

FDA Statistical Review and Evaluation

**Document for the Vaccines and Related Biological Products Advisory
Committee (VRBPAC)**

December 14, 2005

RotaTeq, Rotavirus Vaccine, Live, Oral, Pentavalent (Merck)

Indication: prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1 (e.g., G9).

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1. Overview

In the application for licensure, Merck has submitted information from several clinical trials. Two trials will be discussed here: protocol-006, and protocol-007.

This statistical briefing document presents only the results obtained by the reviewer from the data submitted by Merck. The goal of this document is to provide information to the Vaccine and Related Biological Products Advisory Committee; however, it is not the final statistical review to the FDA.

2. Safety: Intussusception (IT) Cases

The first rotavirus vaccine licensed, RotaShield (Wyeth), has been associated with an increased risk of intussusception. A case-control study conducted by CDC confirmed that the risk of IT appeared to be increased among recipients of RotaShield during the 3- to 14-day period after the first dose and during the 3- to 7-day period after the second dose. Therefore, it is crucial for future rotavirus vaccines to demonstrate safety with regard to IT.

Because of the RotaShield experience, Merck's trial design considered IT as the main safety endpoint for protocol-006, Rotavirus Efficacy and Safety Trial (REST).

One of the two co-primary objectives in REST concerned the intussusception issue:

- To assess the safety of RotaTeq with respect to intussusception within 42 days of any dose of vaccine/placebo.

The related hypothesis for IT was:

Oral RotaTeq will not increase the risk of intussusception relative to placebo within 42 days of any dose.

The corresponding statistical criteria were:

- (a) The distribution of IT cases between vaccine and placebo groups (case split) does not reach the predefined safety boundary for any of the 2 overlapping day ranges (1 to 7 and 1 to 42 days following any dose) being monitored by the Data and Safety Monitoring Board at any time during the trial; and
- (b) The upper bound of the exact 95% confidence interval estimate of the relative risk of IT at the end of the study must be ≤ 10 .

Study design

This is a double-blinded (operating under Merck in-house blinding procedures) placebo-controlled, randomized, international, multicenter study. Subjects who met the eligibility criteria for enrollment were randomized in a ratio of 1:1 to receive either RotaTeq, at potency within the release range intended for the licensed product, or placebo.

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

Intussusception is an uncommon illness with an estimated annual incidence of 1 out of 2000 among infants < 2 years of age. Therefore, a minimum sample size of 60,000 was required in order to evaluate the safety of RotaTeq with respect to IT. The study employed a group-sequential design. Initially 60,000 subjects were to be enrolled. After the first 60,000 subjects completed the safety follow-up after the final vaccination, the DSMB would unblind the treatment arm of positively-adjudicated IT cases (as determined by the SEAC) and assess whether the predefined statistical criteria for the primary safety hypothesis were met. If the criteria were not met with 60,000 subjects, then an additional group of 10,000 subjects would be enrolled. This process of enrolling additional groups of 10,000 subjects would continue until the predefined statistical criteria were met or until 100,000 subjects had been enrolled.

The sequence of decision-making is illustrated in the following figure from the Summary of Clinical Safety submitted to the FDA by Merck.

Figure 2.7.4: 2

Reporting Process for Potential Cases of Intussusception



SEAC = Safety Endpoint Adjudication Committee.

DSMB = Data and Safety Monitoring Board.

Note: For the parent/legal guardian, investigator, and Merck personnel, blinding refers to treatment arm assignment and the final adjudication results. For the SEAC and the Non-Rotavirus Clinical Monitor, blinding refers to treatment arm assignment.

[Ref. 5.3.5.1: P006]

Results from the data submitted as amendment 3 to the original submission of the REST trial

There were 70,219 subjects enrolled, and 70,146 received at least one dose of either RotaTeq or placebo. There were 134 cases of IT reported, of which 32 were positively adjudicated (confirmed).

