Date: March 10, 2008

From: Paul Kitsutani, OVRR, DVRPA

Subject: Clinical Review for STN 125265/0 Rotarix: Rotavirus Vaccine, Live, Oral, GlasoSmithKline Biologicals

To: Laraine Henchal, OVRR, DVRPA

Through: Steve Rosenthal, OVRR, DVRPA

1 Rotarix™ BLA Clinical Review

1.1	Medical Officer's Review Identifiers and Dates	
1.1.1	BLA #:	STN 125265/0
1.1.2	Related IND #(s):	----
1.1.3	Reviewer Name:	Paul Kitsutani, MD, MPH Vaccine Clinical Trials Branch, Division of Vaccines and Related Products Applications, HFM 475
1.1.4	Submission Received by FDA:	June 5, 2007
1.1.5	Review Completed:	March 10, 2008
1.2	Product	
1.2.1	Established Name:	Rotavirus Vaccine, Live, Oral
1.2.2	Proposed Trade Name:	Rotarix™
1.2.3	Product Formulation:	At least $10^{6.0}$ median $CCID_{50}$ G1[P8]; each vaccine dose contains amino acids, dextran, DMEM, sorbitol, sucrose, calcium carbonate, sterile water, and xantham
1.3	Applicant:	GlaxoSmithKline Biologicals Greenford, Middlesex, United Kingdom
1.4	Pharmacologic Class or Category:	Vaccine
1.5	Proposed Indication(s):	Prevention of rotavirus gastroenteritis caused by G1 and non-G1 types
1.6	Proposed Populations(s):	Infants
1.7	Dosage Form(s) and Route(s) of Administration:	Lyophilized vaccine to be reconstituted with 1 mL liquid diluent provided in prefilled oral applicator, oral administration

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3 Executive Summary

This Biologics License Application (BLA) contains efficacy, immunogenicity, and safety data provided by GlaxoSmithKline to support approval of Rotarix™, a live, oral, monovalent rotavirus (RV) vaccine indicated for the prevention of RV gastroenteritis (GE) caused by G1 and non-G1 types. Rotarix™ is to be administered as a 2-dose series to healthy infants 6 to 24 weeks of age, with doses separated by a minimum interval of 4 weeks. The proposed release specification potency is ------- median Cell Culture Infective Dose ($CCID_{50}$) per dose of live, attenuated human RV, with an end-of-shelf-life potency of ≥ $10^{6.0}$ $CCID_{50}$ per dose.

The Biologics Licensing Application (BLA) contains six Phase II trials and five Phase III trials. Two of the Phase III trials are considered pivotal efficacy studies: Rota-023, conducted in 11 Latin American countries, and Rota-036, conducted in six European countries. Rota-023 was also specifically designed and powered to evaluate the risk of definite intussusception (IS), with over 63,000 infants from 11 Latin American countries plus Finland receiving either Rotarix™ or placebo. Rota-033 was a Phase III lot-to-lot consistency study of 3 lots conducted in three Latin American countries. Rota-060, a Phase III trial evaluating the immunogenicity of routine childhood vaccines when co-administered with Rotarix™, was conducted in the U.S.

Efficacy

Two Phase III studies, Rota-023 and Rota-036, are considered pivotal to the efficacy claims in this BLA. The primary objective of Rota-036 was to assess vaccine efficacy (VE) against any RV GE during the first efficacy follow-up period from 2 weeks post-Dose 2 until the end of the first RV epidemic season. The primary objective of Rota-023 was to assess VE against severe RV GE during the first efficacy follow-up period from 2 weeks post-Dose 2 until 12 months of age. Both studies were prospective, randomized, double-blinded, placebo-controlled trials. In each study, the According to Protocol (ATP) efficacy cohort was used for the primary efficacy analyses, and consisted of 17,867 subjects (Rotarix™: 9009, placebo: 8858) in Rota-023 and 3874 subjects (Rotarix™: 2572, placebo: 1302) in Rota-036. VE for each endpoint was calculated using the following formula: 1 – (attack rate in the Rotarix™ group ÷ attack rate in the placebo group).

In Rota-036, RV GE was defined as an episode of GE in which RV other than the vaccine strain was identified in a stool sample collected no later than 7 days after GE symptom onset, while severe RV GE was defined as an episode of RV GE with a score of ≥ 11 points using the Vesikari scale. In Rota-023, the primary case definition of severe RV GE was defined as an episode of RV GE requiring hospitalization and/or rehydration therapy (equivalent to WHO plan B or C) in a medical facility.

The applicant demonstrated that Rotarix™, at $10^{6.5}$ $CCID_{50}$ per dose, was effective in preventing naturally occurring RV GE of any grade of severity and severe RV GE during the first year of life. VE was 87.1% (95% CI: 79.6, 92.1%) against any RV GE in Rota-036. VE against severe RV GE

was 95.8% (95% CI: 89.6, 98.7%) in Rota-036 compared to 84.7% (95% CI: 71.7, 92.4%) in Rota-023, suggesting geographical and/or ethnic differences in efficacy. Protection was also demonstrated against any and severe RV GE caused by circulating G1 and certain non-G1 types, as well as other clinical endpoints during the first-year, second-year, and combined (first- and second-year) efficacy follow-up periods.

