-Rotavirus IgA Response Among SubjectsWith Scheduled 14 Days Post-dose 3 Serum Samples in the Per-Protocol Population(Protocol 006 [REST])

	RotaTeq™	Placebo
Predose 1 Vaccination		
Subjects tested with data available for analysis†	231	228
GMT (units/mL) and 95% confidence interval	0.2 (0.1, 0.2)	0.2 (0.1,0.2)
Postdose 3 Vaccination		
Subjects tested with data available for analysis‡	197	170
GMT (units/mL) and 95% confidence interval	337.6 (265.6, 429.3)	0.3 (0.2, 0.4)
Three-fold rise		
Subjects tested with Predose 1 and Postdose 3 data available for analysis‡	189	161
Number (%) of subjects with ≥3-fold rise in anti-rotavirus IgA, and 95% confidence interval	180 (95.2) (91.2, 97.8)	23 (14.3) (9.3, 20.7)

† Excludes protocol violators and subjects with invalid data based on laboratory determinations.
‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of 9 to 33 Postdose 3 day range.
NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the Data Analysis Plan for Protocol 006 (REST).
GMT = Geometric mean titer; EIA = Enzyme immunoassay.

*From Applicant

Table 29 Immunogenicity Summary for Serum Anti-Rotavirus IgA Response Among Subjects With Scheduled 42 Days Post-dose 3 Serum Samples in the Per-Protocol Population (Protocol 006 [REST])*

	RotaTeq™	Placebo
Predose 1 Vaccination		
Subjects tested with data available for analysis†	275	289
GMT (units/mL) and 95% confidence interval	0.3 (0.3, 0.4)	0.3 (0.2,0.4)
Postdose 3 Vaccination		
Subjects tested with data available for analysis‡	186	162
GMT (units/mL) and 95% confidence interval	365.2 (307.9, 433.1)	1.4 (0.9, 2.0)
Three-fold rise		
Subjects tested with Predose 1 and Postdose 3 data available for analysis‡	183	163
Number (%) of subjects with ≥3-fold rise in anti-rotavirus IgA, and 95% confidence interval	178 (97.3) (93.7, 99.1)	27 (16.5) (11.2, 23.2)

† Excludes protocol violators and subjects with invalid data based on laboratory determinations.
‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of 37 to 61 Postdose 3 day range.
NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the Data Analysis Plan for Protocol 006 (REST).
GMT = Geometric mean titer; EIA = Enzyme immunoassay.

*From Applicant

Table 30 Immunogenicity Summary for Serum Anti-Rotavirus IgA in Per-Protocol Populations at 42 days Post-Dose 3 (Protocol 007) *

Serum Anti-Rotavirus IgA		
	RotaTeq™ at Expiry Potency (≈1.1 x 10^7 IU/Dose)	Placebo
Predose 1		
Subjects tested with data available for analysis†	80	86
GMT (units/mL) and 95% confidence interval		0.2 (0.1, 0.3)
Postdose 3		
Subjects tested with data available for analysis‡	68	74
GMT (units/mL) and 95% confidence interval	200.0 (131.9, 303.0)	0.3 (0.2,0.6)
Three-fold rise		
Subjects tested with Predose 1 and Postdose 3 data available for analysis‡	67	73
Number (%) of subjects with ≥3-fold rise in anti-rotavirus IgA, and 95% confidence interval	64 (95.5) (87.5, 99.1)	9 (12.3) (5.8, 22.1)

† Excludes protocol violators and subjects with invalid data based on laboratory determinations.
‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of a specified day range.
NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the Data Analysis Plan for Protocol 007.
GMT = Geometric mean titer; EIA = Enzyme immunoassay; IU = Infectious units.

*From Applicant.

Breast Feeding

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. The following section is an exploratory analysis of efficacy in breast fed infants. Merck did not provide this analysis in the original BLA submission but submitted this analysis and data (--- transport files) to the BLA upon the FDA’s request during the review period.

Merck exploratory analysis on breast feeding (from the Applicant):

The data used for this analysis were based on the subject’s breast-feeding

status, which was captured at each of the 3 vaccination visits on a worksheet that had 5 possible categories. A numerical value was assigned to each category and values were summed across the vaccination visits to give an overall cumulative score. The breast feeding categories and corresponding numerical values assigned were:

- Breast Feeding only = 4
- Combination of mostly breast and some formula = 3
- Combination of half and half = 2
- Combination of mostly formula and some breast = 1
- Formula Feeding only = 0

After the overall score was determined, the status was subsequently categorized to label a subject's level of breast-feeding for all vaccination visits. These categories and corresponding values are displayed as Never (0) indicating that the subject was exclusively formula-fed [n=1390 subjects contributing to efficacy analysis], Some (1-11) indicating that the subject received a combination of breast and formula feeding [n= 1666 subjects contributing to efficacy analysis], and Always (12) indicating that the subject was exclusively breast-fed [n= 1448 subjects contributing to efficacy analysis].

A status of Unknown was assigned when a subject's breast-feeding status was not determinable due to lack of data. The per-protocol population and case definition as described in the clinical study report was used.

As shown in Tables 30 and 31, for subjects who were never breast-fed, the point estimate for efficacy was 68.3% (95% CI: 46.1, 82.1). For subjects who were partially (some) breast-fed, the point estimate for efficacy was 82.2% (95% CI: 72.3, 89.0), and for subjects who were always breast-fed, the point estimate was 68.0% (95% CI: 53.8, 78.3). In addition, the subjects contributing to the categories of "Some" and "Always" were combined to obtain a category of "Ever." For subjects who were ever breast-fed, the point estimate for efficacy was 75.5% (95% CI: 67.5, 81.7).

Medical Officer comments:
The Applicant concluded that breast-feeding did not appear to impact the efficacy of RotaTeq™. Please see the Applicant analysis presented in Tables 31 and 32 below. The FDA statistician did not perform an exploratory analysis regarding the impact of breast-feeding on efficacy. However, this reviewer provides an exploratory analysis on the proportion of subjects in each study arm who were breast fed and developed rotavirus gastroenteritis.

Table 31 Efficacy Analysis by Breast-feeding Status of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases Occurring Through the First Rotavirus Season That Began at Least 14 Days Post-vaccination Stratified in the Per-Protocol Population Using the Per-Protocol Case Definition*

	Never		Some		Always		Unknown	
	RotaTeq™	Placebo	RotaTeq™	Placebo	RotaTeq™	Placebo	RotaTeq™	Placebo
Subjects contributing to efficacy analysis	676	714	823	843	705	743	3	5
Days of efficacy follow-up	182144	182599	229000	226092	211936	211999	800	1709
Subjects classified as rotavirus gastroenteritis cases per per-protocol case definition	19	60	24	133	39	122	0	0
Efficacy estimate (%) and 95% confidence interval	68.3 (46.1, 82.1)		82.2 (72.3, 89.0)		68.0 (53.8, 78.3)			

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.

*Applicant Analysis

Table 32 Efficacy by Breast Feeding Status Combining Some and Always Categories to get an Ever category*

	Ever	
	RotaTeq™	Placebo
Subjects contributing to efficacy analysis	1528	1586
Days of efficacy follow-up	440936	438091
Subjects classified as rotavirus gastroenteritis cases per per-protocol case definition	63	255
Efficacy estimate (%) and 95% confidence interval	75.5 (67.5, 81.7)	---

*Applicant Analysis

Breast Feeding Data—FDA exploratory analysis

Analyses of the impact of breast-feeding on efficacy may be important because of concerns regarding possible neutralization of vaccine by antibody in breast milk.

The following section outlines the numbers of subjects who “breast-fed at any time” during the course of their participation in the trial and then specifically at “pre-treatment period 3”. The numbers of breast-fed infants at the later time

period before the third vaccination probably decreases because as the children age they are being weaned. Breast-feeding status at “Pre-treatment period 3” was chosen because this was just prior to administration of the third and last vaccine dose of the series and thus it was felt that safety ascertainment would be acceptable and the method of feeding described at that study visit for the “always” and “never” groups might best capture what was consistently done for the infant during the dosing period of the trial. This exploratory analysis did not take into account differences in follow-up time and an estimate of efficacy was not calculated. However, the FDA statistical reviewer provided the “cases” of acute rotavirus gastroenteritis which were taken from the per protocol efficacy analysis.

Treatment Arm “Breast Fed only” at any time	**# subjects**
Five Doses (Placebo, Placebo, RotaTeq, RotaTeq, RotaTeq)	1
Four Doses (Placebo, RotaTeq, Placebo, RotaTeq)	1
Four Doses (Placebo, RotaTeq, RotaTeq, RotaTeq)	6
Four Doses (RotaTeq, Placebo, RotaTeq, RotaTeq)	7
Four Doses (RotaTeq, RotaTeq, Placebo, RotaTeq)	5
Placebo	**15634**
RotaTeq	**15838**
Three Doses (Placebo, Placebo, RotaTeq)	3
Three Doses (Placebo, RotaTeq, Placebo)	1
Three Doses (Placebo, RotaTeq, RotaTeq)	2
Three Doses (RotaTeq, Placebo, Placebo)	1
Three Doses (RotaTeq, Placebo, RotaTeq)	1
Three Doses (RotaTeq, RotaTeq, Placebo)	2
Two Doses (Rotateq, Placebo)	1

Treatment Arm Breast fed only at pre-treatment period 3	**# subjects**
Four Doses (Placebo, RotaTeq, Placebo, RotaTeq)	1
Four Doses (Placebo, RotaTeq, RotaTeq, RotaTeq)	5
Four Doses (RotaTeq, Placebo, RotaTeq, RotaTeq)	4
Four Doses (RotaTeq, RotaTeq, Placebo, RotaTeq)	2
Placebo	**9608**
RotaTeq	**9785**
Three Doses (Placebo, RotaTeq, Placebo)	1
Three Doses (RotaTeq, RotaTeq, Placebo)	1

Breast -feeding Post Hoc FDA exploratory analysis

The efficacy population included 2834 subjects in the RotaTeq™ arm and 2839 subjects in the Placebo arm or a Total of 5673 subjects). The per protocol efficacy dataset has 4512 subjects with 2207 RotaTeq™ and 2305 Placebo for study 006.The number of infants who “breast-fed only” in the per protocol efficacy cohort was 2208 of the 4512 and this included RotaTeq™ 1079 and Placebo 1129 subjects and it was balanced across the treatment arms.

Failures :
Of the “breast fed only” infants at any time, 52/1079 (0.48 or 5%) RotaTeq™ subjects developed rotavirus gastroenteritis using “case date” entry and 182 of 1129 placebo subjects (0.161 or 16.1%) developed rotavirus gastroenteritis.
If you consider “breast fed only” (at pre-treatment period 3 --before 3rd dose—understanding that the numbers are smaller because some infants have probably been weaned) there are 1587 “breast fed only” infants (RotaTeq™ 774 and Placebo 813) with 43/774 RotaTeq™ who failed (0.055 or 6%) compared to 131/813 placebo (0.161 or 16%) subjects who failed.

There are 4590 infants descrbed in the first line Table 33 below and there were 5673 in the Per Protocol (PP) group but only 4512 provided in the efficacy dataset for this analysis. At pre-treatment 3 there are 3851 infants which may represent those most consistently fed by a certain route. There were 82 AGE cases of “any severity” for RotaTeq™ PP and 315 AGE cases for Placebo for any severity in the PP group.

Table 33 Acute Gastroenteritis Cases (AGE) of Rotavirus in the "Breast Feeding Only" vs "Formula Fed ONLY" Subjects in the Per Protocol (PP) Efficacy Cohort* in Study 006 **

	FDA "Breast Fed ONLY" Merck "Always" Breast-fed				**FDA "Formula Fed ONLY" Merck "Never" Breast-fed**			
Numbers of subjects in:	**RotaTeq™ (%)**		**Placebo (%)**		**RotaTeq™ (%)**		**Placebo (%)**	
PP using "ONLY" the method of feeding specified at any time	**1079**		**1129**		**1172**		**1210**	
AGE cases in the PP at any time	**FDA 52 (4.8%)**	Merck 39	**FDA 182 (16.1%)**	Merck 122	**FDA 33 (2.9%)**	Merck 19	**FDA 127 (10.5%)**	Merck 60
PP still using "ONLY" the specified feeding method at pre-treatment #3 visit	**FDA 774**	Merck 705	**FDA 813**	Merck 743	**FDA 1146**	Merck 676	**FDA 1178**	Merck 714
AGE cases in the PP group still using "only " the specified feeding method at pre-treatment #3 visit	**FDA 43 (5.5%)**	Merck 39	**FDA 131 (16.1%)**	Merck 122	**FDA 33 (2.9%)**	Merck 19	**FDA 124 (10.5%)**	Merck 60

*** The Per protocol efficacy cohort for study 006 had 4512 subjects with 2207 subjects in the RotaTeq™ arm and 2305 subjects in the Placebo arm.**

****FDA analysis does not include those subjects who "sometimes" or "mostly" or "50% of the time" breast fed.**

Medical Officer comments:

The percentage of AGE cases are lower in the 'formula fed only' group for both treatment arms. Overall, there were more AGE cases in the placebo subjects when compared to the RotaTeq™ subjects.

Gestational Age less than or equal to 36 weeks

Efficacy in gestational age less than or equal to 36 weeks.

Of the less than or equal to 36 weeks gestational age (GA) infants, 153 infants were included in the Per Protocol efficacy analysis; 78 in the placebo group and 75 in the RotaTeq™ group. In the placebo group, 10 of 78 infants (13%) developed an acute case of rotavirus gastroenteritis when compared to 3 of 75 RotaTeq™ recipients (4%). Please see Table 34 below.

Table 34 Cases of rotavirus gastroenteritis in Pre-Term Infants in REST*

Allocation Number	Chronologic Age (weeks)	Gestational Age (weeks)	Gender	Race	Study Site	Treatment	Case Date
1121	10	35	Male	White	092	Placebo	02/05/2002
1097	10	33	Male	White	092	Placebo	06/16/2002
1096	10	33	Male	White	092	Placebo	06/19/2002
3767	9	35	Female	NatAmer	102	Placebo	01/10/2003
1846	11	34	Female	White	092	Placebo	02/21/2003
30853	9	34	Female	White	067	Placebo	04/28/2003
30854	9	34	Male	White	067	Placebo	04/28/2003
71227	8	35	Female	NatAmer	102	Placebo	01/01/2004
59676	9	35	Female	NatAmer	102	Placebo	01/13/2004
71381	8	34	Female	NatAmer	102	Placebo	01/15/2004
3582	12	35	Male	NatAmer	102	RotaTeq	12/16/2002
3583	12	31	Female	NatAmer	102	RotaTeq	01/13/2003
59688	12	35	Male	NatAmer	102	RotaTeq	01/18/2004

*FDA summary

Analysis of efficacy in pre-term infants was not a primary or secondary endpoint of study 006 . This subset analysis was not perfomed by the FDA statistician. The Applicant performed an efficacy analysis in pre-term infants against any severity of rotavirus gastroenteritis caused by the G-serotypes included in the vaccine through the first rotavirus season after completion of vaccination with the following results: 70.3%, 95% CI (-15, 95)

Medical Officer comments:
The number of infants contributing to the per protocol efficacy analysis who were less than or equal to 36 weeks of age was small (153 subjects) and thus it is difficult to draw any conclusions regarding efficacy in these premature infants.

"Medically Compromised" Subjects
Cases of acute rotavirus gastroenteritis (AGE) that occurred in the placebo and RotaTeq™ arms of the per protocol population who were also considered "medically compromised" are shown in Tables 35 and 36 below.

Table 35 Acute rotavirus gastroenteritis episode (AGE) in the "Medically Compromised" Children in the Per Protocol Efficacy Cohort of REST*

	RotaTeq™	Placebo	Total
All Subjects in Per Protocol (PP) Efficacy Cohort	2207	2305	4512
"Medically Compromised" subjects in REST	301	317	618
"Medically compromised" subjects in the PP Efficacy	86	76	162
AGE cases in the "medically compromised" subjects in the PP efficacy cohort	1	5	6

*FDA analysis

Table 36 AGE cases in "Medically Compromised" Infants In Protocol 006 (REST)*

Allocation Number	Treatment	Case Date
267	**Placebo**	**04/07/02**
1678	**Placebo**	**05/21/02**
1309	**Placebo**	**02/01/03**
58523	**Placebo**	**02/15/03**
59934	**Placebo**	**12/21/03**
3679	**RotaTeq**	**12/12/03**

*FDA analysis

Medical Officer comments:
It is not possible to draw definitive conclusions regarding the efficacy of RotaTeq™ in this small subset of medically compromised subjects. The proportion protected was consistent with the results observed in the larger efficacy cohort.

8.1.1.2.3 SAFETY OUTCOMES
Phase 3 Clinical Trials (Study 006/REST, 007 and 009)

Safety was considered in terms of intussusception as well as general safety issues such as deaths, serious adverse events, adverse events and discontinuations. In addition, solicited adverse events such as fever, diarrhea, vomiting and irritability were considered in the detailed safety cohort. Safety in the premature infant population is discussed. Specific types of adverse events are highlighted such as hematochezia and seizures. This study section also considers Concomitant Vaccination.