Table 2.1 Number of Days Post Dose of Confirmed Intussusception by Dose and Treatment within a 42-day Follow-up Window

	RotaTeq	Placebo
Post-dose 1 (≤ 42 days)		36
Post-dose 2 (< 42 days)	2,19,21,41	28
Post-dose 3 (≤ 42 days)	38, 40	9, 36, 42

Table 2.2 Number of Days Post Dose of Confirmed Intussusception by Dose and Treatment within a 60-day Follow-up Window

	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

Table 2.3 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

Reviewer’s Comments

Since the REST trial was closely monitored by the DSMB, there was no safety concern during the trial as IT cases occurred. However, now that the trial has stopped, one can study the distribution of cases to see if any pattern of concern emerges. The following are the reviewer’s observations based on Merck’s analyses as well as from additional exploratory evaluations considered by the reviewer:

1. There does not seem to be a clustering of IT within a 7-day or 14-day window.

2. Table 2.1 shows the 42-day window results, 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) were obtained. The upper bound of the 95% confidence interval is less than 10, which satisfies the prospectively specified primary safety objective of REST.
3. Although a 42-day window was pre-specified, the size of the window seems to be arbitrary. One could argue for using a 60-day window since the time between any two doses is 60 days. Table 2.2 displays for each IT case the number of days post dose within a 60-day window. This interval shows 8 cases of IT in the RotaTeq group and 6 cases in the placebo group, which produces a relative risk estimate of 1.3 with a 95% confidence interval of (0.4, 4.7). The upper bound 4.7 is also less than 10.
4. Although there seems to be a pattern after dose 2 for the RotaTeq group to show a higher number of cases (4) than the placebo group (1) in Table 2.1 (RR = 4.0 with a 95% CI of (0.4, 197.0)), the ratio is reduced substantially when the window size is expanded to 60 days. In Table 2.2, the number of IT cases in the RotaTeq group is 5 versus 2 in the placebo group (RR = 2.5 with 95% CI of (0.4, 26.3)).
5. No pattern emerges for when the IT cases occurred after each dose, for either the RotaTeq group or the placebo group when examined with a 60-day window.
6. Table 2.3 includes all the IT cases confirmed for all subjects completing the follow-up period. When observed this way, the total number of IT cases is much more in the placebo group (19) than in the vaccine group (13). The relative risk estimate is 0.68 with a 95% CI of (0.3, 1.5).
7. Because of the rarity of intussusception, even though over 70,000 subjects were enrolled in the REST study, there were a total of only 32 cases of confirmed IT. Thus, the need for a long-term well-designed post-licensure phase-4 study may warrant consideration.

3. Efficacy

REST

The other co-primary objectives besides intussusception concerns the issue of efficacy:

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

Below are results for the G1 type only from the reviewer and from Merck in the original submission:

	RotaTeq		Placebo	
Subjects vaccinated	2834		2839	
Subjects in efficacy analysis	2207		2305	
	FDA	Merck	FDA	Merck
Days of follow-up	898,640	625,506	893,688	624,615
G1 serotype	88	72	303	286
Efficacy estimate (%) and 95% confidence interval	71.1 (62.3, 77.5)	74.9 (67.3, 80.9)		

Reviewer’s comment

1. The reason for the days of follow-up time being much higher in the reviewer’s calculations than in those provided by Merck is probably due to some of the subjects being followed for one rotavirus season and some being followed for two. The data submitted to CBER did not include the dates for beginning or ending of each season for each subject enrolled. CBER is in the process of obtaining this information from Merck.
2. Due to the large discrepancies between FDA’s and Merck’s calculation in the days of follow-up, further investigation to reconcile the differences is required. Therefore, the reviewer’s conclusions regarding efficacy based on the REST study are deferred until the review can be completed.

Expiry study – 007

Primary objective:

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.

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 $\leq 0\%$.

The following are results obtained by the reviewer as well as those provided by Merck in the original submission:

	RotaTeq at Expiry Potency (~ 1.1 X10 ⁷ IU/dose)		Placebo	
Subjects vaccinated	650		660	
Subjects in efficacy analysis	551		564	
	FDA	Merck	FDA	Merck
Days of follow-up	78,282	78,791	77,674	78,141
Gastroenteritis cases	15	15	52	54
Efficacy estimate (%) and 95% confidence interval	71.0 (48.4, 85.0)	72.5 (50.5, 85.6)		

Reviewer's Comment

Although Merck's and the reviewer's numbers are different for the total follow-up time and the numbers of gastroenteritis cases, the discrepancies are much smaller than those in REST. Therefore, it is highly likely RotaTeq has achieved the primary objective in this trial.

4. Reviewer's Overall Conclusion

1. No discernible 'pattern' emerges in the distribution of intussusception cases.
2. The efficacy results from REST are inconclusive at this time, pending resolution of discrepancies in counts of follow-up time.
3. Efficacy at expiry dose is highly likely.