Immunogenicity

Immunogenicity to Rotarix™ was assessed by measuring serum anti-RV IgA antibodies, considered a standard measure of immunity in most field studies and vaccine trials, at pre- and post-vaccination time points. Definitions of seropositivity and seroconversion were uniform across studies. Seropositivity was defined as an anti-RV IgA concentration ≥ 20 U/mL. Seroconversion was defined as an anti-RV IgA concentration ≥ 20 U/mL in a subject seronegative for RV pre-Dose 1. Stool samples were also collected to evaluate vaccine take, defined as anti-RV IgA seropositivity in any post-vaccination blood sample or detection of RV antigen in any post-vaccination stool sample in a RV-uninfected subject pre-vaccination. Anti-RV IgA seroconversion rates and geometric mean concentrations (GMCs) were measured in all or a pre-defined subset of subjects from all BLA studies, while vaccine take was estimated in 7 studies, including Rota-033. In each study, the ATP immunogenicity cohort was used for the primary immunogenicity analyses.

In studies that evaluated Rotarix™ at $10^{6.5}$ $CCID_{50}$ to $10^{6.8}$ $CCID_{50}$ per dose (total number of Rotarix™ subjects at these potencies in the ATP immunogenicity cohorts = 2642), 2 doses of Rotarix™ appeared immunogenic in infants, as demonstrated by post-Dose 2 anti-RV IgA seroconversion rates, GMCs, and vaccine take rates. At 1-2 months post-Dose 2, the anti-RV IgA seroconversion rate was 86.5% (95% CI: 83.9, 88.8%) in Rota-036 compared to 76.8% (95% CI: 72.4, 80.9%) in Rota-023. Similarly, 1-2 month post-Dose 2 GMC was higher in Rota-036 (197.2 U/mL; 95% CI: 175.2, 222.0 U/mL) than in Rota-023 (102.6 U/mL; 95% CI: 86.3, 122.0 U/mL). These results suggest that geographical and/or ethnic factors may impact the anti-RV IgA immune response to Rotarix™.

Safety

Intussusception (IS)

In Rota-023, the primary safety objective was to determine the safety of Rotarix™ with respect to IS occurring within 31 days (Days 0-30) after each dose. The safety database consisted of the Total Vaccinated Cohort (Rotarix™: 31,673, placebo: 31,552) that was followed from Dose 1 to 1-2 months post-Dose 2. **Definite IS** was defined as a diagnosis of IS confirmed by intestinal invagination at surgery or autopsy, or by radiologic techniques (gas/liquid contrast enema or abdominal ultrasound). The primary safety objective was achieved if the following two criteria were met: upper limit of the 95% confidence interval (CI) of the risk difference (Rotarix™ minus placebo) for definite IS was <6/10,000 and lower limit of the 95% CI of the risk difference was < 0. An increased risk of definite IS following Rotarix™ vaccination was not observed within 31 days after any dose when the date of IS diagnosis was used to categorize cases (risk difference/10,000 = -0.32; 95% CI: -2.91, 2.18/10,000). An increased risk within 31 days was also not demonstrated in an FDA analysis that used the date of IS onset to categorize cases (risk difference = $-8.48/10^7$; 95% CI: -2.63, 2.61/10,000). Increased risk was not observed after Dose 1 or Dose 2. Temporal clustering after either dose was also not observed.

When pooled safety data from 8 BLA studies of subjects who received Rotarix™ at the proposed licensure potency (≥ $10^{6.0}$ $CCID_{50}$ per dose; n = 36,755) were analyzed (Core Integrated Safety Summary [ISS] analysis), a statistically significant increased risk of IS within 31 days after Rotarix™ was not observed (Rotarix™: 9 [0.024%], placebo: 7 [0.020%]; RR=1.23, 95% CI: 0.41, 3.90). Pooled safety data from 5 BLA studies of subjects who received Rotarix™ at the less-than licensure potency (<

$10^{6.0}$ $CCID_{50}$ per dose; n = 3076) (Supplementary ISS analysis) also did not demonstrate a significantly increased risk of IS within 31 days after Rotarix™ (Rotarix™: 1 [0.033%], placebo: 0 [0%]; LL 95% CI: 0.01).

Serious adverse events - deaths

A total of 118 deaths (0.158% of all study subjects) were reported throughout the course of the studies. Overall death rates were 0.184% (68/36,755) in the Rotarix™ (≥ $10^{6.0}$ $CCID_{50}$ potency) group, 0.163% (5/3076) in the Rotarix™ (< $10^{6.0}$ $CCID_{50}$ potency) group, and 0.158% (55/34,739) in the placebo group. In the Core and Supplementary ISS analyses for deaths, there were no significant imbalances between treatment groups in the rates of fatalities during the 31 days post-vaccination or entire study follow-up periods. For either follow-up period, there were no significant imbalances in fatalities between groups for any Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT).