The discussion of safety will consider the collective results for the three phase 3 trials i.e. studies 006 (REST), 007 and 009. Please see Table 36 below which outlines the subject numbers in the treatment arms for the individual phase 3 studies.

The REST trial included over 70,000 subjects (35,027 RotaTeq™ arm) who provided most of the phase 3 safety data. Study 007 (End-Expiry) contributed 1310 subjects (650 RotaTeq™ arm) and Study 009 (Lot Consistency) contributed 791 subjects (679 subjects RotaTeq™ arm) to the safety data base which included infants who received at least one vaccination of either the study vaccine or placebo. Please see the synopses for studies 007 and 009 (see page 147 and page 158, respectively) which includes demographic information and efficacy and safety summaries for each individual study.

When considering the overall demographics 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 37 below describes treatment allocation per study.

Table 37 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:

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. See Table 36 (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" 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).

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 were11753 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.

Medical Officer Comments:
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. Although not directly relevant to U.S. licensure, 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 38 below.

Table 38 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).

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 the next distal segment. Intussusception is an uncommon illness, with an estimated annual incidence of 1 out of 2000 among infants less than 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 of the abdomen. 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. It was important to define the procedure for establishing a case date because the primary safety hypothesis in the protocol was based on specific time intervals after vaccination. The **case date** was the date of the first (inpatient or outpatient) diagnostic radiographic or surgical procedure used to judge whether the potential case fulfills the criteria for a confirmed case. In situations where records did not indicate the date of the procedure, the hospital admission date was recorded as the case date.

The Applicant stated 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)

Medical Officer comments:
Criteria similar to Brighton level 2 and level 3 criteria, which may be more sensitive but less specific, were not used in the clinical trials (see Reference 15 which desribes the Brighton criteria in more detail).

The Brighton case definition and criteria for the diagnosis of acute intussusception in infants and young children: Intussusception is the invagination of one segment of intestine into a segment of distal intestine.

• **Level 1 of Diagnostic Certainty**
Surgical *criteria*: The demonstration of invagination of the intestine at surgery; *and*/*or* ***Radiologic*** *criteria*: The demonstration of invagination of the intestine by either air or liquid contrast enema; *or* The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be *reduced* by hydrostatic enema on *postreduction ultrasound*; *and/or* ***Autopsy*** *criteria*: The demonstration of invagination of the intestine.

• **Level 2 of Diagnostic Certainty**
Clinical criteria: Two major criteria (see table for major and minor criteria for diagnosis below); *or* 1 major criteria and 3 minor criteria (see table for major and minor criteria for diagnosis below).

• **Level 3 of Diagnostic Certainty**
Clinical criteria: Four or more minor criteria (see minor criteria for diagnosis below).

• **Any Level of Diagnostic Certainty**
In the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (e.g. volvulus or congenital pyloric stenosis).

Major and minor criteria used in the case definition for the diagnosis of IT:
Major criteria
1. Evidence of intestinal obstruction:
I. History of bile-stained vomiting;
and either
II. Examination findings of acute abdominal distension
and abnormal or absent bowel sounds;
or
III. Plain abdominal radiograph showing fluid levels *and*
dilated bowel loops.
2. **Features of intestinal invagination*:***
One or more of the following:
I. abdominal mass;
II. rectal mass;
III. intestinal prolapse;
IV. plain abdominal radiograph showing a visible intussusceptum
or soft tissue mass;
V. abdominal ultrasound showing a visible intussusceptum
or soft tissue mass;
VI. abdominal CT scan showing a visible intussusceptum

or soft tissue mass.

3. Evidence of intestinal vascular compromise or venous congestion:

I. Passage of blood per rectum;

or

II. Passage of a stool containing “red currant jelly” material;

or

III. Blood detected on rectal examination.

Minor criteria

• Predisposing factors: age <1 year and male sex;
• Abdominal pain;
• Vomiting;[4]
• Lethargy;[5]
• Pallor;[5]
• Hypovolemic shock;
• Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.

1 http://brightoncollaboration.org
2 Target sign or doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section.
3 If one major criterion is the passage of blood per rectum that is mixed in a diarrheal stool, consideration should be given to infectious causes (e.g., E. coli, shigella, or amoebiasis). In such cases two major criteria should be met.
4 If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion.
5 Lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with deterioration in cardiovascular status and impending hypovolemic shock.

Investigator Monitoring for Intussusception Cases

Active and passive surveillance was used to capture cases of intussusception. For active surveillance, parents/guardians of all subjects were contacted on approximately days 7, 14 and 42 after each dose of vaccine/placebo to follow up on any serious adverse experiences (SAEs) that may have occurred. In REST, from day 43 to day 365 after dose one or until the end of the trial, a postal or electronic mailing, telephone call, or home visit was used to contact the parent/guardian approximately every 6 weeks. The parent/guardian was asked if the child had been hospitalized or had received treatment in an emergency department or health care center. If the parents did not reply, or if the parents indicated that they sought medical care, the parent/guardian was contacted by telephone or home visit. The local investigator questioned the parents about the hospitalization using a questionnaire/checklist. This questionnaire/checklist had been designed to capture all cases of intussusception. If the case fulfilled the criteria, it was sent for adjudication. Information about deaths was also collected. For passive surveillance of intussusception, parents and guardians were asked to immediately notify study personnel if a subject was hospitalized. In REST, they received a study card to show to healthcare personnel which identified the subject as a participant in a rotavirus vaccine trial sponsored by the Applicant.

Impact of Different Immunization Schedules on Ascertainment for Intussusception at 42 days post vaccine dose

Infants enrolled in REST were from the U.S. and overseas sites such as Finland which contributed 33% and the U.S which contributed 48 % of the subjects. Consequently, children resided in countries where immunization schedules differed e.g. the U.S. schedule of vaccine administration is 2, 4, 6 months and Europeans may use a 2, 3, 4 month schedule. However, for all subjects the first of the 3 vaccine doses was given at 6-12 weeks of age and the interval between subsequent doses was 4-10 weeks and the 3 dose schedule had to be completed by 32 weeks of age.

The Timeline below demonstrates the different dosing schedules comparing children on the Finnish (2,3,4 month) schedule with the U.S.(2, 4,6 month) immunization schedule. For demonstration purposes, Day 0 represents the first dose as given at 2 months of age (8 weeks) and all other points on the Timeline represent days post dose #1. For U.S. subjects, the days where a 42 day post dose assessment was made included day 42 (post dose #1), day 102 (postdose #2) and day 162 (post dose #3). The Finnish infants on the 2, 3, 4 month immunization schedule shared with the U.S. infants a similar 42 day follow-up assessment day on day 102 (which was 42 days post dose #3 on the Finnish schedule or 42 days post dose #2 on the U.S schedule).

Timeline:

FINLAND **1st dose at age 8 weeks: 2, 3 ,4 month schedule; finishes at age 16 weeks**

Dose #1	***Dose #2***	***Dose #3***
8 weeks old	***12 wks old***	***16 wks old***
X	**X**	**X**

Day 0 **7 -14 -21 Days Post Dose #1** **Day 30** **Day 42** **Day 60** **Day 90** **Day 102** **Day 120** **Day 162**

/----------/---/---/-------/-----------/----------/----------/---------/----------/----------/----------

X	**X**	**X**
Dose # 1	***Dose #2***	***Dose #3***
8 wks. old	***16 wks old***	***24 wks old***

U.S. **1st dose at age 8 wks.: 2, 4, 6 month schedule; finishes at age 24 weeks**

Table 39 depicts the number and percentage of vaccinated subjects with follow-up for intussusception at 7, 14 and 42 days post vaccine dose. Safety ascertainment was greater than 90% except at 42 days post dose #1 and post dose #2 where it was 45 to 50% and similar across the treatment arms. This lower rate of ascertainment at 42 days post dose #1 and #2 was in part due to children not being counted because they were on a vaccine schedule (see above timeline) with a 30 day interval between doses. Thus, at an assessment time of 42 days, these infants on a 2,3,4 month schedule had already received two vaccine doses i.e. they were 30 days post dose #1 and 12 days post-dose #2.

Table 39 Number of Subjects in REST with follow-up for Intussusception*

Number of Subjects Vaccinated (34788)		Follow-up Time for Intussusception in relationship to vaccine dose # and time post dose	Number of Subjects Vaccinated (34837)	
Placebo (n)	Placebo %		RotaTeq™(n)	RotaTeq %
34768	99.9	7 day 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 day 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 day 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 then follow-up resumes thereafter for the next period post vaccine dose.

All cases of intussusception were captured and are depicted in Tables 40 and 41. In the relative risk calculation for intussusception for the primary endpoint within 42 days of any vaccine dose, the Applicant had taken into account the differences in follow-up time depending on the subject's immunization schedule. Within 42 days of any vaccine dose, there were 6 cases of intussusception in the RotaTeq™ arm (4 U.S. infants, 1 Costa-Rican infant and 1 German infant) and 5 intussusception cases in the placebo arm (3 U.S. infants and 2 Jamaican infants). Please see Table 39 below which depicts the children in each study arm who developed intussusception including their schedule of vaccination.

Table 40 Intussusception Cases within 42 days of any Vaccine Dose *

AN	Age at first vaccine dose (weeks)	Treatment	Vaccination schedule (day each dose was given)	Day Of IT	Vaccine Dose after which IT occurred	Sex	Race
76379	10	Placebo	1-67	28	2	Male	Hispanic
80926	8	Placebo	1-47-63	36	3	Male	Black
95433	9	Placebo	1	36	1	Female	White
77263	7	Placebo	1-43-85	42	3	Male	Black
93540	8	Placebo	1-62-125	9	3	Female	Hispanic
58531	10	RotaTeq™	1-71	19	2	Female	Multiracial
79306	10	RotaTeq™	1-67	2	2	Female	Native American
62653	9	RotaTeq™	1-47-89**	21	2	Male	White
65484	10	RotaTeq™	1-43-78	38	3	Female	White
76380	10	RotaTeq™	1-62-125	40	3	Female	Hispanic
67365	9	RotaTeq™	1-69	41	2	Male	Hispanic

*FDA analysis

**This infant enrolled at non-IND site #441, developed intussusception after dose #2 but a 3rd dose of RotaTeq™ was still administered.

AN =allocation number

IT = intussusception

Medical Officer Comments:

Although intussusception did not appear to be related to a particular schedule of vaccine administration, there were only 11 cases that occurred within 42 days of any vaccine dose and thus, it is not possible to draw definitive conclusions.

The calculation of relative risk and its confidence interval was based on the number of vaccinated cases conditioned on the total number of cases that developed during the trial. Estimates of relative risk and confidence limits computed were based on the number of subjects with confirmed cases of intussusception per number of subjects with complete 42 day follow-up.This IT analysis was pre-specified and the final intussusception (IT) analysis was adjusted for multiplicity, using a group sequential design according to the Jennison-Turnbull approach. See Section 8.1.1.2.2 which includes the Applicant's End of Study Analysis which is taken from p. 4607 CSR 006 (REST).

Adjudication and Data Safety Monitoring

Over approximately 467 days, across the phase 3 trials, there were 125 cases that were adjudicated (67 RotaTeq and 57 Placebo and 1 cross treated i.e. RotaTeq™- RotaTeq™- Placebo). There were 35 investigator diagnosed cases of intussusception (IT) and 32 of these were positively adjudicated by the SEAC (13 RotaTeq™ vs 19 placebo). There were 5 placebo cases that were adjudicated where there was not unanimous agreement on interpretation of the

radiographic reports. Four of the five final collaborative decisions for these cases were thus decided by majority vote (2/3). One of these five cases (AN 47937) involved disagreement on the radiographic interpretation but the intussusception was confirmed at surgery and thus the final collaborative decision was unanimous for this subject. The allocation numbers are provided for these placebo subjects AN 42089, 47937, 67514, 80926 and 62830 (See Table 41 below). Only one of these placebo cases (AN 62830) fell within the 42 day primary endpoint window and it was a placebo case that was negatively adjudicated.

Table 41 Potential Cases of Intussusception (IT) reviewed by the SEAC where members did not unanimously agree on radiographic results or where the final vote was not unanimous *

Subject Allocation Number (AN)	Treatment Arm	Relative Day to first Vaccine Dose	Final IT Adjudication	Procedure used to Confirm IT Diagnosis
42089	Placebo	320	Yes (2/3)	X-ray
47937	Placebo	122	2/3 said No but then case went to surgery so final adjudication was 3/3 Yes	Surgery
67514	Placebo	117	Yes (2/3) but considered non-adjudicated because x-ray data insufficient	X -ray
80926	Placebo	122	Yes (2/3)	X-ray
62830	Placebo	28	No (2/3)	X-ray

FDA summary*

Medical Officer comments:
Table 40 is included to illustrate how the SEAC functioned and to show the challenges related to the radiographic diagnosis of intussusception.

Data Safety Monitoring
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.

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, unblended 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.

Intussusception (Results)

In the Phase I and II studies, among 2470 recipients of RotaTeq and 716 placebo recipients, there was a single case of intussusception in a 7-month old male in study 005. This case occurred in a 7 month old Caucasian male who received a low-dose (5×10^5 pfu) 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. 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.

Medical Officer comments:
Although this case of IT occurred in a recipient of an earlier formulation of RotaTeq ™, the Applicant was asked to perform an analysis adding this case, which had occurred within the 42 day window, to the cases of IT identified in REST. 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).

In the smaller phase 3 studies 007 and 009, there were no positively adjudicated intussusception (IT) cases. There were cases from these two trials that were reviewed by the SEAC and were negatively adjudicated for intussusception. In study 007, there were 5 cases in the placebo arm that were negatively adjudicated. In study 009, there were 2 placebo, 1 RotaTeq™ and 1 cross-treated(RotaTeq™-RotaTeq™-Placebo) subject who were negatively adjudicated for intussusception.

In study 006 (REST), 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose. For the primary safety outcome, cases of intussuception occurring within 42 days of any dose, there were 6 cases among RotaTeq™ recipients and 5 cases among placebo recipients (see Table 40)

The mean age for receipt of first vaccine dose in both study groups was age 6-16 weeks; the majority of subjects received their first vaccine dose at age 6-13 weeks. The mean age at intussusception for subjects within the RotaTeq™ group was 18 weeks (range 14-20 weeks) and in the placebo group was 15 weeks (range 12 – 19 weeks). There were 3 girls and 3 boys who developed intussusception in the RotaTeq™ arm and 2 girls and 3 boys in the placebo arm. Two of the 6 infants in the RotaTeq arm were "breast fed only" and two of the 5 infants in the placebo arm were "breast fed only". "Breast-fed only" was a term used in the datasets to denote that the infant was not receiving formula.

Medical Officer comments:
The highest risk period to naturally develop intussusception is approximately age 5 to 9 months. In REST, the age at which vaccine and placebo recipients developed intussusception was slightly younger, approximately 4 to 5 months, but similar between the treatment arms.

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 40 below.

Table 42 depicts the REST intussusception case splits at intervals of 0-7 days, 0-14 days, 0-42 days, 0-60 days, 0-365 days and at 0-467 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 42
Intussusception cases by day range in relation to dose in REST*

	Dose 1		Dose 2		Dose 3		Any Dose	
Day Range	**RotaTeq**	**Placebo**	**RotaTeq**	**Placebo**	**RotaTeq**	**Placebo**	**RotaTeq**	**Placebo**
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	**3**	**0**	0	1	3	1
1-42	0	1	**4**	**1**	2	3	6	5
1-60	1	1	**5**	**2**	2	3	8	6
1-365							13	15
1-467							13	19

*FDA analysis

The 0-7 day and 0-14 day evaluation window for intussusception (IT) demonstrated no clustering of IT cases.

When compared to placebo, there are more cases of IT in the RotaTeq™ arm after the second dose in the 0-21, 0-42 and 0-60 day windows.

The primary endpoint, 0-42 day IT evaluation window (Any Dose):
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.

Medical Officer comments:
The FDA analysis which produced a RR of 1.2 was not adjusted for the group sequential design. The relative risk (RR) adjusted by the Applicant for the group sequential design was 1.6 with a 95% CI (0.4, 6.4) and this also satisfied the primary safety hypothesis.

Relative Risk Calculations at time points other than within the 42 day window post vaccine dose

The 0-60 day IT evaluation window:
A 42-day window was pre-specified. However, it was also reasonable to consider 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 after any 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) was obtained by the FDA statistician. No pattern emerged 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.

The FDA statistical analysis also demonstrated the following:
At 42 days 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 was expanded to 60 days, the number of IT cases in the RotaTeq ™ group was 5, versus 2 in the placebo group [RR = 2.5 with 95% CI of (0.4, 26.3)]. See Table 40 above.

When evaluating all of the IT cases confirmed for all subjects completing the follow-up period (see Table 43 below), the total number of IT cases is greater in the placebo group (19) than in the vaccine group (13). In the FDA analysis, the unadjusted relative risk estimate is 0.68 with a 95% CI of (0.3, 1.5).