Pneumonia deaths – Rota-023

In Rota-023, an FDA analysis revealed statistically significant difference between treatment groups in the rate of subjects with pneumonia-related deaths between Dose 1 and Visit 3 (1-2 months post-Dose 2 or 2-4 months post-Dose 1) (Rotarix™: 0.051%, placebo: 0.019%; p = 0.0354). The applicant provided a p-value of 0.054. Pneumonia-related death rates within 31 days post-vaccination were still higher in Rotarix™ compared to placebo recipients (0.022% [7/31,673] vs. 0.010% [3/31,552]). However, there were no differences between the treatment groups in rates of non-fatal pneumonia events and pneumonia hospitalizations (Dose 1 to Visit 3, within 31 days and beyond 31 days post-vaccination).

Serious adverse events

In the Core and Supplementary ISS analyses for severe adverse events (SAEs), there were no significant imbalances between treatment groups in the rates of subjects with at least 1 SAE during the 31 days post-vaccination or during the entire study follow-up period. In the Core ISS analysis, PTs *Diarrhea*, *Gastroenteritis*, *Dehydration*, and *Ileus* were reported significantly less during the entire study follow-up periods in the Rotarix™ group than in the placebo group. There were no significant imbalances for any other specific PT except *Foreign body trauma* (Rotarix™: 11/36,755 [0.035%], placebo: 1/34,739 [0.003%]; RR = 9.11, 95% CI: 1.31, 394.8). However, all cases involved swallowing a foreign body between 48-483 days post-dose, and were assessed by the applicant as not related to vaccination.

Convulsions – Rota-023

In Rota-023, a statistically significant difference between treatment groups was observed in the rate of PT *Convulsions* between Dose 1 and Visit 3 (Rotarix™: 16/31,673 [0.051%], placebo: 6/31,552 [0.019%]; p = 0.034). However, when convulsion-related PTs (*Convulsions, Epilepsy, Grand mal convulsion, Status epilepticus,* and *Tonic convulsion*) were pooled in a post-hoc analysis, a statistically significant difference between groups was not demonstrated (Rotarix™: 20/31,673 [0.063%], placebo: 12/31,552 [0.038%]; p = 0.219). Furthermore, convulsion-related episodes within 31 days after any dose occurred less in Rotarix™ recipients than placebo recipients. Among subjects who experienced a convulsion-related event within 31 days after any dose, 7 (0.022%) were Rotarix™ and 9 (0.029%) were placebo recipients. Within 43 days post-vaccination, 12 (0.04%) Rotarix™ and 9 (0.03%) placebo recipients reported a convulsion-related event.

Imbalances between groups in convulsion-related PTs within 31 or 43 days post-vaccination were not observed in Rota-036.

Pneumonia – Rota-036

In Rota-036, rates of PT *Pneumonia* were significantly higher in the Rotarix™ compared to the placebo group from Dose 1 to Visit 7 (end of the second RV epidemic season) (24 vs. 4, p = 0.029). Of the 28 cases, only one (Rotarix™ group) was reported within 31 days after vaccination. CBER's analysis showed that 3 cases in the Rotarix™ group compared to 0 in the placebo group reported PT *Pneumonia* within 43 days after vaccination. Furthermore, when the CBER reviewer combined the pneumonia-related PTs (*Pneumonia, Bronchopneumonia, Lobar pneumonia, Pneumonia viral*), an imbalance was still seen from Dose 1 to Visit 7 (Rotarix™: 31, placebo: 7), within 31 days post-vaccination (Rotarix™: 2, placebo: 0) and within 43 days post-vaccination (Rotarix™: 5, placebo: 0).

Imbalances between groups in pneumonia-related PTs within 31 or 43 days post-vaccination were not observed in Rota-023.

Unsolicited adverse events (non-SAEs)

In the Core and Supplementary ISS analyses for unsolicited AEs 31 days post-vaccination, there were no significant imbalances between groups in the rates of subjects with at least 1 AE of any intensity or Grade 3 intensity after any dose. In the Core ISS analysis, there were small but statistically significant increases in Rotarix™ compared to placebo recipients in rates of PTs *Irritability* (11.4% vs. 8.7%) and *Flatulence* (2.2% vs. 1.3%). However, no significant imbalances in Grade 3 *Irritability* and *Flatulence* were observed. In the Supplementary ISS analysis, there was a statistically significant increase in rates of PT *Bronchitis* in Rotarix™ compared to placebo recipients (1.85% vs. 0.74%, RR=2.39, 95% CI: 1.27, 4.90%). Grade 3 *Bronchitis* occurred in 6 Rotarix™ compared to 0 placebo recipients. The applicant stated that this imbalance was driven by an imbalance of *Bronchitis* in Rota-006. FDA calculated a total of 44 (3.9%) Rotarix™ recipients (< $10^{6.0}$ $CCID_{50}$ groups) compared to 10 (1.8%) placebo recipients in Rota-006 who reported PT *Bronchitis* during Days 0 to 30 post-vaccination. Grade 3 *Bronchitis* occurred in 1 Rotarix™ compared to 0 placebo recipients. In Rota-006, the rate of any *Bronchitis* in the Rotarix™ group receiving the licensure potency was higher than in the placebo group during this same interval (3.7% vs. 1.8%); no Grade 3 *Bronchitis* was reported in this Rotarix™ group. In the Core ISS analysis, when PTs *Bronchitis* and *Bronchitis acute* were combined, 116 (2.3%) Rotarix™ recipients compared to 45 (1.6%) placebo subjects reported an AE. Grade 3 AE rates were comparable (Rotarix™: 0.16%, placebo: 0.14%).

Solicited adverse events

In the Core and Supplementary ISS analyses for solicited symptoms 8 days (Days 0-7) post-vaccination, there were no significant imbalances in rates of fever, irritability, loss of appetite, vomiting, or diarrhea, of any severity or Grade 3 severity, between the Rotarix™ and placebo groups after any dose. The exception was Grade 3 cough/runny nose after any dose in the Core ISS analysis (Rotarix™: 3.6%, placebo: 3.2%, RR=1.41, 95% CI: 1.01, 1.99). However, imbalances in rates of cough/runny nose after each dose were not observed.

Shedding and Transmission

Post-vaccination RV antigen shedding in stools was evaluated in all or a subset of subjects from 7 BLA studies. In all studies (total number of Rotarix™ subjects in the ATP immunogenicity cohorts = 1086), samples were collected on Day 7 after each dose, while in 4 studies, samples were also collected on Day 15 post-dose. In addition, 4 studies collected samples at 30 days post-Dose 1 (pre-Dose 2), while 4 studies collected samples at 60 days post-Dose 1 (pre-Dose 2).

Among Rotarix™ treatment groups from studies that administered vaccine at $10^{6.5}$ $CCID_{50}$ to $10^{6.8}$ $CCID_{50}$ per dose, post-Dose 1 RV antigen shedding ranged from 50.0% to 80.0% of subjects at Day 7, 19.2% to 64.1% at Day 15, 0% to 24.3% at Day 30, and 0% to 2.6% at Day 60. The highest rates

of post-Dose 1 shedding at Days 7, 15, and 30 occurred in subjects from Rota-007, a Phase II study conducted in Singapore. The applicant stated that these results may be due to a population effect or older age at Dose 1 (median = 13 weeks) when maternal antibodies known to have an impact on RV immune response have already declined. Among the same Rotarix™ treatment groups, post-Dose 2 shedding ranged from 4.2% to 18.4% at Day 7, 0% to 16.2% at Day 15, and 0% to 1.2% at Day 30. Shedding at Day 45 post-Dose 2, monitored only in Rota-033, was 0%. Highest post-Dose 2 shedding rates at Days 7 and 15 were also in subjects from Rota-007.

In 2 BLA studies that administered Rotarix™ at $10^{6.5}$ $CCID_{50}$ per dose, an estimated 25.6% to 26.5% of subjects shed live RV at Day 7 post-Dose 1. In addition, data from 4 other studies combined demonstrated that among RV antigen-positive samples, live RV was detected in fewer samples from Rotarix™ vaccinated subjects than samples from wild-type RV GE episodes (14.6% vs. 68.6%)

Transmission of Rotarix™ was not formally evaluated in any of the BLA studies.

Co-Administration with Other Childhood Vaccines

Concomitant administration of other routine childhood vaccines with Rotarix™ or placebo was allowed in 10 of the 12 BLA studies. Only one study (Rota-014, Phase II, South Africa; n = 447) allowed concomitant administration of oral poliovirus vaccine.

Only Rota-060 was specifically designed to evaluate non-inferiority of immune responses to diphtheria, tetanus, pertussis, hepatitis B, poliovirus, *Haemophilus influenza* type b (Hib), or *S. pneumoniae* antigens when these routine vaccines were co-administered with Rotarix™. All study subjects received 3 doses each of Pediarix® (DTaP-HepB-IPV), Prevnar® (pneumococcal 7-valent conjugate vaccine), and ActHIB®. In the co-administration group, Rotarix™ was administered with the first two routine vaccine doses, while in the separate administration group, Rotarix™ was administered one month after routine vaccine Doses 1 and 2. Antibody responses to diphtheria, tetanus, pertussis (PRN, FHA, PT), hepatitis B (HBs), poliovirus (types 1, 2, 3), Hib (PRP), and *S. pneumoniae* (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) antigens were measured one month after Dose 3 of routine vaccinations. Non-inferiority criteria were based on comparisons of seroprotection rates (diphtheria, tetanus, hep B, Hib, polio) and GMCs (pertussis, *S. pneumoniae*) between treatment groups. Non-inferiority criteria were met for all antigens, indicating that co-administration of Rotarix™ with routine childhood vaccines did not impair the immune responses to any of these vaccine antigens.