Table 43 Number of Days Post Dose of Confirmed Intussusception by Dose and Treatment among Subjects Completing the Study*

	RotaTeq™	Placebo
Post-dose 1 (~ 60 days)	46	36
Post-dose 2 (~ 60 days)	2, 19, 21, 41, 43	28, 49
Post-dose 3 (≤ 60 days)	38, 40	9, 36, 42
> 60 days post-dose 3	96, 116,126,139,166	85, 97, 121, 122, 136, 141, 165, 172, 257, 336, 337, 404, 456

*FDA analysis

In addition, to calculating the relative risk for developing intussusception within 42 days of any dose, the relative risk for developing intussusception was calculated within 42 days of each vaccine dose (see Table 44)

Table 44 Relative Risk of Intussusception by Days after Vaccine Dose (REST)*

Number of Subjects Vaccinated (34788)			**Follow-up Time for Intussusception in relationship to vaccine dose # and time post dose**	**Number of Subjects Vaccinated (34837)**			
Placebo (n)	**Placebo %**	**# IT cases**		**RotaTeq™(n)**	**RotaTeq %**	**# IT Cases**	**RR (95% CI)**
34768	99.9	0	6 day post dose #1 7	34821	>99.9	0	-
34740	99.9	0	14 days post dose #1	34794	99.9	0	-
17502**	50.3**	1	**42 days post dose #1**	17573	50.4	0	**0.0 (0,38.8)**
32745	94.1	0	7 day post dose #2	32773	94.1	1	- (0.03,-)
32733	94.1	0	14 days post dose #2	32757	94.0	1	- (0.03,-)
15856**	45.6**	1	**42 days post dose #2 (unadjusted)**	15838	45.5	4	**4.0** (0.4,197)
31810	91.4	0	7 day post dose #3	31911	91.6	0	-
31802	91.4	1	14 days post dose #3	31903	91.6	0	0.0 (0,38.9)
31555	90.7	3	**42 days post dose #3 (unadjusted)**	31631	90.8	2	**0.67 (0.06,5.81)**
		5	**42 days post any dose (unadjusted)**			6	**1.2** (0.3, 5.0)
		5	**42 days post any dose (adjusted for group sequential design)**			6	**1.6** (0.4-6.4)

*FDA analysis.
**Infant Immunization schedules differed e.g. 2, 3, 4 months or 2, 4, 6 months.

Medical Officer comments:
There was no increased risk of intussusception at 42 days post any vaccine dose and at 365 days of dose #1 for RotaTeq™ recipients when compared to placebo.

In the evaluation of intussusception relative risk at 42 days post-dose #1 and 42 days post-dose #2, the size of the study population contributing to the analysis was only 45.5-50.4% because of the different schedules of childhood immunization used in the U.S. (2, 4, 6 month schedule) vs in countries such as Finland (2, 3, 4 month schedule).The relative risk of intussuception was 4.0 for the RotaTeq™ arm post-dose #2 but this was not the primary endpoint. In the post-marketing period, it will be important to identify whether a pattern of intussusception cases emerges in relation to specific vaccine doses.

The confirmed cases of intussusception within 365 days of dose #1 were 13 in the RotaTeq™ arm (N=34,387) and 15 in the placebo arm (N= 34, 788). At 365 days of dose #1, the relative risk (95% CI) adjusted for the group sequential design was 0.9 (0.4, 1.9).

Intussusception and Surgical Reduction
There were 5 cases of Intussusception that required surgical reduction in each of the study arms**.**

RotaTeq™ Intussuception (IT) cases that required surgical reduction:

Allocation No.	IT Day	Vaccine dose #
43717	96	3
64286	121	3
65484	38	3
76380	40	3
79306	2	2

Placebo Intussusception cases that required surgical reduction:

Allocation No.	IT Day	Vaccine dose #
01210	122	3
09934	404	3
22289	121	3
38225	49	2
47937	336	3

Medical Officer comments:
There was no evidence to suggest that vaccine recipients required more surgical intervention for intussusception. There was one death due to intussusception that occurred in the RotaTeq™ group approximately 3 months after the third dose of RotaTeq™. Subject 43717 developed

intussusception, required surgery, developed post-operative complications and died (please see the narrative summary below).

Intussusception and Death in Study 006 (REST)

All of the children that developed intussusception recovered without sequelae with the exception of a 9 month old male that developed intussusception 98 days after dose 3 who died of post-operative sepsis. 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.

Hematochezia in the Positively and Negatively Adjudicated cases of Intussusception

Hematochezia has been associated with intussusception. Hematochezia was evaluated in positively and negatively adjudicated subjects for intussusception as well as in the detailed safety cohort. Hematochezia was not a solicited adverse event. In Table 45 positively adjudicated cases are depicted but no particular trends related to hematochezia were identified.

Table 45 Positively Adjudicated Intussusception (IT) Cases with Hematochezia*

	RotaTeq™ **Total Number IT Cases (N=13)**			**Placebo** **Total Number IT Cases (N=19)**		
	Hematochezia (N = 10)			Hematochezia (N = 7)		
Days post-dose	Post-dose 1	Post-dose 2	Post-dose 3	Post-dose 1	Post-dose 2	Post-dose 3
0-21	0	3	0	0	0	0
22-42	0	1	2	0	1	1
>42	1	1	2	0	1	4

FDA analysis*

The data in Table 46 regarding the negatively adjudicated cases of intussusception are derived using the Applicant Table 2.7.4.11 on page 259 of the Safety Update (SUR) and the narrative case summaries. When compared to the Applicant analysis, there may be more cases of hematochezia in the FDA analysis which includes "currant jelly" stool in the definition.

Table 46 Negatively Adjudicated Cases with Hematochezia*

	RotaTeq™ (32,837 subjects) Total Number Negatively Adjudicated Cases (N=45)			Placebo (34,788 subjects) Total Number Negatively Adjudicated Cases (N=47)		
	Hematochezia (N = 17)			Hematochezia (N = 9)		
Days post-dose	Post-dose 1	Post-dose 2	Post-dose 3	Post-dose 1	Post-dose 2	Post-dose 3
0-21	**7**	**3**	**1**	**4**	**2**	**0**
22-42	0	1	0	0	1	0
>42	0	2	3	0	0	2

FDA analysis*

Regarding the RotaTeq™ arm, 17 infants were negatively adjudicated for intussusception who had hematochezia: 12 infants with hematochezia at ≤ 42 days and 5 infants at greater than 42 days. The distribution of hematochezia for within 42 days post-dose for the 12 infants who received RotaTeq™ is as follows:

Post-Dose 1 7 cases
Post-Dose 2 4 cases
Post-Dose 3 1 case

Medical Officer Comments:
When considering Table 45, in the 0-21 day window post any dose it appears that there were more cases of hematochezia in the RotaTeq™ arm (11 cases) when compared to placebo (6 cases)

The negatively adjudicated cases who had hematochezia in the RotaTeq™ arm did not match any subjects who shed vaccine virus but most of the shedding studies were done at 4-6 days post vaccination and may not have been done when these subjects were symptomatic with hematochezia.

Regarding the placebo arm, 9 infants were negatively adjudicated for intussusception who had hematochezia and 7 of these cases occurred at ≤ 42 days post vaccine dose. The post-dose distribution of these 7 placebo cases is noted below in Table 47. However, 2 of these 7 infants had *Salmonella* and these two cases occurred at day 15 after the second dose of placebo (AN 42254 and AN 65540). Therefore, ultimately five of 7 placebo cases of hematochezia occurred at less than or equal to 42 days in the placebo arm who were negatively adjudicated for intussusception.

Table 47*

Negatively Adjudicated Cases of Intussusception in Placebo Arm with Hematochezia at ≤ 42 days after vaccine dose (REST)		
Post Dose	Initial Number Subjects with Hemaotchezia	Final Adjusted Number Hematochezia Cases minus the 2 cases of Salmonella which occurred post-dose 2
1	4	4
2	**3**	**1**
3	0	0
All doses	7	5

FDA analysis*

Medical Officer comments:
Regarding the negatively adjudicated cases of intussusception who had hematochezia, the final adjusted comparison at any time post vaccine dose was 17 cases of hematochezia in the RotaTeq™ arm vs 7 cases in the placebo arm. Hematochezia was not solicited on the Vaccine Report Card (VRC) used in REST. Therefore, it was not possible to definitively rule out whether hematochezia may be associated with administration of RotaTeq™. It will be important to monitor for hematochezia in post-marketing studies.

Hematochezia in the Phase 3 trials

Hematochezia in the Detailed Safety Cohort
The Applicant also evaluated hematochezia across the phase 3 trials during the 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 any vaccine dose, the incidence of hematochezia was similar across the treatment arms, i.e., at 7 days the incidence of hematochezia for subjects in the RotaTeq™ treatment arm was 0.3% compared to 0.4% in placebo. At ≤42 days the incidence of hematochezia for RotaTeq™ was 0.8% compared to 0.7% in placebo. However, hematochezia was not a solicited adverse event on the VRC or AGE workbook thus cases may not have been fully captured in the database.

Hematochezia in the Overall Safety Cohort
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 (Table 48)

Table 48 Hematochezia (Phase 3)*

Subjects who had hematochezia in studies 006, 007 and 009	RotaTeq™ (N = 36,356)	Placebo (N=35,750)
≤ 7 days post any vaccine dose	13	21
≤ 14 days post any vaccine dose	29	30
<21 days post any vaccine dose	40	33
<42 days post any vaccine dose	45	39

*FDA analysis

Medical Officer comments:
When compared to placebo, the overall incidence of hematochezia was not increased in the RotaTeq™ arm in either the overall safety or the Detailed Safety cohorts. However, it appears that in the negatively adjudicated cases, the RotaTeq™ arm had a higher incidence of hematochezia. It will be important to monitor for hematochezia in the post-marketing studies.

Intussusception (Spontaneous Reduction)
A 2.0-month-old white female, allocation number (AN) 64082, entered the study and was randomized to receive placebo. Shortly after receiving Dose 1, the subject developed diarrhea that lasted five weeks, which was considered to be a non-serious adverse experience. There were no concomitant medications. Then, on Day 85 Postdose 1, the subject vomited once and cried vehemently; there was no diarrhea of pyrexia. Upon physical examination, the subject had a distended abdomen, which was sensitive to pressure, and there was no peristalsis noted. The investigator performed an abdominal ultrasound and "target-like" structures could be seen repeatedly in the left hypogastric region. The investigator's diagnosis was intussusception and the subject was referred to a hospital. At the hospital, there were no further clinical signs and a repeat abdominal ultrasound did not show any pathological findings. The diagnosis of intussusception was ruled out by the hospital physicians. The subject was sent home after a short ambulatory period of observation. The investigator suspected that the intussusception had resolved spontaneously on the way to the hospital. The subject was discontinued from further vaccinations but continued with safety follow-up. The investigator determined that the serious adverse experience of intussusception was definitely not related to RotaTeq™/placebo. Of note, the investigator reported this adverse experience as 'other important medical event'; it is being reported because intussusception is an adverse experience of special interest.

Medical Officer comments:
The case of AN 64082 was unanimously adjudicated as negative by the SEAC. However, it illustrates the concern that even a large clinical study such as this may have missed cases of intussusception that spontaneously reduce. It will be important to continue surveillance for intussusception in post-marketing studies.

Intussusception (Conclusions)
Overall, the data did not suggest an increased risk of intussusception relative to placebo for the pre-specified endpoint assessment times i.e. within 42 days of any dose or within 365 days of the first dose. Although, there was no increased rate of hematochezia noted in either the Detailed Safety or Overall Safety Cohorts, hematochezia was not a solicited adverse event in the phase 3 clinical trials. In the negatively adjudicated cases of intussusception, hematochezia was reported more frequently. In order to ascertain if hematochezia is associated with this vaccine, it will be important to monitor this in the post-marketing studies. These results were obtained from clinical trials performed mainly in the developed world. Consequently, results can not be extrapolated to populations in the developing world where infants may be malnourished, co-infected with intestinal parasites, have HIV infection and/or reside in a country where administration of live oral poliovirus vaccine is the standard of care. Finally, when compared to placebo, more cases of intussusception occurred in the RotaTeq™ arm at 0-21, 0-42 and 0-60 days post vaccine dose #2. Although the phase 3 program enrolled over 70,000 infants, it will be important to have large post-marketing studies in place to further evaluate and characterize any risk for intussusception that might result from RotaTeq™ administration in the general population.

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 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

Seizures

In phase 3 studies, seizures were reported by vaccination group and interval after dose (see Table 49)

Table 49 Seizures reported by day range in relation to any dose in the Phase 3 trials of RotaTeq™*

Day range	1-7	1-14	1-42
RotaTeq	10	15	33
Placebo	5	8	24

*FDA analysis

Within 7 days after any dose, there were 10 RotaTeq recipients and 5 placebo recipients who had seizures. Within 14 days after any dose, 15 RotaTeq recipients and 8 placebo recipients had seizures. Overall, serious adverse

events due to seizures occurred in less than 0.1% of RotaTeq and in less than 0.1% placebo recipients. Seizures reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten febrile seizures were reported as serious adverse experiences, 5 were observed in vaccine recipients and 5 in placebo recipients.

In the phase 3 studies there were 31 subjects who received placebo and 20 subjects who received RotaTeq™ who had a history of seizure and none of these infants developed a seizure during the 42 days after a vaccine dose during the trials.

Seizures in phase 1 and 2

In study 003 there were two male subjects who received an earlier RotaTeq™ formulation (ROTA(G1/G2) 1.0 ML-No Buffer) and one developed a seizure at 35 days post-dose 1 and the other infant at day 8 post-dose 1 and both infants recovered. In study 005, a 5 month old female infant developed a seizure at 17 days post dose 1 and recovered. She received an earlier formulation of RotaTeq™ (ROTA (G1,G2,G3,G4,P1) $5X10^6$ PFU).

Medical Officer comments:

Seizures have been reported with natural rotavirus infection. Please see references 11 and 12 listed in the literature section 6.1.2 of this review where Komori et al discuss benign convulsions associated with gastroenteritis and Hongou et al discuss a case of rotavirus encephalitis which mimicked afebrile benign convulsions.

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 $\leq$ 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 50 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 50 Serious Adverse Events (SAEs) Phase 3 Studies 006, 007 & 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 51 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 51 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 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 52 below.

Table 52 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.

Adverse Events

Parents/guardians of the 11,711 infants were also asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose.

Fever was observed at similar rates in vaccine (N=6,138) and placebo (N=5,573) recipients (42.6% vs. 42.8%). Adverse events that occurred at a statistically higher incidence (i.e., 2-sided p-value <0.05) within the 42 days of any dose among recipients of RotaTeq as compared with placebo recipients are shown in Table 53.

Table 53 Adverse events that occurred at a statistically higher incidence within 42 days of any dose among recipients of RotaTeq as compared with placebo recipients*

Adverse event	RotaTeq N=6,138 n (%)	Placebo N=5,573 n (%)
Diarrhea	1,479 (24.1%)	1,186 (21.3%)
Vomiting	929 (15.2%)	758 (13.6%)
Otitis media	887 (14.5%)	724 (13.0%)
Nasopharyngitis	422 (6.9%)	325 (5.8%)
Bronchospasm	66 (1.1%)	40 (0.7%)

*Applicant Analysis

Solicited Adverse Events

Detailed safety information was collected from 11,711 infants (6,138 recipients of RotaTeq) which included a subset of subjects in REST and all subjects from studies 007 and 009 (Detailed Safety Cohort). A Vaccination Report Card was used by parents/guardians to record the child's temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. Table 54 summarizes the frequencies of these adverse events and irritability.

Table 54 Solicited adverse experiences within the first week after doses 1, 2, and 3 (Detailed Safety Cohort)*

Adverse experience	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature**	n=5616 17.1%	n=5077 16.2%	n=5215 20.0%	n=4725 19.4%	n=4865 18.2%	n=4382 17.6%
Vomiting	n=6130 6.7%	n=5560 5.4%	n=5703 5.0%	n=5173 4.4%	n=5496 3.6%	n=4989 3.2%
Diarrhea	10.4%	9.1%	8.6%	6.4%	6.1%	5.4%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%

*Applicant Analysis

**Temperature ≥100.5°F [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures.

Medical Officer comments:

The majority of the episodes of diarrhea and vomiting were described as mild to moderate in the RotaTeq™ arm. Overall, when compared to placebo, infants appeared to tolerate RotaTeq™.

Respiratory Adverse Events

Rspiratory adverse events, included in decreasing frequency: upper respiratory infection, bronchiolitis, croup, respiratory syncytial virus, and bronchospasm. Table 55 depicts the number of these respiratory adverse events in each treatment arm per study within 7 days of any vaccine dose. Although it appears that there is a marked imbalance in study 009, the randomization was 3:1 in this study. The overall rate of respiratory events within 7 days of any dose for the RotaTeq arm was 2% compared to the placebo arm with 1.8%.

Table 55 Respiratory Adverse Events in the Phase 3 Studies Within 7 days of Any Vaccine Dose*

Study	RotaTeq™ (N= 36356)	Placebo (N= 35750)
006	565	558
007	70	72
009	88	11
Total	717	641

FDA analysis*

Hospitalizations within 7 days of each vaccine dose were evaluated and this included hospitalizations for respiratory events; see the distribution below and no major trends or concerns were identified.