Conclusion

Rotarix™ at a potency of $10^{6.5}$ $CCID_{50}$ per dose was effective in preventing RV GE of any grade of severity and in preventing severe RV GE caused by naturally-occurring RV strains during the first year of life across heterogeneous geographical populations. Protection against any and severe RV GE was also demonstrated against circulating G1 and certain non-G1 types that are similar in distribution in the U.S. Co-administration of Rotarix™ with other routine vaccines in the U.S. did not cause interference of the immune response to each of these vaccine antigens. Rotarix™ had no increased risk of intussusception. However, increases in pneumonia-related deaths and convulsion-related SAEs were observed in Rotarix™ compared to placebo recipients from Dose 1 to Visit 3 in Rota-023, although the difference in pneumonia-related deaths occurring within 31 days post-vaccination was smaller. Rates of bronchitis within 31 days post-vaccination were also generally higher in Rotarix™ recipients, most notably in Rota-006.

Recommendation:
The reviewer recommends that Rotarix be approved for use in infants 6 to 24 weeks of age.

As part of the pre-BLA agreement, the applicant will conduct a prospective US post-licensure observational safety study that will be adequately powered to evaluate the risk of intussusception. Other measured outcomes will include deaths from all causes, hospitalizations due to acute lower respiratory tract infections (including pneumonia), convulsions, and Kawasaki disease.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

Description of the Product
GSK Biological's candidate oral live attenuated human RV (HRV) vaccine, Rotarix®, was developed from the 89-12 candidate vaccine strain, a G1P[8] strain isolated from a naturally infected 15-month study subject (subject #----, 1988-89 RV season, Cincinnati, OH) and attenuated by 33 passages in African Green Monkey cell culture.[48, 49, 50] The 89-12 vaccine, licensed by Avant Immunotherapeutics (US), was subsequently sub-licensed by GSK Biologicals in 1997, after which time several process changes were implemented to obtain a cloned 89-12 strain at passage --, referred to as the RIX4414 vaccine strain and subsequently used as GSK Biological's candidate HRV vaccine.

GSK Biological's candidate HRV vaccine used for clinical testing was prepared by reconstituting the lyophilized preparation with separately supplied liquid calcium carbonate based buffer prior to oral administration in subjects. The composition of 1 mL of Rotarix is shown below in Table 3.

Table 3. Composition of Rotarix*

Ingredient	Quantity per 1 mL
Active substance	
Human RV, live attenuated, RIX4414 strain	At least $10^{6.0}$ $CCID_{50}$**
Excipients	
Lyophilized with active substance:	
- Sucrose	----
- Dextran	-----
- Sorbitol	-------
- Amino acids	-----
- Dulbecco's Modified Eagle Medium	--------
In liquid diluent:	
- Calcium carbonate	-----
- Xanthan	------
- Sterile water q.s. ad	1 mL

*Data extracted from Clinical Overview, pg. 16

**$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)

The CMC reviewer did not identify any major manufacturing issues and control problems. Two comments raised by the reviewer related to the applicant's choice of ≥ $10^{6.0}$ $CCID_{50}$ as the end of shelf-life potency and ----- $CCID_{50}$ as the proposed specification potency. The applicant stated that clinical lots from a Phase II trial (Rota-006) containing $10^{5.6}$ $CCID_{50}$and $10^{6.6}$ $CCID_{50}$ were chosen to select the final dose potency. The CMC reviewer questioned these lots, rather than the Phase III lots, were not chosen. The reviewer also raised the question as to why the applicant ----------

---------- rotavirus titer allowable per vaccine dose. At the time of this review, these potency-related issues were still being discussed and further investigated by the review team. The bioassay reviewer did not identify statistical bioassay related issues that may preclude the BLA submission from being approved by the agency.

Please refer to CBER's CMC and bioassay reviews for more details.

4.2 Animal Pharmacology/Toxicology

One single dose combination repeat dose toxicity study was submitted in support of the BLA. In this study, 21-day old ---------- rats were given 4 doses of rotavirus vaccine orally. The four doses used exceeded the number of injections intended for use in the clinic, with dosing intervals of 2 weeks. The full human dose of 0.5 ml of vaccine was used in the study. Four groups of rats were studied: saline group, $CaCO_3$ group, human rotavirus strain RIX 4414 at $10^{6.7}$ ffu and $CaCO_3$ group, and RIX 4414 at $10^{6.1}$ ffu.