Hospitalizations within 7 days post-vaccine dose:
Hospitalizations were evaluated in infants for the first 7 days after each vaccine dose and this is depicted in Tables 56 and 57; 2 cross-treated subjects are not depicted. There were 5 infants who were hospitalized twice: 3 RotaTeq™ and 2 placebo recipients. Therefore, the actual number of subjects hospitalized at 7 days or less included 236 in the RotaTeq™ arm and 246 in the Placebo arm.

Table 56 Hospitalizations within 7 days of each vaccine dose

Hospitalizations ≤ 7 days post vaccine dose	RotaTeq™ N = 36,656	Placebo N = 35,750
Post Dose 1	133	114
Post Dose 2	66	81
Post Dose 3	40	53
Total	239	248

*FDA analysis

Table 57 Most common reasons for hospitalization within 7 days post any vaccine dose

	RotaTeq™ N = 36,656	Placebo N = 35,750
Bronchiolitis	54	59
Gastroenteritis	18	25
Pyrexia	8	15
UTI	14	9
Pneumonia	11	14

*FDA analysis

Medical Officer comments:
There was no evidence that more subjects in the RotaTeq™ arm were being hospitalized in the first week post vaccination for adverse events that could be associated with vaccination such as fever and gastroenteritis. However, the number of cases of UTI was numerically increased in the RotaTeq™ arm but it is difficult to draw conclusions with such a small number of cases.

Safety in "Cross-treated"Subjects
A summary of the adverse events that occurred in the "cross treated" subjects can be found on page 305 of the safety update (SUR) and in table 8.9 of that submission. Page 4565 of the clinical study 006 report contains the procedure to follow for subjects who received an incorrect vial of vaccine/placebo. There were 76 "cross –treated" infants in the phase 3 studies. Sixteeen of these subjects (21%) developed adverse events and 7 developed serious adverse events but no specific pattern emerged. None of these subjects developed intussusception or died. The subjects who received their first dose of RotaTeq™ at dose 3 are outlined in bold below; no cases of intussusception occurred in these subjects who received their initial dose of RotaTeq™ as dose 3.

Type of "Cross-treatment"	**Number of subjects**
Cross Lots (Lot 2, Lot 2, Lot 1 in Study 009)	1
Cross Treated (Placebo arm but 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

Initial Administration of a "Late" Dose and Issues of "Catch up" immunization

Natural Intussusception most frequently occurs at 5-9 months of age. Post-maketing data indicated that the incidence of intussusception after RotaShield® vaccination was most frequent in the 2 week period after the first vaccine dose was administered.

In the phase 3 clinical trials, RotaTeq™ was administered on a strict schedule with the first dose administered at 6-12 weeks of age, followed by two additional doses that were separated by 4-10 week intervals between doses and the series had to be completed by 32 weeks of age. This schedule was chosen by the Applicant in order to ascertain whether RotaTeq™ was similar to RotaShield ® in carrying a risk to cause intussuception in that early period after the first dose. In addition, completion of the 3 dose vaccine schedule by 32 weeks of age was stipulated in order to minimize the period of overlap with the time when natural intussusception is expected to occur, i.e. 5-9 months of age (22-36 weeks).

In the BLA, there were 103 placebo subjects and 99 RotaTeq™ subjects who were older than 12 weeks when they started the 3 dose vaccine series. Most of these 202 infants were 13 weeks old except for 1 infant who received placebo at 16 weeks of age and 3 infants who received RotaTeq™ at age14 weeks. No cases of intussusception occurred in these infants. However, it is important to keep in mind that in an earlier phase 2 trial, study 005, an infant who received his

first dose of RotaTeq™ at age 7 months, developed intussusception that required surgical reduction within 9 days of this first dose administered at an older age.

Medical Officer comments:
The safe administration of RotaTeq™ is predicated on adherence to the strict schedule that was utilized in the phase 3 clinical trials. Children should be vaccinated according to the recommended schedule for dose administration that is outlined in the FDA approved-label. In the United States, rotavirus is a disease with high morbidity but not high mortality. The safety of "catch-up immunization" for this usually non-fatal disease, has not been established. For the post-marketing studies, the Applicant will be requested to perform an additional analysis of intussusception and general safety outcomes among infants who may inadvertently be administered RotaTeq™ outside of the age indicated in the product label.

8.2 Concomitant Vaccination Issues

Evaluation of Antibody Responses to Concomitant Pediatric Vaccines
All subjects in Phase 3 were permitted to receive licensed pediatric vaccines on the same day or within 42 days of vaccination. Subjects enrolled in the U.S. Concomitant Use Cohort were evaluated for efficacy, immunogenicity, and safety of RotaTeq™ and immunogenicity and safety of other licensed pediatric vaccines, which included COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ when administered concomitantly (same day). The Applicant stated that the safety, efficacy, and immunogenicity of RotaTeq™ when given alone without concomitant vaccines was not evaluated because of the ethical concern about delaying administration of licensed pediatric vaccinations in these young infants and the desire to give RotaTeq™ at a young age. No specific safety hypothesis with respect to concomitant use of other licensed pediatric vaccinations was assessed in this study. Because of the young age of infants in this study and the difficulty in obtaining a large enough volume of serum to measure all the antibody responses, not all assays could be performed on a single subject. Therefore, not all serum samples were tested by each assay and assays were pre-assigned for the subjects in this study cohort. Groups were selected by using 3 independent ranges of consecutive allocation numbers in order to ensure equal distribution of vaccine and placebo recipients within each group.

A total of 1,358 subjects were randomized in the U.S. Concomitant Use Cohort to 1 of 2 treatment groups; of these subjects, 1,358 (100%) received at least the first vaccination of RotaTeq™ or placebo. Of the 1,358 subjects who were randomized in this study cohort, 1,351 subjects (99.5%) completed the dosing phase of the study, receiving all 3 study vaccinations, as well as the prespecified licensed pediatric vaccinations that were provided by the Applicant as study vaccinations, and safety follow-up for 42 days following the third vaccination. There were 4 subjects (0.3%) who discontinued before receiving all 3 study vaccinations and/or 42 days of safety follow-up (Table 58).

Table 58 Subject Accounting for Protocol 006 (REST) Through Day 42 After the Third Vaccination Among Subjects in the U.S. Concomitant Use Cohort

	APP				SUR				CUM					
	RotaTeq™		Placebo		RotaTeq™		Placebo		RotaTeq™		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized (N):	662		696		2		3		662†		696		1358	
Vaccinated At:														
Visit 1	662	(100)	696	(100)	2	(100)	3	(100)	662	(100)	696	(100)	1358	(100)
Visit 2	662	(100)	696	(100)	2	(100)	3	(100)	662	(100)	696	(100)	1358	(100)
Visit 3	662	(100)	696	(100)	2	(100)	3	(100)	662	(100)	696	(100)	1358	(100)
Completed the Third Study	657	(99.2)	694	(99.7)	2	(100)	3	(100)	660	(99.7)	695	(99.9)	1355	(99.8)
Vaccination and the 42-Day Safety Follow-Up Period After This Vaccination Visit‡:														
Randomized (N):	662 3 (0.5)		696 1 (0.1)		2 0 (0.0)		3 0 (0.0)		662† 2 (0.3)		696 1 (0.1)		1358 3 (0.2)	
Discontinued at Any Time Before the Completion of the Third Study Vaccination and/or the 42-Day Safety Follow-Up Period After This Vaccination Visit Due To:														
Lost to follow-up ;Moved	**1 (0.2) ;2 (0.3)**		**1 (0.1) ;0 (0.0)**		**0 (0.0) ;0 (0.0)**		**0 (0.0) ;0 (0.0)**		**0 (0.0) ;2 (0.3)**		**1 (0.1) ;0 (0.0)**		**1 (0.1); 2 (0.1)**	

† Includes one subject who was randomized to receive RotaTeq™ but received a mixed regimen of RotaTeq™ and placebo. A display of the actual treatment regimen received by this subject is shown in Appendix 2.7.4: 4. ‡ These data are based on the subject status after the dosing phase and not on actual follow-up dates. 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 d

From Applicant Table 2.7.4: 5 CSR 006

Serum samples were evaluated for antibody responses to RotaTeq™ and to the following antigens in the concomitant vaccines: hepatitis B surface antigen (HBsAg); polyribosyl ribitol phosphate (PRP), the primary polysaccharide component of the capsule of *H. influenza* type b; polio virus types 1, 2, and 3; diphtheria toxoid; tetanus toxoid; pertussis (anti-PT IgG, anti-FHA IgG, and anti-pertactin); and pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Only subjects for whom receipt of PREVNAR™ could be documented were assigned for the testing of antibody responses against the 7 serotypes of Streptococcus pneumoniae.

There was a subset of 1358 infants (662 RotaTeq® and 696 Placebo) who received concomitant COMVAX®, INFANRIX®, IPOL® and PREVNAR® and were evaluated for immune responses. Responses were measured at age 7-8 months after 3 doses of vaccine for diphtheria, tetanus, pertussis and pneumococcal serotypes. Responses were measured at age 5-6 months after 2 doses of vaccine for PRP, HBV and polio.

The statistical criterion for declaring that the immune responses are similar (noninferior) between the 2 treatment groups was that the 95% confidence interval on the difference in proportions of subjects who achieved seroprotection /seroconversion (RotaTeqTM - placebo) must exclude a decrease of 10 percentage points or more, for polio virus types 1, 2, and 3, HBsAg, PRP, diphtheria, and tetanus responses, and that the 95% confidence interval on the ratio of Postdose 3 GMTs (RotaTeqTM ÷ placebo) must exclude a decrease of 2-fold or more, for pertussis PT, pertussis FHA, pertussis pertactin, and for PN4, 6B, 9V, 14, 18C, 19F, 23F responses. These results are depicted in Tables 59-64.

The non-inferiority criteria for RotaTeq® vs Placebo were met for all antigens except the pertussis antigens.

Table 59 presents the differences in proportions among recipients of RotaTeq™versus placebo who achieved seroprotection/seroconversion to polio virus types 1, 2, and 3.

Table 59 Immunogenicity Analysis for Antibody Responses to Polio Virus Types 1, 2, 3 Among a Subset of Subjects in the U.S. Concomitant Use Cohort in the Per-Protocol Population**

		RotaTeq™	Placebo	Difference in % (RotaTeq™-Placebo)	95% Confidence Interval on the Difference	p-Value§	Conclusion‡
Polio Virus Type 1	Subjects tested with data available for analysis†	341	360				
	Number (%) of subjects with NA ≥1:8	328 (96.2)	349 (96.9)	-0.8	(-3.7, 2.1)	<0.001	Non-inferior
Polio Virus Type 2	Subjects tested with data available for analysis†	341	359				
	Number (%) of subjects with NA ≥1:8	311 (91.2)	326 (90.8)	0.4	(-4.0, 4.7)	<0.001	Non-inferior
Polio Virus Type 3	Subjects tested with data available for analysis†	341	359				
	Number (%) of subjects with NA ≥1:8	324 (95.0)	343 (95.5)	-0.5	(-3.9, 2.7)	<0.001	Non-inferior

†Excludes protocol violators and subjects with invalid data based on laboratory determinations.
‡A conclusion of "similar" indicates that the criterion for similarity in immune response between the group that received RotaTeq™and the group that received placebo was met, i.e., the
confidence interval on the difference (RotaTeq™-placebo) excludes a decrease of 10 percentage points or more.
§p-Value computed for testing null hypothesis of a decrease of 10 percentage points or more between RotaTeq™versus placebo.
NA = Neutralizing antibody.

*From Applicant

Table 60 depicts the differences in proportions among recipients of RotaTeq™ versus placebo who achieved seroprotection/seroconversion to HBsAg and PRP.

Table 60
Immunogenicity Analysis for Antibody Responses to HBsAg and PRP Among a Subset of Subjects in the U.S. Concomitant Use Cohort in the Per-Protocol Population

		RotaTeq™	Placebo	Difference in % (RotaTeq™ - Placebo)	95% Confidence Interval on the Difference	p-Value§	Conclusion‡
HBsAg	Subjects tested with data available for analysis†	202	214				
	Number (%) of subjects with ≥10 mIU/mL	197 (97.5)	203 (94.9)	2.7	(-1.2, 6.8)	<0.001	Non-inferior
PRP	Subjects tested with data available for analysis†	558	592				
	Number (%) of subjects with >1.0 µ g/mL	417 (74.7)	426 (72.0)	2.8	(-2.4, 7.9)	<0.001	Non-inferior

†Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡A conclusion of "similar" indicates that the criterion for similarity in immune response between the group that received RotaTeq™ and the group that received placebo was met, i.e., the confidence interval on the difference (RotaTeq™ - placebo) excludes a decrease of 10 percentage points or more. §p-Value computed for testing null hypothesis of a decrease of 10 percentage points or more between RotaTeq™ versus placebo.
HBsAg = Hepatitis B surface antigen.
PRP = Polyribosyl ribitol phosphate.

From Applicant

Table 61 depicts the differences in proportions among recipients of RotaTeq™ versus placebo who achieved seroprotection/seroconversion to diphtheria and tetanus.

Study 006
Rotavirus Efficacy and Safety Trial

Table 61*

Immunogenicity Analysis for Antibody Responses to Diphtheria and Tetanus Toxoids Among a Subset of Subjects in the U.S. Concomitant Use Cohort in the Per-Protocol Population

		RotaTeq™	Placebo	Difference in % (RotaTeq™-Placebo)	95% Confidence Interval on the Difference	p-Value§	Conclusion‡
Diphtheria	Subjects tested with data available for analysis†	136	144				
	Number (%) of subjects with ≥0.01 IU/mL	136 (100.0)	142 (98.6)	1.4	(-1.4, 4.9)	<0.001	Non-inferior
Tetanus	Subjects tested with data available for analysis†	132	140				
	Number (%) of subjects with ≥0.01 IU/mL	132 (100.0)	140 (100.0)	0.0	(-2.8, 2.7)	<0.001	Non-inferior

†Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡A conclusion of "similar" indicates that the criterion for similarity in immune response between the group that received RotaTeq™and the group that received placebo was met, i.e., the confidence interval on the difference (RotaTeq™-placebo) excludes a decrease of 10 percentage points or more. §p-Value computed for testing null hypothesis of a decrease of 10 percentage points or more between RotaTeq™versus placebo.

*From Applicant

Table 62 depicts the ratios of GMTs to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, among recipients of RotaTeq™ versus placebo. The associated 95% confidence intervals and p-values are also presented within each table

Table 62* Immunogenicity Analysis for Antibody Responses to PN Types 4, 6B, 9V, 14, 18C, 19F, 23F Among A Subset of Subjects in the U.S. Concomitant Use Cohort in the Per-Protocol Population

		RotaTeq™	Placebo	Ratio of GMTs (RotaTeq™÷ Placebo)	95% Confidence Interval on the Ratio	p-Value§	Conclusion‡
PN Type 4	Subjects tested with data available for analysis†	181	196				
	GMT (µg/mL)	1.1	1.0	1.2	(1.0, 1.4)	<0.001	Non-inferior
PN Type 6B	Subjects tested with data available for analysis†	185	198				
	GMT (µg/mL)	2.4	1.7	1.4	(1.0, 1.9)	<0.001	Non-inferior
PN Type 9V	Subjects tested with data available for analysis†	166	181				
	GMT (µg/mL)	1.9	1.8	1.1	(0.9, 1.3)	<0.001	Non-inferior
PN Type 14	Subjects tested with data available for analysis†	178	198				
	GMT (µg/mL)	4.2	4.3	1.0	(0.7, 1.3)	<0.001	Non-inferior
PN Type 18C	Subjects tested with data available for analysis†	166	180				
	GMT (µg/mL)	2.6	2.0	1.3	(1.1, 1.6)	<0.001	Non-inferior
PN Type 19F	Subjects tested with data available for analysis†	180	196				
	GMT (µg/mL)	2.0	1.8	1.1	(0.8, 1.4)	<0.001	Non-inferior
PN Type 23F	Subjects tested with data available for analysis†	185	198				
	GMT (µg/mL)	1.7	1.5	1.1	(0.9, 1.5)	<0.001	Non-inferior

†Excludes protocol violators and subjects with invalid data based on laboratory determinations.
‡A conclusion of "similar" indicates that the criterion for similarity in immune response between the group that received RotaTeq™and the group that received placebo was met, i.e., the confidence interval on the ratio (RotaTeq™÷ placebo) excludes a decrease of 2-fold or more.
§p-Value computed for testing null hypothesis of a decrease of 2-fold or more between RotaTeq™versus placebo.
PN = Pneumococcal. *From Applicant

Table 63 presents ratios of GMTs to pertussis PT, pertussis FHA, and pertussis pertactin among recipients of RotaTeq™ versus placebo.