No treatment-related effects were observed on the following endpoints: clinical signs, mortality, body weight, food intake, ophthalmology, body temperature, coagulation, macroscopic findings upon necropsy, histopathology and clinical chemistry. Of note, no histopathological changes were found in the intestinal villi such as epithelial syncytia and no intracytoplasmic eosinophilic inclusions in the ileum.

Low seroconversion rates of 10% and 20% were observed in the study population. Variable viral shedding was observed in rats given the rotavirus strain.

Please refer to CBER's toxicology review for more details.

5 Clinical and Regulatory Background

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

Epidemiology

Rotavirus (RV) infection is the leading cause of severe acute gastroenteritis (GE) in infants and young children worldwide. In the United States, RV infection causes 2.7 million GE episodes, over 400,000 outpatient visits, and up to 70,000 hospitalizations and 60 deaths annually in children under 5 years of age.[1, 2]

RV is transmitted primarily by the fecal-oral route through close person-to-person contact and through fomites.[3] Respiratory droplets may be another mode of transmission.[4]

RV disease occurs from winter to spring in temperate climates, and year-round in tropical and subtropical areas.[5, 6, 7, 8, 9] In the US, disease occurs from November to March.[10, 11, 12] In North America and Europe, most RV infections occur in the first and second years of life, while severe GE occurs mainly in 3 to 35 month-old children.[1, 13, 14] Subsequent infections usually result in much milder disease.[13]

Virology/Molecular Epidemiology

RV is classified according to a binary system based on two protein types: G (glycoprotein) types and P (protease-cleaved protein) types. Ten G types and 11 P types have been isolated from humans. These human RVs can further be classified into two major genetically distinct groups: Wa

genogroup and DS-1 genogroup. The Wa genogroup includes most human G1, G3, G4, and G9 strains, while the DS-1 genogroup is comprised mainly of G2 strains.

Worldwide, 88.5% of childhood RV diarrhea is caused by G types 1 to 4 associated with P types P[8] and P[4].[15, 16, 17, 18, 19, 20] In the 1990's, G9 type appeared to emerge as the fifth most common type, with mostly G9P[8] strains circulating in the US and Europe.[21,22, 23, 24, 25, 26, 27, 28, 29] In North America, Europe and Australia, G1P[8], G2P[4], G3P[8], and G4P[8] represent over 90% of RV infections.[20] In the US, the yearly prevalence of G1, G2, G3, and G4 types have been 70%, 6-15%, 1-8%, and 0-2%.[20, 21, 24, 30]These figures are similar to those of other developed countries.[20] Other uncommon types such as G1P[4] and G2P[8] also circulate in these countries.[20, 22, 23, 26, 31]

As shown in Table 4 below, distribution of prevalent RV types are comparable between North America, Latin America, and Europe, areas where the HRV vaccine efficacy has been demonstrated.

Table 4. Distribution of predominant human RV G types by region, 1973 to 2003*

Region	N	G1	G2	G3	G4	Other types
Latin America	2,950	57.5%	18.3%	4.4%	8.8%	11.0%
Europe	17,475	69.4%	10.2%	3.5%	15.5%	1.4%
North America	2,892	73.7%	11.0%	10.6%	2.7%	2.0%

*Data extracted from Clinical Overview, pg. 11; source – reference #20

Immunity

RV infection in children induces serum and intestinal antibody responses that result in protection against diarrhea, especially severe diarrhea, upon subsequent infection. Serum antibodies consist of specific IgM, followed by anti-RV IgA and IgG. Small intestinal antibodies are predominantly IgA. Specific serum IgA antibodies are generally considered the standard measure of immunity in most field studies and vaccine trials.

While the humoral immune response is considered the key mechanism of protection, human and animal studies have also demonstrated that cell-mediated immunity may play a more prominent role in the RV immune response.[32, 33, 34] However, mice studies indicate that although RV-specific cytolytic T cells help to resolve infection, they are less protective against reinfection than antibody.[35]

The G (VP7) and P (VP4) proteins are the two main targets of neutralizing antibodies.[36] However, it is likely that a protective immune response involves all structural and non-structural proteins of RV.

In children 0 to 24 months old, RV infections during the first life protect against severe RV reinfection during the second year of life, even when the second infection is caused by a different G type from the first.[37] In most cases, homotypic immunity (immunity against the same RV type) develops after the first infection, with heterotypic immunity (immunity against different RV types) developing with successive RV infections.[37] Even asymptomatic infection during the first year of life induces the same level of protection as symptomatic infection, thereby allowing reasonable assumption that vaccines that cause asymptomatic RV infection may provide adequate protection.[37, 38, 39, 40]

Clinical disease

After a 2 to 4 day incubation period, abrupt onset of fever, abdominal distress, diarrhea and vomiting occur. Diarrheal stools are typically loose and water and occur frequently; mucus is found less often, with blood being rare. Symptoms usually last 3 to 9 days, and can lead to severe dehydration. Untreated severe RV GE in infants can be rapidly fatal. Viral shedding can be measured by enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase-polymerase chain reaction (RT-PCR), and can persist for as long as 57 days after disease onset in immunocompetent hosts.[41, 42]

Treatment of RV GE is supportive and focuses on preventing dehydration or restoring fluid and electrolyte balance, such as with oral rehydration solutions and/or IV fluid treatment. Anti-diarrheal agents are not recommended.