Table 63*

Immunogenicity Analysis for Antibody Responses to Pertussis PT, FHA, and Pertactin Among a Subset of Subjects in the

U.S. Concomitant Use Cohort in the Per-Protocol Population

				Ratio of GMTs	95% Confidence Interval		
		RotaTeq™	Placebo	(RotaTeq™ ÷ Placebo)	on the Ratio	p-Value§	Conclusion‡
Pertussis PT	Subjects tested with data available for analysis†	59	78				
	GMT (ELISA units/mL)	20.2	22.7	0.9	(0.7, 1.1)	<0.001	Non-inferior
Pertussis FHA	Subjects tested with data available for analysis†	59	78				
	GMT (ELISA units/mL) Subjects tested with data available for analysis†	55.7	64.3	0.9	(0.7, 1.1)	<0.001	Non-inferior
Pertussis	Subjects tested with data available for analysis	59	78				
Pertactin							
	GMT (ELISA units/mL)	34.8	59.2	0.6	**(0.4, 0.8)** **	0.193	**Did not satisfy Non-inferiority**

†Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡A conclusion of "similar" indicates that the criterion for similarity in immune response between the group that received RotaTeq™and the group that received placebo was met, i.e., the confidence interval on the ratio (RotaTeq™÷ placebo) excludes a decrease of 2-fold or more. §p-Value computed for testing null hypothesis of a decrease of 2-fold or more between RotaTeq™versus placebo.

PT = Pertussis toxin.

FHA = Filamentous hemagglutinin.

ELISA = Enzyme-linked immunosorbent assay.

*From the Applicant

**LL of 2-sided 95% CI for ratio must be $\geq$ 0.5 and this result was 0.4

Issues related to Pertussis Immunogenicity

In order to state in the label that one can concomitantly administer RotaTeq™ with a pertussis vaccine such as INFANRIX®, the Applicant had to show that no interference occurs with the immune response to all 3 antigens (pertussis toxoid, pertussis FHA and pertussis pertactin) in a validated assay using the appropriate non-inferiority criteria (Table 64).

Assays that are utilized to assess seroresponse to pertussis antigens and data supporting validation must be found acceptable by FDA. Definitions of seroresponse for pertussis should be pre-defined and are based in part on particular characteristics of the assay e.g. lower limit of quantitation (considering product and assay variability issues). Once the assay is validated, the pertussis immunogenicity endpoint has included showing no greater that a 1.5 fold difference in GMT's between the placebo arm and the RotaTeq™ arm. This 1.5 fold margin was chosen based on the characteristics of the assays being used and it allows one to discriminate between variability in the assay vs true differences in the results for the product. An additional endpoint has included seroresponse using the criteria outlined below.

Table 64* Criteria applied to evaluate immunogenicity for pertussis vaccines

Antigen	Comparisons	Non-inferiority Criteria
Pertussis (PT, FHA, Pertactin, FIM)	GMT ratio (Test/Control) % ≥4-fold rise/seroresponder (Control – Test)	**LL 95% CI for GMT ratios ≥ 2/3 (0.66)** UL 95% CI for difference in rates ≤10%

*FDA

Two issues that occurred in regard to the evaluation of pertussis immunogenicity with concomitant administration of RotaTeq™ included the following:

1) the assay validation was determined to be incomplete by CBER (see Dr. Bruce Meade's FDA review) and
2) the criteria used (2 fold difference in GMTs between RotaTeq™ and placebo), although agreed to by both the Applicant and FDA, were less conservative than what is typically used (1.5 fold difference in GMT's between study vaccine and placebo).

In an unvalidated assay, using less conservative criteria, the non-inferiority criteria for RotaTeq™ vs placebo were met for all antigens except pertactin. Regarding pertactin, the lower limit of the 95% CI for anti-pertactin GMT ratio RotaTeq™ ÷ placebo was 0.4 and in order to meet non-inferiority criteria ($\underline{\leq}$2 fold difference in GMT's) the lower limit (LL) of the 95% confidence interval (CI) for the GMT ratios should have been $\underline{\geq}$0.5. Again, the criteria that should have been used for non-inferiority was a lower limit on the 95% CI for GMT ratios ≥ 0.66.

Medical Officer comments:
At present, the FDA label states that insufficient immunogenicity data are available to confirm lack of interference of immune responses when RotaTeq™ is concomitantly administered with childhood vaccines to prevent pertussis. The Applicant has agreed to conduct a clinical trial in the post-marketing period to further assess concomitant administration of RotaTeq™ with a pertussis vaccine using a validated assay and non-inferiority criteria of no greater that a 1.5 fold difference in GMT's between the placebo and RotaTeq™ arm.

Cases of Pertussis in the phase 3 clinical trials

Global Pertussis Cases: 9 Placebo cases vs 4 RotaTeq™

Study #	AN*	Age** (Wks)	Treatment	Diagnosis	Day Onset	Vaccine No.
006	93523	7	Placebo	Pertussis	42	1
006	26959	11	Placebo	Whooping cough	9	1
006	4671	10	Placebo	Whooping cough	7	1
006	17688	11	Placebo	Pertussis	2	1
006	74540	9	Placebo	Pertussis	35	1
006	23828	10	Placebo	Pertussis	34	3
007	451	7	Placebo	Pertussis	1	1
007	452	7	Placebo	Pertussis	16	1
007	2184	10	Placebo	Pertussis	20	2
006	34302	11	RotaTeq	Whooping cough	16	1
006	20444	10	RotaTeq	Whooping cough	3	2
006	21210	10	RotaTeq	Whooping cough	2	1
006	46665	7	RotaTeq	Pertussis	12	2

***AN = allocation number**
****Age weeks when received 1st vaccine dose**
****Day onset = day of diagnosis relative to vaccine dose**

Medical Officer comments:
There were 13 cases of pertussis in the phase 3 trials with 9 cases reported in the placebo arm and 4 in the RotaTeq™ arm. It is uncertain what diagnostic criteria were used to make this diagnosis. There did not appear to be an increased number of pertussis cases in the RotaTeq™ arm.

Prevnar™ and Fever

The incidence of fever did not appear to be increased in recipients of RotaTeq™ when compared to placebo. Because there had been shortages of Prevnar™ reported during the course of the REST trial, FDA questioned whether perhaps there may have been an imbalance where more placebo recipients received Prevnar™ when compared to RotaTeq™ recipients. Consequently, FDA requested the Applicant to do the following analysis of subjects who received Prevnar™ and may or may not have developed fever.

Elevated temperatures among those who did and did not receive Prevnar™ in the US Concomitant Use Cohort in Protocol 006 (REST)

There were 1,358 vaccinated subjects in the US Concomitant Use Cohort in Protocol 006 (REST). The subjects enrolled in this cohort received COMVAX™ (Haemophilus b conjugate [meningococcal protein conjugate] and hepatitis B [recombinant] vaccine, Merck & Co., Inc.), INFANRIX™ ([diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed], GlaxoSmithKline Biologicals), IPOL™ ([trivalent poliovirus vaccine inactivated], Aventis Pasteur), and PREVNAR™ (pneumococcal 7-valent conjugate vaccine [diphtheria CRM197 protein], Wyeth) concomitantly (same day) with oral RotaTeq™. Among these subjects, there were 1208 subjects (89%) who had follow-up after any dose and received Prevnar™ and 108 subjects (8%) who had follow-up after any dose and did not receive Prevnar™.

The following Table 65 displays the number and percent of subjects with and without the receipt of Prevnar™ with elevated temperatures (≥100.5^{o}F, rectal equivalent) by treatment arm following Dose 1 and following any dose. As shown in this table, of the subjects who received RotaTeq™ and Prevnar™ concomitantly, 26.8% of subjects had an elevated temperature as compared to 21.2% of subjects who received RotaTeq™ without Prevnar™ following the first dose and 50.6% compared to 39.7% of subjects following any dose, indicating that receipt of Prevnar™ may be contributing to some increase in the number of subjects with elevated temperatures. Also shown in this table, is that among subjects who received placebo and Prevnar™, 26.2% of subjects had an elevated temperature as compared to 26.8% of subjects who received RotaTeq™ and Prevnar™ concomitantly following the first dose. A similar trend was observed following any dose, suggesting that the receipt of RotaTeq™ and Prevnar™ concomitantly does not cause an additive affect on the number of subjects with elevated temperatures. Interesting to note is that among subjects who received placebo and did not receive Prevnar™, 29.8% and 42.0% of subjects had an elevated temperatures following Dose 1 and following any dose, respectively, which may be due to the administration of other concomitant vaccines.

Table 65 Number (%) of Subjects Stratified by Those Who Received And Did Not Receive Prevnar™† With Specific Clinical Adverse Experiences (Elevated Temperatures [≥100.5°F (≥38.1°C), Rectal Equivalent] in the US Concomitant Use Cohort in Protocol 006 (REST) (Within 7 Days Postvaccination)*

	Received Prevnar™			
	Yes		No	
	RotaTeq™	Placebo	RotaTeq™	Placebo
Postdose 1				
Number of subjects with follow-up	560	596	52	47
Number (%) of subjects with elevated temperatures:				
≥ 100.5 ˚F (38.1 ˚C), rectal equivalent	150 (26.8)	156 (26.2)	11 (21.2)	14 (29.8)
Post Any Dose				
Number of subjects with follow-up	581	627	58	50
Number (%) of subjects with elevated temperatures:				
≥ 100.5 ˚F (38.1 ˚C), rectal equivalent	294 (50.6)	339 (54.1)	23 (39.7)	21 (42.0)

†Prevnar™ (pneumococcal 7-valent conjugate vaccine [diphtheria CRM197 protein], Wyeth
*Applicant analysis

Medical Officer comments:
Recipients of RotaTeq™ did not appear to have an increased incidence of fever. The Applicant was asked to provide an analysis to show that there was not an imbalance in the administration of Prevnar™ between the treatment arms. The numbers of subjects who received Prevnar™ were similarly distributed across the treatment arms. A higher proportion of subjects who received Prevnar™ had fever except in the placebo arm at post-dose 1 (29.8% vs 26.2%). No major increase in fever was detected in the subjects who received RotaTeq™ with and without Prevnar™ when compared to placebo subjects who did or did not receive Prevnar™.

8.3 Shedding and Transmission

From the Applicant:
Fecal shedding of vaccine-virus strains was evaluated among a subset of approximately 300 subjects (the first 150 subjects randomized in Finland and the first 150 subjects randomized in the United States) in the Efficacy Cohort. A stool sample was collected from each subject in this subset during Days 4 to 6 following vaccination Visits 1, 2, and 3. Vaccine-virus replication in the intestinal tract peaks during the 4- to 6-day period after a dose, with minimal replication occurring after a week. The time-frame evaluated for potential shedding was based on data obtained in previous clinical trials. The percent of subjects who shed vaccine-virus strains Days 4 to 6 following vaccination Visit 1 was 12.7% in the group that received RotaTeq™, and there

was no fecal shedding of vaccine-virus strains in the group that received placebo. There was no shedding reported Days 4 to 6 days following vaccination Visits 2 and Visits 3.

The number and percent of subjects who shed vaccine-virus strains at any time following each vaccination were also summarized. This included vaccine-virus shedding data from scheduled samples and those that were collected off-schedule and those collected as a result of a potential AGE. It is important to recall that any stool sample collected during a potential AGE that was rotavirus EIA-positive was evaluated for vaccine-virus strains. The majority of fecal shedding of vaccine-virus strains occurred within the week following vaccination Visit 1. There was one subject who experienced shedding on Day 15 following vaccination Visit 1, which was the latest time period observed. There was one subject who experienced shedding following vaccination Visit 3, and this occurred on Day 4 following the vaccination. There were 2 subjects (AN 00054 and AN 02489) who received placebo and experienced vaccine-virus shedding following vaccination Visit 1. Evaluation of the data did not reveal an obvious reason for these occurrences (e.g., mistaken treatment regimen, twin-to-twin transmission, or transmission via a common caretaker).

In summary (from the label):
Shedding was evaluated among a subset of subjects in REST 4 to 6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time. RotaTeq™ was shed in the stools of 32 of 360 [8.9%, 95% CI (6.2%, 12.3%)] vaccine recipients tested after dose 1; 0 of 249 [0.0%, 95% CI (0.0%, 1.5%)] vaccine recipients tested after dose 2; and in 1 of 385 [0.3%, 95% CI (<0.1%, 1.4%)] vaccine recipients after dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission was not evaluated.

Medical Officer comments:
Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient close contacts such as: individuals with malignancies or who are otherwise immunocompromised; or individuals receiving immunosuppressive therapy. There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinated contacts. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

8.4 Special Populations

Safety in Pre-Term Infants
RotaTeq™or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in REST. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences.

There were 4 deaths throughout the study, 2 among vaccine recipients (1 SIDS and 1 motor vehicle accident) and 2 among placebo recipients (1 SIDS and 1 unknown cause). No cases of intussusception were reported. Serious adverse experiences occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in 1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse experiences and irritability within the week after dose 1 are summarized in Table 66.

Table 66 Solicited adverse experiences within the first week of doses 1, 2, and 3 among pre-term infants**

	Dose 1		Dose 2		Dose 3	
Adverse event	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
	N=127	N=133	N=124	N=121	N=115	N=108
Elevated temperature	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	N=154	N=154	N=137	N=137	N=135	N=129
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3.9%	5.2%	2.9%	4.4%	8.1%	5.4%

*Temperature ≥100.5°F [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures
**Applicant Analysis

Medically Compromised Infants (Issues of Shedding, Efficacy and Safety)
On June 17, 2005 a dataset on 618 medically compromised infants (317 placebo and 301 RotaTeq™) was submitted to the BLA on FDA request. The Applicant describes the dataset as a convenience sample. Prior to unblinding the data-base 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 equate to 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.

Review of vaccine virus shedding data revealed that one of the medically compromised subjects who received RotaTeq ™ (Allocation number 1 i.e. AN 1), did actually shed vaccine virus* (G1 + P1 Vaccine Type). *He shed vaccine virus at the post dose 1 period which is the time when you would be most likely to detect shedding of vaccine virus. However, because this Finnish subject was not yet medically compromised until the post dose 3 period when he received steroids and antibiotics for an upper respiratory infection, he is consequently not counted as a medically compromised vaccine virus shedder. Therefore, when assessing vaccine virus shedding data on immunocompromised or medically compromised subjects, it is important to capture data in the period when the subjects are both immuno- or medically compromised but are also most likely to be shedding vaccine virus, which was not done in this subset analysis.

This reviewer did not perform additional exploratory analyses to assess whether all of the medically compromised subjects were medically compromised in the first week post dose #1 and whether they were also systematically evaluated for vaccine virus shedding in this period which is when you would be most likely to capture vaccine virus shedding.

Data on infants who shed vaccine virus in study 006

AN	Rx arm	Strain Shed	#subjects
54	**Placebo**	**Serotype 3 - Vaccine Type**	**1**
1	RotaTeq	G1 + P1 Vaccine Type	1 medically compromised
10098	RotaTeq	P1 vaccine type + G3 vaccine type	1
1125	RotaTeq	Serotype P1 - Vaccine Type	1
1618	RotaTeq	Serotype P1 - Vaccine Type	1
18	RotaTeq	Serotype P1 - Vaccine Type	1
31326	RotaTeq	Serotype 4 - Vaccine Type	1
332	RotaTeq	G3 + P1 Vaccine Type	1
332	RotaTeq	Serotype P1 - Vaccine Type	1
352	RotaTeq	Serotype 3 - Vaccine Type	1
365	RotaTeq	Serotype 3 - Vaccine Type	1
391	RotaTeq	G3 + P1 Vaccine Type	1
41586	RotaTeq	Serotype P1 - Vaccine Type	1
480	RotaTeq	P1 Vaccine type + P1G1 Vaccine	1
58645	RotaTeq	Serotype P1 - Vaccine Type	1
58896	RotaTeq	Serotype P1 - Vaccine Type	1
6	RotaTeq	Serotype P1 - Vaccine Type	1
629	RotaTeq	Serotype P1 - Vaccine Type	1(shed G1, G1 + Bovine G3)
70	RotaTeq	Serotype 3 - Vaccine Type	1
78529	RotaTeq	Serotype P1 - Vaccine Type	1
82639	RotaTeq	Serotype P1 - Vaccine Type	1
95149	RotaTeq	Serotype P1 - Vaccine Type	1

Another placebo subject, AN 02489, also shed vaccine virus.

Medical Officer comments:

There were 22 RotaTeq™ recipients and 2 placebo recipients who shed vaccine virus. The Applicant has not been able to identify a reason for why the healthy placebo recipients shed vaccine virus. One infant who received RotaTeq™ and shed vaccine virus is delineated as medically compromised (AN 1) but he was not yet actually medically compromised at the time that he was found to be shedding vaccine virus in the post-dose 1 period.

Regarding efficacy in the medically compromised children please see Table 67.

Table 67 Acute rotavirus gastroenteritis episode (AGE) in the medically compromised children (Per protocol efficacy cohort) *

	RotaTeq™	Placebo	Total
Subjects in Per Protocol (PP) Efficacy	2207	2305	4512
Medically Compromised subjects in study 006	301	317	618
Medically compromised subjects in the PP efficacy	86	76	162
AGE cases in the medically compromised in the PP efficacy cohort	1	5	6

*FDA analysis

AGE cases in the medically compromised infants in protocol 006 (REST):

AN	case date	study	Treatment arn
267	04/07/2002	006	Placebo
1678	05/21/2002	006	Placebo
1309	02/01/2003	006	Placebo
58523	02/15/2003	006	Placebo
3679	12/12/2003	006	RotaTeq
59934	12/21/2003	006	Placebo

Medical Officer comments:
It was not possible to draw definitive conclusions regarding the efficacy of RotaTeq™ in this small subset of medically compromised subjects.

9.0 Study 007 (End Expiry)

Because of the differences in how the vaccines were produced and released between the Phase 2 and 3 studies, CBER requested an additional study of the efficacy of the final formulation of RotaTeq™ at the assigned expiry potency. Protocol 007 was designed to confirm the efficacy of the assigned expiry potency using vaccine produced with the final process, buffered formulation, and potency assay (M-QPA) intended for licensure. The potency of the vaccine evaluated in this study was similar to that of the middle-potency pentavalent vaccine shown to be tolerated, efficacious, and immunogenic in Protocol 005. The decision to administer a 3-dose regimen was based on a previous study demonstrating that 3 doses are required to induce an 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 children than a 2-dose regimen. This study was completed before the Applicant began the clinical development program for RotaTeq™, therefore, all subsequent studies have utilized a 3-dose regimen.

The potency of RotaTeq™ evaluated in this Study 007 was based on results from Protocol 005, a Phase II dose-ranging, placebo-controlled study intended to serve as the basis for assignment of the expiry dose of the pentavalent vaccine. The dose-ranging study evaluated 3 different potencies of pentavalent vaccine (approximately $5x10^6$ PFU, approximately $1.6x10^6$ PFU, and approximately $5x10^5$ PFU per reassortant, respectively) and a single potency of quadrivalent (G1, G2, G3, and G4) and monovalent P1 vaccine (approximately $5x10^6$ PFU per reassortant). However this study was conducted using vaccine produced with the research manufacturing process and in an unbuffered formulation, and the potency assay used to release the vaccine was the plaque assay.

Protocol 007 was a phase 3 Study of the Efficacy, Safety, and Immunogenicity of RotaTeq™ at Expiry Potency. The study was conducted at 30 sites; 27 in the United States, and 3 in Finland. The study was conducted from September 2002 to February 2004 . Three doses of RotaTeq™ or placebo were administered 28 to 70 days apart, with up to 42 days of safety follow-up after each vaccination, and follow-up for acute gastrointestinal episodes (AGEs) through the first rotavirus season post-vaccination only.

The primary objectives were 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. Secondary objectives included (1) To assess the safety of RotaTeq™ at expiry potency with respect to

all adverse experiences within 42 days of any dose of vaccine/placebo. (2) To evaluate the efficacy of a 3-dose regimen of RotaTeq™ at expiry potency against moderate-and-severe and severe 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. (3) To assess the immunogenicity of RotaTeq™ at expiry potency as measured by the serum neutralizing antibody (SNA) responses to vaccine serotypes (G1, G2, G3, G4, P1, and WC3), and serum anti-rotavirus IgA in a subset of subjects. The WC3 serotype is also characterized as G6 and P7[5].

The study design was a randomized, multicenter, double-blinded, placebo-controlled, efficacy trial.

Table 68 Demographics for Study 007 *

Study 007	RotaTeq™ At Expiry Potency (1.1 x 10^7 IU/dose)		Placebo	
Randomized (N):	651		661	
	n	%	n	%
Gender				
Male	347	53.3	338	51.1
Female	304	46.7	323	48.9
Age (weeks)				
6 to 12	648	99.5	658	99.5
Over 12	3	0.5	3	0.5
Mean	10.1		10.1	
SD	1.5		1.5	
Median	10.0		10.0	
Range Male Female	6 to 13 6 to 12 7 to 13		6 to 13 7 to 13 6 to 12	
Race				
White	525	80.6	540	81.7
Hispanic-American	79	12.1	77	11.6
Black	21	3.2	23	3.5
Multiracial	17	2.6	15	2.3
Other	9	1.4	6	0.9

*from Applicant's Appendix 2.7.4:7, p. 250, Cumulative Data

Table 69 Subject Accounting for Protocol 007 Through Day 42 After the 3rd Study Treatment

Study 007	**RotaTeq™at Expiry Potency (~1.1 x 10^7 IU/Dose)**		**Placebo**		**Total**	
	n	%	n	%	n	%
Screening Failures					15	
Randomized	651		661		1312	
Vaccinated at visit 1	650	99.8	660	99.8	1310	99.8
Vaccinated at visit 2	618	94.9	627	94.9	1245	94.9
Vaccinated at visit 3	593	91.1	608	92.0	1201	91.5
Completed safety follow-up	593	91.1	607	91.8	1200	91.5
Completed only safety follow-up for 42 days post 3rd vaccination	3	0.5	2	0.3	5	0.4
Completed safety follow-up for 42 days post 3rd vaccination and continued in rotavirus season follow-up	590	90.6	605	91.5	1195	91.1
Discontinuations due to:	58	8.9	54	8,2	112	8.5
-Adverse event	9	1.4	13	2.0	22	1.7
-Protocol deviation	11	1.7	9	1.4	20	1.5
-Refused	9	1.4	11	1.7	20	1.5
-Lost to followup	7	1.1	3	0.5	10	0.8
-Moved	5	0.8	5	0.8	10	0.8
-Other	17	2.6	13	2.0	30	2.3

(from Applicant Safety Update, July 25, 2005, Appendix Table 2.7.4:3, p. 242)

The **regimen** consisted of three 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™ at expiry potency (Lot Nos. V260 VAO 019Q001 and V260 VAO019Q002) contained approximately ---- mg of sucrose, approximately --- mg of sodium citrate,approximately -- mg of sodium phosphate, --- mL of tissue culture medium, and ---------- mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate potency of ~1.1 x10^7 infectious units (IU)/dose in approximately 2.0 mL of buffer/stabilizer. Theoretical calculation of ---------- material --------- was -- µg/dose. Trace components of fetal bovine serum may have also been present. The **placebo** (Lot No. ----------) was approximately 2.0 mL per dose that contained approximately ----

---
---.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1ºC (≥100.5ºF) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Efficacy: The case definition for rotavirus gastroenteritis required subjects to meet both of the following criteria: (1) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms. All rotavirus-positive stools were evaluated for serotype identification by polymerase chain reaction (PCR). Only naturally-occurring rotavirus AGEs caused bythe human rotavirus G- serotypes in the vaccine were included in the primary analysis.

Immunogenicity: In a subset of approximately 175 subjects, antibody responses to the vaccine were evaluated by several assays. Serum samples were collected before Dose 1 and approximately 42 days after Dose 3. Serum was tested by modified enzyme-linked immunosorbent assay (ELISA) for serum neutralizing antibodies (SNA) against the rotavirus serotypes contained within the vaccine (G1, G2, G3, G4, P1, and WC3 (the WC3 serotype is also characterized as G6 and P7[5] throughout this document)). Serum anti-rotavirus IgA was also evaluated.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following

vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and/or diarrhea.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: 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 Postdose 3 through one rotavirus season would be **≤ 0%**. This hypothesis was tested using an exact binomial procedure based on the proportion of subjects with rotavirus gastroenteritis. Assuming 437 evaluable subjects in each group, and assuming the true rotavirus attack rate was 10% and RotaTeq™had a true efficacy of 60% , (one-sided $\alpha = 0.025$), there was 90% power to declare that RotaTeq™ at expiry potency was efficacious.

Medical Officer comments:
The statistical primary null hypothesis for this study was different than that used in study 006 (REST). Please see the FDA statistical review of efficacy for study 007.

Immunogenicity: A secondary objective of this study was to assess the immunogenicity of RotaTeq™ at expiry potency based on serum neutralizing antibody (SNA) responses to G1, G2, G3, G4, P1, G6, and P7[5], and to serum antirotavirus IgA. In order to evaluate this, the proportion of subjects achieving a ≥3-fold rise in titer and geometric mean titers (GMTs) as measured by SNA responses to G1, G2, G3, G4, P1, G6 and P7[5], and serum anti-rotavirus IgA were summarized by treatment group, in the per-protocol population.

Safety: The safety hypothesis was that RotaTeq™ at expiry potency would be generally safe and well tolerated with respect to all adverse experiences. Adverse experiences were summarized as frequencies and percentages by treatment group and type of adverse experience (AE), along with associated risk differences and exact 95% confidence intervals. Solicited AEs such as elevated temperatures, diarrhea, irritability, and vomiting were evaluated in a similar fashion, with 2-sided p-value provided. All subjects with safety follow-up were included in the safety summaries.

Medical Officer comments:
Subjects in study 007 were included in the Detailed Safety Cohort which included a subset of infants from the large REST trial and all of the subjects from the two smaller phase 3 studies 007 and 009. However, the Applicant's analysis of safety data from this individual study is provided below.

RESULTS:

Efficacy: The primary per-protocol analysis of efficacy against any naturally-occurring rotavirus gastroenteritis caused by serotypes G1, G2, G3, or G4 regardless of severity is presented in the table that follows. As shown in Table 70, the statistical criterion for demonstrating efficacy was met; the lower bound on the 95% confidence interval of the efficacy estimate for RotaTeq™ at expiry potency was >0.0%.

Medical Officer comments:
Based on the 'episode' defined in the previous efficacy section of this review, the FDA statistical reviewer concurred that study 007 met the primary efficacy objective.

Table 70*
Primary Efficacy Analysis of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases Occurring at Least 14 Days Postdose 3 Through the First Rotavirus Season Postvaccination in the Per-Protocol Population Using Per-Protocol Case Definition

	RotaTeq™ at Expiry Potency (≈1.1 x 107 IU/Dose)	Placebo
Subjects vaccinated	650	660
Protocol violators †	66	61
Subjects with no follow-up	0	0
Subjects classified as unevaluable per per-protocol case definition‡	33	35
Subjects contributing to efficacy analysis	551	564
Days of efficacy follow-up	77929	77037
Subjects classified as rotavirus gastroenteritis cases per per-protocol case definition	15	54
Efficacy estimate (%) and 95% confidence interval	72.5 (50.6, 85.6)	---
p-Value for efficacy >0%	<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, or who had 4 vaccinations. ‡ 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™at expiry potency (≈1.1 x 107infectious units/dose) exceeds 0%. 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, andthe first positive episode is used as the date of the case. EIA = Enzyme immunoassay, IU = Infectious units.

*From Applicant (study 007, Table 7-1)

Table 71 presents Predose 1 and Postdose 3 GMTs and the percentage of subjects who achieved a ≥3-fold rise in titer and associated 95% confidence intervals of the following: G1 SNA, G2 SNA, G3 SNA, G4 SNA, P1 SNA.

Table 71*

	RotaTeq™ at Expiry Potency (≈1.1 x 10^7 IU/Dose)					**Placebo**				
	G1	G2	G3	G4	P1	G1	G2	G3	G4	P1
Predose 1 Subjects tested with data available for analysis† GMT (dilution units) and 95% confidence interval	80 30.1 (22.1, 41.2)	74 9.3 (7.4, 11.7)	80 8.3 (6.5, 10.4)	75 16.6 (12.6, 22.0)	74 21.3 (16.2, 27.8)	86 31.1 (23.7, 40.7)	83 8.9 (7.5, 10.5)	87 8.8 (7.0, 10.9)	83 21.4 (16.3, 28.0)	83 25.4 (20.0, 32.4)
Postdose 3 Subjects tested with data available for analysis‡ GMT (dilution units) and 95% confidence interval	68 124.3 (83.6, 185.0)	68 10.4 (8.1, 13.3)	68 9.8 (7.7, 12.6)	68 47.2 (34.7, 64.4)	67 27.9 (20.2, 38.5)	75 7.7 (6.3, 9.4)	75 5.3 (5.0, 5.6)	76 5.2 (5.0, 5.5)	75 6.7 (5.8, 7.7)	74 7.1 (5.8, 8.7)
Three-fold rise Subjects tested with Predose 1 and Postdose 3 data available for analysis‡ Number (%) of subjects with ≥3-fold rise in antibody titer, and 95% confidence interval	67 38 (56.7) (44.0, 68.8)	62 9 (14.5) (6.9, 25.8)	67 6 (9.0) (3.4, 18.5)	63 25 (39.7) (27.6, 52.8)	61 15 (24.6) (14.5, 37.3)	73 2 (2.7) (0.3, 9.5)	70 0 (0.0) (0.0, 5.1)	75 0 (0.0) (0.0, 4.8)	70 1 (1.4) (0.0, 7.7)	69 2 (2.9) (0.4, 10.1)

† Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of a specified day range. NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the Data Analysis Plan. SNA = Serum neutralization assay; GMT = Geometric mean titer; EIA = Enzyme immunoassay; IU = Infectious units. * From the Applicant

Table 72 presents Predose 1 and Postdose 3 GMTs and the percentage of subjects who achieved a ≥3-fold rise in titer and associated 95% confidence intervals of the following: G6 SNA, P7[5] SNA.

Table 72*

	RotaTeq ™at Expiry Potency (≈1.1 x 107IU/Dose)		**Placebo**	
	G6	P7	G6	P7
Predose 1				
Subjects tested with data available for analysis†	76	76	84	84
GMT (dilution units) and 95% confidence interval	8.7 (7.2, 10.4)	8.8 (7.2, 10.7)	8.3 (7.0, 9.8)	10.8 (8.9, 13.1)
Postdose 3				
Subjects tested with data available for analysis‡	68	68	74	74
GMT (dilution units) and 95% confidence interval	20.8 (16.0, 27.2)	45.7 (32.8, 63.6)	5.1 (4.9, 5.2)	5.2 (5.0, 5.5)
Three-Fold Rise				
Subjects tested with Predose 1 and Postdose 3 data available for analysis‡	63	63	71	71
Number (%) of subjects with ≥3-fold rise in antibody titer, and 95% confidence interval	18 (28.6) (17.9, 41.3)	34 (54.0) (40.9, 66.6)	0 (0.0) (0.0, 5.1)	0 (0.0) (0.0, 5.1)

† Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of a specified day range. NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the DAP [3.10]. SNA = Serum neutralization assay; GMT = Geometric mean titer; EIA = Enzyme immunoassay; IU = Infectious units.

*From Applicant

Table 73 presents Predose 1 and Postdose 3 GMTs and the percentage of subjects who achieved a ≥3-fold rise in titer and associated 95% confidence intervals for serum anti-rotavirus IgA.

Table 73*

Serum Anti-Rotavirus IgA		
	RotaTeq™ at	
	Expiry Potency (≈1.1 x 10^7 IU/Dose)	**Placebo**
Predose 1		
Subjects tested with data available for analysis†	80	86
GMT (units/mL) and 95% confidence interval	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)
Postdose 3		
Subjects tested with data available for analysis‡	68	74
GMT (units/mL) and 95% confidence interval	200.0 (131.9, 303.0)	0.3 (0.2, 0.6)
Three-fold rise		
Subjects tested with Predose 1 and Postdose 3 data available for analysis‡	67	73
Number (%) of subjects with ≥3-fold rise in anti-rotavirus IgA,	64 (95.5)	9 (12.3)
and 95% confidence interval	(87.5, 99.1)	(5.8, 22.1)
† Excludes protocol violators and subjects with invalid data based on laboratory determinations. ‡ Excludes protocol violators, subjects with invalid data based on laboratory determinations, subjects with rotavirus-positive stool antigen EIA prior to 14 days Postdose 3, subjects with samples taken after rotavirus-positive stool antigen EIA results, or with samples taken out of a specified day range. NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations and 3-fold rise in antibody titer calculations according to different rules, which are outlined in the Data Analysis Plan. GMT = Geometric mean titer; EIA = Enzyme immunoassay; IU = Infectious units.		

*From Applicant.

Medical Officer comments:
This evaluation of immunogencity was a secondary analysis and was not performed by the FDA statistical reviewer.

Safety: The Applicant reports that there were no statistical differences between the groups that received RotaTeq™ at expiry potency and the placebo group with respect to the compared incidences of all adverse experiences, except for the reporting of watery stools, sinusitis, and atopic dermatitis. For the watery stools and sinusitis, the incidence was statistically higher in the placebo group and for atopic dermatitis, the incidence was statistically higher in the vaccine group.

RotaTeq™ is a live-virus vaccine, it was of interest to compare the incidence of diarrhea, irritability, vomiting, and elevated temperature (≥100.5ºF [≥38.1ºC], rectal equivalent) for RotaTeq™ at expiry potency with that of placebo. There was no statistical increase in the reporting of diarrhea, irritability, or vomiting in the group that received RotaTeq™ at expiry potency within 7 days following any vaccination. However, there was a statistical increase in the reporting of elevated temperature within the 7 days following vaccination Visit 1 in the group that received RotaTeq™ at expiry potency (13.4%) compared to the placebo group (8.8%) and following any vaccination in the group that received RotaTeq™ at expiry potency (30.0%) compared to the placebo group (23.9%).