Current preventive measures have had only limited impact on global RV disease burden. Therefore, vaccination against RV represents an important strategy to control disease morbidity and mortality.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

Development of RV vaccines began with monovalent bovine RV vaccine candidates, including RIT4237 and WC3, which demonstrated variable efficacy leading to discontinuation of development.[43, 44]

The first U.S. licensed RV vaccine was RotaShield®, a tetravalent (G1-4) rhesus-human reassortant vaccine given in a 3-dose schedule.[45] However, this vaccine was withdrawn from the US market due to the development of an unexpected association with intussusception (IS).[46]

In 2006, RotaTeq®, a live oral pentavalent recombinant human-bovine RV vaccine given in a 3-dose schedule, was licensed in the US, and has shown no safety concerns.[47]

5.3 Previous Human Experience with the Product Including Foreign Experience

Rotarix at a potency of at least $10^{6.0}$ $CCID_{50}$ was initially licensed in Mexico on July 12, 2004, and has been subsequently licensed in 99 other countries worldwide. Safety information from post-marketing surveillance and unblinded SAEs from ongoing clinical trials during the period from July 2006 to January 2007 and January 2007 to July 2007 were submitted in the BLA (Periodic Safety Update Report; m5.3.6). Please refer to section 10.4.13 for further review of post-marketing safety.

------- studies, in which a total of ----- subjects (------ infants) received ----------
Rotarix or placebo, were not submitted as part of the BLA because of their limited relevance to use of Rotarix in US infants, as indicated below in Table 5.

Table 5: -- clinical studies of Rotarix not submitted in the BLA*

Rota-001	Adults 18-45 years of age
Rota-002	Children 1-3 years of age
Rota-003	Infants; different vaccine formulation (excipients, diluents)
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Rota-020	Infants; different vaccine formulation
Rota-021	Infants; different vaccine formulation
Rota-013	Infants; vaccine evaluated according to EPI schedule
Rota-045	Infants; vaccine evaluated according to EPI schedule
Rota-041	Infants; designed specifically to support licensure in Korea
Rota-044	Infants; designed specifically to support licensure in India

*Data extracted from Clinical Overview, pg. 17

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

During a CBER-GSK teleconference on May 5, 2006, CBER requested that GSK further investigate the greater number of subjects that withdrew consent, not due to an AE, from Lot A compared to other study groups in Rota-033. Also during this teleconference, CBER requested further investigation of the lower GMC observed with lot B in Rota-033.

A pre-BLA meeting between Center for Biologics Evaluation and Research (CBER) and GSK representatives was held on July 17, 2006 to discuss the general structure, format, and content of the US BLA for licensure of Rotarix. The final list of 10 studies to be submitted in the BLA was agreed to by both parties during a telephone conference call on July 31, 2006.

Subsequently, during a pre-BLA meeting follow-up telephone conversation between CBER and GSK on September 22, 2006, it was agreed that immunogenicity results of Rota-060 would be submitted during the BLA review, within 60 days of the BLA submission, followed by submission of the 6-month follow-up safety report in September 2007.

The statistical analysis plan for the integrated safety summary involving the 10 studies submitted in the BLA was agreed upon by CBER and GSK on December 5, 2006, during a planned teleconference.

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

6.1 Material Reviewed

6.1.1 BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review

Submitted June 1, 2007
Module 1.3.4 Financial Disclosure Statement
Module 1.14.1 Draft Labeling
- Module 1.14.1.1 Draft Carton and Container Labels
- Module 1.14.1.2 Annotated Draft Labeling Text
- Module 1.14.1.3 Draft Labeling Text

Module 1.16 Risk Management Plans
Module 2.2 Introduction to Summary
Module 2.3.P Drug Product – Rota Diluent
Module 2.5 Clinical Overview
Module 2.7.3 Summary of Clinical Efficacy
Module 2.7.4 Summary of Clinical Safety
Module 3.2.P.8.3 Stability Data
Module 5.2 Tabular Listing of All Clinical Studies
Module 5.3.5.1 Study Report Rota-023
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.4 Sample Case Report Form
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.6 Consent Forms/Written Information
- Module 5.3.5.1.11 Audit Certificates Report
- Module 5.3.5.1.12 Statistical Methods Interim Analysis Plan
- Module 5.3.5.1.25 Individual Subject Data Listing
  - Module 5.3.5.1.25.3 Analysis Datasets
    - Module 5.3.5.1.25.3.1 Analysis Dataset
    - Module 5.3.5.1.25.3.3 Analysis Data Definition
  - Module 5.3.5.1.25.4 Annotated CRF