Medical Officer comments:
These results were not consistent with what was found in the larger Detailed Safety Cohort where fever was not found to be increased in RotaTeq™ recipients but diarrhea, vomiting and irritability were statistically increased when compared to placebo.

During the course of this study, 5 subjects were medically evaluated for possible intussusception. None of these were confirmed cases of intussusception as determined by the Safety Endpoint Adjudication Committee. All 5 of these subjects were randomized to the placebo group.The overall summary of adverse experiences reported within 42 days following any vaccination is provided in the following table.

Table 74* Study 007 Safety Experience

		RotaTeq™ at Expiry Potency (≈ 1.1 x 10^7IU/Dose)		Placebo	
		(N=650†)		(N=661)	
		n	(%)	n	(%)
Number of subjects		649		660	
Subjects without follow-up		0		2	
Subjects with follow-up		649		658	
Number (%) of subjects:					
with no adverse experience		76	(11.7)	67	(10.2)
with one or more adverse experiences		573	(88.3)	591	(89.8)
with vaccine-related‡ adverse experiences		298	(45.9)	326	(49.5)
with serious adverse experiences		21	(3.2)	27	(4.1)
with serious vaccine-related adverse experiences		1	(0.2)	4	(0.6)
who died		1	(0.2)	0	(0.0)
discontinued§ due to an adverse experience		9	(1.4)	12	(1.8)
discontinued due to a vaccine-related adverse experience		7	(1.1)	5	(0.8)
discontinued due to a serious adverse experience		1	(0.2)	5	(0.8)
discontinued due to a serious vaccine-related adverse experience		0	(0.0)	0	(0.0)

† One subject received four vaccinations of RotaTeq™ at expiry potency, and is excluded from this table. This subject had a serious adverse experience of accidental overdose reported and continued in the study until completion. ‡ Determined by the investigator to be possibly, probably, or definitely related to the vaccine. § Discontinued = Subject discontinued from therapy. Calculation of percentage: The number of subjects evaluated divided by the number of subjects with follow-up. N = Number of subjects randomized; n= Number of subjects evaluated; IU = Infectious units.

*From Applicant p. 25 CSR 007

CONCLUSIONS: Among healthy infants, 6 to 12 weeks of age at enrollment, who received RotaTeq™ at expiry potency (≈ $1.1x10^7$ IU/Dose), the following conclusions were drawn: (1) During the first rotavirus season postvaccination, the vaccine is efficacious against naturally occurring rotavirus gastroenteritis caused by the composite of the serotypes contained within the vaccine (G1, G2, G3, G4) that occurs at least 14 days following the third dose. The vaccine is also efficacious against moderate and- severe and severe disease. (2)There is a modest increase in fever (temperatures ≥100.5ºF (38.1ºC), rectal equivalent) following vaccination Visit 1 in the group that received RotaTeq™ at expiry potency. The majority of reported fevers were low grade (temperatures ≥100.5ºF (38.1ºC) and <101.5ºF (38.6ºC, rectal equivalent).

Medical Officer comments:

Subjects in study 007 were included in both the Detailed Safety and Overall FDA safety analyses. The individual study 007 safety analysis presented here was performed by the Applicant. Efficacy results for study 007 can be found in the FDA statistical review and in Table 75 below.

Table 75* Study 007

Primary Efficacy Analysis of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases Occurring at Least 14 Days Postdose 3 Through the First Rotavirus Season Postvaccination in the Per-Protocol Population Using Per-Protocol Case Definition		
	RotaTeq™ at	
	Expiry Potency	
	(≈1.1 x 10^7	
	IU/Dose)	Placebo
Subjects vaccinated	650	660
Protocol violators †	66	61
Subjects with no follow-up	0	0
Subjects classified as unevaluable per per-protocol case definition‡	33	35
Subjects contributing to efficacy analysis	551	564
Days of efficacy follow-up	77929	77037
Subjects classified as rotavirus gastroenteritis cases per per-protocol case definition	15	54
Efficacy estimate (%) and 95% confidence interval	72.5 (50.6, 85.6)	---
p-Value for efficacy >0%	<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, or who had 4 vaccinations. ‡ 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™at expiry potency (≈1.1 x 107infectious units/dose) exceeds 0%. 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, andthe first positive episode is used as the date of the case. EIA = Enzyme immunoassay, IU = Infectious units.		

*From Applicant (CSR 007 Table 7-1)

10.0 Study 009 (Lot Consistency)

Study 009 was a comparison of the immunogenicity and safety of three consistency lots of RotaTeq™ in healthy infants. This phase 3 study was conducted at 10 sites in the United States beginning from May 2003 to August 2004. Treatment consisted of three doses of RotaTeq™ which were administered 28 to 70 days apart, with up to 42 days of safety follow-up after each vaccination.

The primary objective was (1) To demonstrate consistency in the antibody responses to 3 manufactured lots of RotaTeq™, an oral pentavalent (G1, G2, G3, G4, and P1) human-bovine reassortant rotavirus vaccine, based on the serum neutralizing antibodies (SNA) Postdose 3 geometric mean titers (GMTs)

against rotavirus serotypes G1, G2, G3, G4, and P1. (2) To evaluate the safety of RotaTeq™.
Secondary objectives were (1) To evaluate consistency in the antibody responses to 3 manufactured lots of RotaTeq™ based on the Postdose 3 GMTs to serum anti-rotavirus IgA. (2) To summarize the proportion of subjects with a ≥3-fold rise in SNA levels (against rotavirus serotypes G1, G2, G3, G4, and P1) from baseline to Postdose 3.

Study design: This was a randomized, multicenter, double-blind, placebo-controlled, immunogenicity and safety trial conducted in the U.S.

Dosage and formulation:

Regimen: Three doses of the clinical material were to be administered to each subject orally. The volume of each vaccination was approximately 2.0 mL of vaccine or placebo. Vaccination 1 was administered on Day 1, Vaccination 2 was tadministered 28 to 70 days after Vaccination 1, and Vaccination 3 was administered 28 to 70 days after Vaccination 2.
Clinical Material: RotaTeq™ (Lot 1 No.: V260 VAO 020 R001; Lot 2 No.: V260 VAO 020 R002; and Lot 3 No.: V260 VAO 020 R003) was approximately 2.0 mL per dose that contained approximately ---- mg of sucrose, approximately --- mg of sodium citrate, approximately -- mg of sodium phosphate, --- mL of tissue culture medium, and no greater than --- mg of polysorbate 80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 in approximately 2.0 mL of buffer/stabilizer with a measured aggregate potency of 8.81 X 107 Infectious Units (IU)/dose, 8.01 X 107 IU/dose, and 6.91 X 107 IU/dose for Lot 1, Lot 2, and Lot 3, respectively.

The placebo (Lot No. ----------) was approximately 2.0 mL per dose that contained approximately ----------
---

Diagnosis/inclusion and exclusion criteria: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1ºC (≥100.5ºF) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no

receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

Evaluation criteria:

Immunogenicity: Antibody responses (SNA Postdose 3 GMTs against rotavirus serotypes G1, G2, G3, G4, and P1 and serum anti-rotavirus IgA) to RotaTeq™/placebo were evaluated in all subjects. These assays were performed on one serum sample collected from each subject approximately 42 days Postdose 3. In addition, Predose 1 serum samples were to be collected in a subset of approximately 140 subjects (approximately 40 subjects per vaccine lot and approximately 20 subjects in the placebo group) at predetermined study sites. Predose 1 serum samples were assayed for SNA against rotavirus serotypes G1, G2, G3, G4, and P1.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and diarrhea.

Statistical Planning and Analysis:

Immunogenicity: The primary null hypothesis was that the difference in GMTs between any pair of lots was at least 2 fold in either direction. In order to address this hypothesis, 3 pairs of one-sided tests were conducted at the α=0.05 level for each serotype (Lot 1 with Lot 2, Lot 1 with Lot 3, and Lot 2 with Lot 3); because there were 3 consistency lots, there were 6 one-sided comparisons for each serotype. Statistical significance for the 2 one-sided equivalence tests for each pair of lots was established if the p-value for each hypothesis test was less than 0.05. This corresponds to the 90% confidence interval for the fold difference between the 2 lots being contained entirely within (0.5, 2). Using two 1-sided tests for each pair of lots controls the alpha level for each pairwise comparison of lots at 0.05 (2-sided). Requiring success for all 3 lots for all 5 antigens controls the overall alpha for the study at 0.05 (2-sided). Assuming that the Postdose 3 natural log titers of the type-specific SNA responses were normally distributed with a variance of 2.5 (based on previous Merck studies) and that 90% of the subjects would be evaluable for the per-protocol analysis (resulting in ~200 evaluable subjects per vaccine lot), there was approximately 90% power to declare the 3 lots consistent.

Safety: The safety hypothesis was that all 3 lots of RotaTeq™ would be generally well tolerated. Adverse experiences were summarized as frequencies

and percentages, by type of adverse experience, for each vaccine lot separately, the 3 vaccine lots combined, and the placebo group. The percentage of subjects with clinical adverse experiences, overall and specific, with an incidence ≥1% in one or more treatment groups (within 42 days following any vaccination visit) was compared between each pair of vaccine lots and between the pooled vaccine lots and placebo using risk differences and associated exact 95% confidence intervals on those differences. Adverse experiences of special interest in this study (diarrhea, vomiting, behavioral changes (irritability), and elevated temperatures (≥100.5ºF [≥38.1ºC], rectal equivalent) during 7 days postvaccination) were evaluated in a similar fashion, with 2-sided p-values provided. All subjects with safety follow-up were included in the safety summaries.

Immunogenicity results: The results of the primary per-protocol analysis of consistency are summarized in the table below. As shown in the table, the 90% confidence intervals for each of the 5 serotypes were contained within (0.5, 2.0) and the p-values were all <0.001, satisfying the statistical criterion for equivalence. The observed lower bounds of the 90% confidence intervals for the ratios of estimated GMTs were all greater than or equal to 0.7 and the observed upper bounds were all less than or equal to 1.5.

Study 009 Lot Consistency (FDA Statistical Reviewer Comments)

Primary hypothesis concerning lot consistency:
Three manufactured lots of RotaTeq will induce similar antibody responses based on the serum neutralizing antibody (SNA) Postdose 3 geometric mean titers (GMTs) against rotavirus serotypes G1, G2, G3, G4, and P1. (The statistical criterion for consistency requires that the two-sided 90% confidence interval on the ratio of each pair of GMTs excludes a difference of 2-fold or more, for each of the serology components measured.)

FDA Statistical Reviewer's Comments

1. The reviewer has confirmed the geometric mean titer (GMT) results shown in Table 76 below (sponsor's Table 7-1).
2. In Table 77 below (sponsor's Table 7-2), the sponsor provided "Estimated GMTs' based on a statistical analysis model adjusting for study center. Since the sponsor did not provide the details of the analysis, those particular results could not be confirmed. However, the "Estimated Fold Differences" (ratios of GMTs) and 90% confidence intervals (CIs), are almost identical to the fold differences and 90% CIs the reviewer obtained from the observed GMTs. Furthermore, all the upper limits of the 90% confidence intervals are less than 2. Therefore, these results suggest that study 009 met its primary objective.

Medical Officer comments:
The FDA statistical reviewer has determined that the product has shown consistency in the manufacturing of 3 consecutive lots, based on human immune response.

Table 76*

Immunogenicity Summary of Postdose 3 Geometric Mean Titers (Per-Protocol Population Study 009)

	RotaTeq								Placebo	
	Lot 1		Lot 2		Lot 3		Total			
	M=226		M=225		M=229		M=680		M=113	
	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)	n	Observed GMT (95% CI)
G1 SNA (dilution units)	185	167.9 (135.7, 207.7)	195	193.2 (157.6, 236.8)	171	171.0 (140.6, 208.1)	551	177.4 (157.7, 199.6)	89	9.3 (7.2, 11.9)
G2 SNA (dilution units)	185	20.7 (17.3, 24.7)	195	22.6 (19.1, 26.8)	171	17.8 (15.1, 20.9)	551	20.4 (18.5, 22.5)	89	5.9 (5.3, 6.6)
G3 SNA (dilution units)	185	18.0 (15.2, 21.2)	195	18.5 (15.7, 21.9)	171	14.6 (12.4, 17.2)	551	17.0 (15.5, 18.8)	89	9.6 (7.4, 12.5)
G4 SNA (dilution units)	185	66.0 (57.0, 76.4)	195	74.3 (64.4, 85.7)	171	65.7 (55.6, 77.5)	551	68.7 (63.0, 75.0)	89	7.8 (6.5, 9.4)
P1 SNA (dilution units)	185	71.1 (60.0, 84.2)	195	72.3 (61.4, 85.3)	171	65.6 (55.0, 78.2)	551	69.8 (63.3, 76.9)	89	10.2 (7.6, 13.5)
Serum anti-rotavirus IgA (units/mL)	186	292.7 (241.0, 355.5)	196	272.5 (227.9, 325.7)	172	266.2 (220.1, 321.8)	554	277.1 (248.8, 308.6)	89	0.4 (0.2, 0.8)

NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations according to rules which are outlined in the DAP

M = Number of subjects vaccinated.

n = Number of subjects with data available for analysis. Excludes protocol violators and subjects with inadequate data based on laboratory determinations, missing assay results, or samples taken out of specified data range.

GMT = Geometric mean titer; CI = Confidence interval; SNA = Serum neutralizing antibody.

*From Applicant CSR 009 Table 7-1

Table 77* **(Per-Protocol Analysis Study 009)**
Statistical Analysis of the Consistency of GMTs of SNA Against Rotavirus Serotypes G1, G2, G3, G4 and P1 Among Lots of RotaTeq™

		Group A			Group B					
Rotavirus Serotype	Comparison (Group A vs. Group B)	M	n	Estimated GMT†	M	n	Estimated GMT†	Estimated Fold Difference‡ (90% CI)†	One-Sided p-Values†§ for Lower Bound, Upper Bound	Conclusion
G1 SNA	Lot 1 vs. Lot 2	226	185	164.6	225	195	190.1	0.9 (0.7,1.1)	<0.001*, <0.001*	Similar
	Lot 1 vs. Lot 3	226	185	164.6	229	171	172.9	1.0 (0.8,1.2)	<0.001*, <0.001*	Similar
	Lot 2 vs. Lot 3	225	195	190.1	229	171	172.9	1.1 (0.9,1.4)	<0.001*, <0.001*	Similar
G2 SNA	Lot 1 vs. Lot 2	226	185	20.5	225	195	22.5	0.9(0.7,1.1)	<0.001*, <0.001*	Similar
	Lot 1 vs. Lot 3	226	185	20.5	229	171	18.0	1.1 (0.9,1.4)	<0.001*, <0.001*	Similar
	Lot 2 vs. Lot 3	225	195	22.5	229	171	18.0	1.3 (1.0,1.5)	<0.001*, <0.001*	Similar
G3 SNA	Lot 1 vs. Lot 2	226	185	18.0	225	195	18.5	1.0 (0.8,1.2)	<0.001*, <0.001*	Similar
	Lot 1 vs. Lot 3	226	185	18.0	229	171	14.7	1.2 (1.0,1.5)	<0.001*, <0.001*	Similar
	Lot 2 vs. Lot 3	225	195	18.5	229	171	14.7	1.3 (1.0,1.5)	<0.001*, <0.001*	Similar
G4 SNA	Lot 1 vs. Lot 2	226	185	65.6	225	195	74.0	0.9 (0.7,1.1)	<0.001*, <0.001*	Similar
	Lot 1 vs. Lot 3	226	185	65.6	229	171	66.7	1.0 (0.8,1.2)	<0.001*, <0.001*	Similar
	Lot 2 vs. Lot 3	225	195	74.0	229	171	66.7	1.1 (0.9,1.3)	<0.001*, <0.001*	Similar
P1 SNA	Lot 1 vs. Lot 2	226	185	70.7	225	195	71.7	1.0 (0.8,1.2)	<0.001*, <0.001*	Similar
	Lot 1 vs. Lot 3	226	185	70.7	229	171	66.2	1.1 (0.9,1.3)	<0.001*, <0.001*	Similar
	Lot 2 vs. Lot 3	225	195	71.7	229	171	66.2	1.1 (0.9,1.3)	<0.001*, <0.001*	Similar
All serotypes anallyzed	Overall Conclusion									Similar

* A p-value <0.05 implies that the difference is statistically significantly less than the prespecified difference of 2 fold. Within the pair of lots being compared, both p-values being <0.05 corresponds to the two-sided 90% CI on the fold difference in GMTs being entirely contained in (0.5, 2.0) fold and allows for a conclusion of similarity. † Responses, their differences, associated confidence intervals, and p-values are based on a statistical analysis model adjusting for study center. ‡Group A/Group B. § The p-values are for the comparison of the lower bound to 0.5 and of the upper bound to 2.0. NOTE: Data that fall outside limits of detection and/or include "<" or ">" signs are eligible for GMT calculations according to rules which are outlined in the DAP [3.11]. M = Number of subjects vaccinated. n = Number of subjects with data available for analysis. Excludes protocol violators and subjects with inadequate data based on laboratory determinations, missing assay results, or with samples taken out of specified data range. CI = Confidence interval; GMT = Geometric mean titer (dilution units); SNA = Serum neutralizing antibody.

*From Applicant CSR 009, Table 7-2

Safety: For the majority of adverse experiences reported during 42 days postvaccination, the 95% confidence intervals on the risk differences for individual comparisons between pairs of lots and between combined vaccine lots and placebo did contain 0, and in the few cases where the CIs did not contain 0, the incidences for the adverse experiences were not unexpected for this age group and the observed differences were of limited clinical significance. Furthermore, there were no statistically significant differences detected between any pair of lots or between the combined vaccine lots and placebo with respect to the adverse experiences of special interest in this study (diarrhea, vomiting, behavioral changes [irritability], and elevated temperatures (≥100.5ºF [≥38.1ºC], rectal equivalent) during 7 days postvaccination. During the course of this study, 2 subjects were medically evaluated for possible intussusception. Neither of these were a confirmed case of intussusception as determined by the Safety Endpoint Adjudication Committee. Of these subjects, 1 subject received RotaTeq™ (Lot 3) and 1 subject received placebo. The overall summary of adverse experiences reported within 42 days following any vaccination is provided in the table that follows.

Conclusions: Among healthy infants, 6 to 12 weeks of age at enrollment, who received RotaTeq™, the following conclusions can be drawn:
1. Three manufactured lots of RotaTeq™ induce similar antibody responses based on the SNA Postdose 3 GMTs against rotavirus serotypes G1, G2, G3, G4, and P1.
2. In study 009 infants tolerated RotaTeq™.

Medical Officer comments:
Subjects in study 009 were included in both the Detailed Safety and Overall FDA safety analyses that have already been discussed in this BLA. The individual study 009 safety analysis presented here was performed by the Applicant. There were no cases of positively adjudicated intussusception in study 009. See Table 78 below for a summary of the adverse experiences in study 009.

Table 78* Summary Adverse Experiences Reported up to 42 days after vaccine dose in Study 009

	RotaTeq™									
	Lot 1 (N=226)		Lot 2 (N=224)†		Lot) (N=229)		Combined Lots (N=679)†		Placebo (N=112)‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	226		224		229		679		112	
Subjects without follow-up	0		0		0		0		1	
Subjects with follow-up	226		224		229		679		111	
Number (%) of subjects:										
with no adverse experience	19	(8.4)	11	(4.9)	17	(7.4)	47	(6.9)	10	(9.0)
with one or more adverse experiences	207	(91.6)	213	(95.1)	212	(92.6)	632	(93.1)	101	(91.0)
with vaccine-related§ adverse experiences	167	(73.9)	173	(77.2)	165	(72.1)	505	(74.4)	78	(70.3)
with serious adverse experiences	4	(1.8)	4	(1.8)	2	(0.9)	10	(1.5)	3	(2.7)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued_ due to an adverse experience	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)	1	(0.9)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)	1	(0.9)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)

† Excludes one subject who received RotaTeq™ (Lot 2) at vaccination Visits 1 and 2, and RotaTeq™ (Lot 1) at vaccination Visit 3. ‡ Excludes one subject who received placebo at vaccination Visit 1, and subsequently 3 doses of RotaTeq™ (Lot 1). § Determined by the investigator to be possibly, probably, or definitely related to the vaccine. _ Discontinued = Subject discontinued from study. Calculation of percentage: The number of subjects evaluated divided by the number of subjects with follow-up. N = Number of subjects randomized; n = Number of subjects evaluated.

*Applicant Analysis CSR 009 p. 23.

FDA Statistical Overall Efficacy Conclusion for Study 009;

1. The product has shown consistency in the manufacturing of 3 consecutive lots, based on human immune response.

Table 79 Subject Accounting for Study 009*

Study 009	RotaTeq™				Placebo	Total
	Lot 1 (n)	Lot 2 (n)	Lot 3 (n)	Combined Lots (n)	(n)	(n)
Screening Failures						4
Randomized	226	225**	229	680**	113***	793** ***
Male (Age in weeks)	108 (7-12)	127 (7-13)	121 (7-12)	356 (7-13)	70 (8-12)	426 (7-13)
Female (Age in weeks)	118 (7-14)	98 (7-12)	108 (7-13)	324 (7-14)	43 (8-12)	367 (7-14)
Vaccinated at visit 1	226	225	229	680	113	793
Vaccinated at visit 2	208	217	210	635	104	739
Vaccinated at visit 3	202	210	200	612	98	710
Completed study	201	208	200	609	97	706
Discontinuations due to:	25	17	29	71	16	87
-Adverse event	0	0	1	1	1	2
-Protocol deviation	5	7	8	20	6	26
-Refused	13	5	16	34	6	40
-Lost to follow-up	2	2	1	5	2	7
-Moved	1	1	0	2	1	3
-Other	4	2	3	9	0	9

* (taken from Applicant Clinical Study 009 Report p. 19)

** (Includes one subject who received RotaTeq™ (Lot 2) at vaccination Visits 1 & 2 and RotaTeq ™ (Lot 1) at vaccination Visit 3).

*** (Includes one subject who received placebo at Vaccination Visit 1 and subsequently 3 Dose of RotaTeq™ Lot 1).

Table 80* Summary of Subject Demographic Characteristics Study 009*

	RotaTeq™									
	Lot 1		Lot 2		Lot 3		Total Lots		Placebo	
	(N=226)		(N=225)†		(N=229)		(N=680)†		(N=113)‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender										
Male Female	108118	(47.8) (52.2)	12798	(56.4) (43.6)	121108	(52.8) (47.2)	356324	(52.4) (47.6)	7043	(61.9) (38.1)
Age (weeks)										
6 to 12	225	(99.6)	224	(99.6)	228	(99.6)	677	(99.6)	113 (100)	
Over 12	1	(0.4)	1	(0.4)	1	(0.4)	3	(0.4)	0 (0.0)	
Mean	9.9		9.9		9.9		9.9		9.9	
SD	1.00		1.02		1.07		1.03		1.05	
Median	10.0		10.0		10.0		10.0		10.0	
Range	7 to 14		7 to 13		7 to 13		7 to 14		8 to 12	
Male	7 to 12		7 to 13		7 to 12		7 to 13		8 to 12	
Female	7 to 14		7 to 12		7 to 13		7 to 14		8 to 12	
Race										
White	139	(61.5)	144	(64.0)	147	(64.2)	430	(63.2)	68	(60.2)
Hispanic American	57	(25.2)	49	(21.8)	52	(22.7)	158	(23.2)	28	(24.8)
Multi-racial	10	(4.4)	10	(4.4)	16	(7.0)	36	(5.3)	6	(5.3)
Black	13	(5.8)	11	(4.9)	6	(2.6)	30	(4.4)	5	(4.4)
Other	7	(3.1)	11	(4.9)	8	(3.5)	26	(3.8)	6	(5.3)

† Includes one subject (AN 4980) who received RotaTeq™ (Lot 2) at vaccination Visits 1 and 2, and RotaTeq™ (Lot 1) at vaccination Visit 3. ‡ Includes one subject (AN 4340) who received placebo at vaccination Visit 1, and subsequently 3 doses of RotaTeq™ (Lot 1). Calculation of percentage: The number of subjects evaluated divided by the number of subjects randomized. N = Number of subjects randomized; n = Number of subjects evaluated; SD = Standard deviation; AN = Allocation number.

*From Clinical Study Report 009, Table 6.4, p. 66

11.0 Overdose Experience

An overdose of RotaTeq™ was defined for the purpose of the clinical trials in the development of RotaTeq™ as a subject receiving a dose of RotaTeq™ within 12 days of a previous dose. There were 4 cases of overdose, 2 in the RotaTeq™ arm and 2 in the Placebo arm. No reported clinical adverse experiences were associated with cases of overdose.

11.1 Directions for Use and Administration

Adapted from the FDA approved label:
FOR ORAL USE ONLY. NOT FOR INJECTION.
The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age. There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with RotaTeq.
Do not mix the RotaTeq vaccine with any other vaccines or solutions. Do not reconstitute or dilute Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch. In clinical trials, RotaTeq was routinely administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), *H. influenzae* type b conjugate vaccine (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine.

Store and transport refrigerated at 2-8°C (36-46°F). RotaTeq should be administered as soon as possible after being removed from refrigeration. For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90. Protect from light. RotaTeq should be discarded in approved biological waste containers according to local regulations. The product must be used by the expirations date.

To administer the vaccine:

Tear open the pouch and remove the dosing tube.

Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.

Open the dosing tube in 2 easy motions:

1. Puncture the dispensing tip by screwing cap ***clockwise*** until it becomes tight.

2. Remove cap by turning it ***counterclockwise***.

Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)

If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), a replacement dose is not recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

Discard the empty tube and cap in approved biological waste containers according to local regulations.

12.0 Conclusions

Overall
Data from the phase 3 clinical trials support the efficacy and safety of a 3 dose oral regimen of RotaTeq™ when administered to healthy infants with the first dose given at age 6-12 weeks, followed by 2 additional doses given at 4 to 10 week intervals with completion of the vaccine series by 32 weeks of age.

Data do not support administration of this product using any schedule other than that utilized in the phase 3 clinical trials. The safety of "catch-up immunization" has not been established for this product.

Benefit
The vaccine was 60-74% effective at preventing rotavirus gastroenteritis of any grade of severity that was caused by serotypes contained in the vaccine. Using the Applicant's definition/scoring system for "severe disease", vaccine efficacy was higher (96-98%) in preventing severe rotavirus disease. The vaccine was 95-96% effective at decreasing the number of hospitalizations due to rotavirus gastroenteritis caused by the vaccine serotypes. Whether this vaccine provides cross-protection against disease caused by non-vaccine serotypes such as G9 is an area for further study. Although, shedding of vaccine virus was infrequent, additional and more systematic shedding and transmission studies may clarify whether this product contributes toward herd immunity or whether it could pose a transmission risk for immunosuppressed household members residing with an infant vaccinated with RotaTeq™.

Rotavirus is a universal childhood disease; however it is not universally severe in U.S. children. Data suggest there are groups at higher risk to develop severe rotavirus gastroenteritis requiring hydration in the emergency room or inpatient hospital setting.[13] It would be optimal if one could effectively target a rotavirus vaccine program toward those who would most benefit. However, the characteristics of these infants at higher risk to develop complications from rotavirus infection include factors such as prematurity, low birth weight, being born to a low income and/or young mother and other socio-economic factors which may be difficult to easily capture in a rotavirus vaccine delivery program. Restricting this product to infants receiving Medicaid or to those enrolled in a state-funded vaccine program may exclude other groups of infants who are also at higher risk to develop severe disease.

Risk
In the phase 3 clinical trials for this product, the risk of intussusception was not increased relative to placebo within 42 days of any vaccine dose; but the risk was not zero. The upper bound on the 95% confidence interval for the relative risk was 6.4 and it is imperative to pursue additional post-marketing studies to further characterize any risk that may occur when this product is used in a larger U.S. infant population. The potential risk of developing a serious adverse event from

the vaccine, such as intussusception, must be weighed against the benefit derived from a vaccine that prevents a disease that is not severe in most U.S. children.

Additional issues include:

Regarding concomitant administration with vaccines to prevent pertussis, it will be important to complete a concomitant vaccine study using a validated assay and the appropriate non-inferiority criteria in order to characterize whether RotaTeq™ interferes with the immunogenicity of pertussis vaccines.

This is a live, oral viral vaccine that replicates in the intestine and may cause diarrhea and hematochezia. Hematochezia which was not captured as a solicited adverse event on the vaccine report cards will be monitored in the post-marketing studies. The patient circular will contain information for parents regarding the signs and symptoms of intussusception including hematochezia.

General safety issues such as seizures and other adverse events that could be due to the intestinal or extra-intestinal manifestations of rotavirus infection due to vaccine virus will need to be monitored in the post-marketing studies.

Extrapolation of both the safety and efficacy data can not be made to populations in which this vaccine was not studied such as infants in countries where oral polio vaccines are the standard of care or in children with immuno-deficiencies such as HIV or who are co-infected with other gastrointestinal parasites. Additional studies of RotaTeq™ in these populations would be helpful.

This vaccine provides protection against the most common serotypes currently causing disease in the U.S. population but in the ensuing years, it will be important to monitor for serotype replacement and changes in the global epidemiology of rotavirus.

13.0 Recommendations

13.1 Approval

13.2 Recommendations on Post –Marketing Actions

The Applicant's post-marketing plan was accepted by FDA with specific comments by FDA's Office of Biostatistics and Epidemiology that are included below:

Objective 1:
Assess the incidence of intussusception that results in emergency room visits or hospitalizations after infants receive one or more doses of RotaTeq™ vaccination:
For the primary analysis, 44,000 vaccinated subjects will be evaluated for 30-days after each dose of vaccine to provide a total of approximately 10,850 infant-

years of follow-up. The observed rate of intussusception among vaccinated subjects will be compared to the expected rate of intussusception derived from the retrospective baseline study. Based on published data and the rate observed in clinical trials, it is expected that the population-based background rate of intussusception is approximately 1 per 2,000 infant-years. Using these parameters and a 1-sided alpha of 0.05, it is estimated that the post-licensure study will have 80% probability of detecting a true overall increased risk of intussusception attributable to the vaccine of 2.5 or greater. Should the baseline study detect a rate that is significantly different from the expected rate of 1:2000, then adjustments will be made to the sample size in order to maintain the 80% probability of detecting a true overall increased risk of intussusception attributable to the vaccine of 2.5 or greater.

Objective 2:
Describe the general short-term safety profile of RotaTeq™. Diagnosis specific Adverse event rates for outpatient clinic visits, emergency room visits, and hospitalizations, as well as mortality rates will be calculated. Rate comparisons will be performed by comparing the rate of diagnosis-specific clinical events that occur in the 0,1 to 7, 8 to 14, and 0 to 30 day risk periods to the rate of the same clinical events occurring in: (a) the comparison time period 31 to 60 days post-vaccination (self control) or to the date of next vaccination, whichever comes first; and (b) equivalent time periods following vaccination among a historical comparison group vaccinated with routine pediatric vaccines before RotaTeq™ was available. The probability of the relative risk occurring by chance alone will be calculated using exact p-values. Exact mid-probability confidence intervals will be calculated based on person-time and the Poisson distribution. Rate comparisons will be done separately for Doses 1, 2, and 3 of RotaTeq™.

FDA/VAERS response to the Applicant's proposed post-marketing plan:

1. Primary Objectives: Include as a secondary analysis the assessment of the incidence of intussusception that results in emergency room visits or hospitalizations within days 1 to 7, 8 to 14 and 15 to 21 immediately following a dose of RotaTeq™

2. Add a secondary objective:
Catch up immunizations: The Sponsors should perform an additional analysis of intussusception and general safety outcomes among infants who are administered RotaTeq™ outside of the age indicated in the product label.

3. General Safety Surveillance: The following should be considered for inclusion among the specific adverse events (AEs) that will constitute outcomes of the general surveillance study:
(a) Gastrointestinal: Hematochezia, Diarrhea, Vomiting
(b) Respiratory: Bronchospasm, pneumonia, pertussis, nasopharyngitis/pharyngitis, otitis media, other acute respiratory infections

(c) Neurological: Seizures

4. General Safety Surveillance: The Sponsor should make regularly available to CBER a written explanation of the rationale used by the Safety Monitoring committee to identify adverse events (AEs) that occur in the study as possibly related (or with no relation) to vaccination. Also, the Sponsor will provide CBER results of the medical chart reviews of events considered potentially related to RotaTeq™.

5. Safety measurements. Timeliness of reporting:
(a) Reporting of intussusception cases identified during the Phase 4 study to VAERS: The Sponsor will report all intussusception cases to VAERS as serious and unexpected (i.e..15-day reports).
(b) Reporting of other AEs identified during the phase 4 study to VAERS: The Sponsor will report all AEs identified by the Safety Monitoring Committee as possibly related to vaccination within 30 days of identification.

6. Deadlines: As presented during the January 12, 2006 meeting the Sponsor should specify the following deadlines for the Phase 4 study (contingent upon approval of the vaccine by February 3, 2006):

a. Provide a final study protocol to CBER by May 5, 2006
b. Initiate the Baseline Study during the beginning of the third quarter of 2006
c. Initiate the Post-licensure study itself during the third quarter of 2006
d. Based on projected vaccine uptake and on the size of the study birth cohort, to complete the study by the fourth quarter of 2008
e. Provide annual reports to CBER on study progress.

13.3 Labeling

The Applicant plans to submit data to support efficacy in prevention of rotavirus gastroenteritis due to the G9 serotype.

Hematochezia was not found to be increased in RotaTeq™ recipients and it was not highligted as an adverse event in the FDA -approved label. However, it will be monitored in the post-marketing studies and depending on the post-marketing adverse event experience, appropriate changes may be made to the label.

The patient package insert contains information regarding the signs and symptoms, including hematochezia, that may be associated with intussusception in order that parents can monitor their infant and seek medical evaluation if concerns arise.