Module 5.3.5.1 Study Report Rota-023 Year 1
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.6 Consent Forms/Written Information
- Module 5.3.5.1.11 Audit Certificates Report
- Module 5.3.5.1.12 Statistical Methods Interim Analysis Plan

Module 5.3.5.1 Study Report Rota-023 Annex 2
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.6 Consent Forms/Written Information
- Module 5.3.5.1.12 Statistical Methods Interim Analysis Plan

Module 5.3.5.1 Study Report Rota-023 Safety IS Cases
- Module 5.3.5.1.3 Study Report Body

Module 5.3.5.1 Study Report Rota-036
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.6 Consent Forms/Written Information
- Module 5.3.5.1.11 Audit Certificates Report
- Module 5.3.5.1.12 Statistical Methods Interim Analysis Plan
- Module 5.3.5.1.25 Individual Subject Data Listing
  - Module 5.3.5.1.25.3 Analysis Datasets
    - Module 5.3.5.1.25.3.1 Analysis Dataset
    - Module 5.3.5.1.25.3.3 Analysis Data Definition
  - Module 5.3.5.1.25.4 Annotated CRF

Module 5.3.5.1 Study Report Rota-036 Annex 2
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.6 Consent Forms/Written Information
- Module 5.3.5.1.11 Audit Certificates Report

Module 5.3.5.1 Study Report Rota-004
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.7 List Description Investigator Site
- Module 5.3.5.1.8 Signatures Investigators
- Module 5.3.5.1.12 Statistical Methods Interim Analysis Plan
- Module 5.3.5.1.25 Individual Subject Data Listing
  - Module 5.3.5.1.25.3 Analysis Datasets
    - Module 5.3.5.1.25.3.1 Analysis Dataset
    - Module 5.3.5.1.25.3.3 Analysis Data Definition
  - Module 5.3.5.1.25.4 Annotated CRF

Module 5.3.5.1 Study Report Rota-004 Annex Report 1
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.8 Signatures Investigators

Module 5.3.5.1 Study Report Rota-004 Annex Report 2
- Module 5.3.5.1.3 Study Report Body

Module 5.3.5.1 Study Report Rota-006
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.4 Protocol or Amendment
- Module 5.3.5.1.5 Sample Case Report Form
- Module 5.3.5.1.7 List Description Investigator Site
- Module 5.3.5.1.8 Signatures Investigators
- Module 5.3.5.1.25 Individual Subject Data Listing
  - Module 5.3.5.1.25.3 Analysis Datasets
    - Module 5.3.5.1.25.3.1 Analysis Dataset
    - Module 5.3.5.1.25.3.3 Analysis Data Definition
  - Module 5.3.5.1.25.4 Annotated CRF

Module 5.3.5.1 Study Report Rota-006 Annex 1
- Module 5.3.5.1.3 Study Report Body
- Module 5.3.5.1.8 Signatures Investigators

Module 5.3.5.1 Study Report Rota-005

Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1.25 Individual Subject Data Listing
Module 5.3.5.1.25.3 Analysis Datasets
Module 5.3.5.1.25.3.1 Analysis Dataset
Module 5.3.5.1.25.3.3 Analysis Data Definition
Module 5.3.5.1 Study Report Rota-007
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1 Study Report Rota-014
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1 Study Report Rota-033
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1.25 Individual Subject Data Listing
Module 5.3.5.1.25.3 Analysis Datasets
Module 5.3.5.1.25.3.1 Analysis Dataset
Module 5.3.5.1.25.3.3 Analysis Data Definition
Module 5.3.5.1 Study Report Rota-033 Annex
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1 Study Report Rota-039
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1 Study Report Rota-048
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.1 Study Report Rota-060
Module 5.3.5.1.3 Study Report Body
Module 5.3.5.3 Study Report SAE Listing 1 (non-BLA studies)
Module 5.3.5.3.3 Study Report Body
Module 5.3.5.3 Study Report Statistical Report (sensitivity analysis)
Module 5.3.5.3.3 Study Report Body
Module 5.3.6 Study Report PSUR Rotarix – 3rd report
Other materials

PASS protocol: Post-Marketing Surveillance for Intussusception and Lower Respiratory Tract-Related Post-Neonatal Mortality Following RotarixTM Introduction into the IMSS (Instituto Mexicano del Seguro Social) in Mexico

Rotavirus Surveillance in Europe: Determining the Diversity of Co-circulating Rotavirus Strains in Consecutive Rotavirus Seasons

Rota-052 protocol: A phase IIIB, randomized, double-blind, placebo-controlled study to explore the existence of horizontal transmission of the RIX4414 vaccine strain between twins within a family

Rota-054 protocol: A phase IIIB, double blind, randomised, placebo-controlled, multi-country, multicentre study to assess the safety, reactogenicity and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated Human Rotavirus (HRV) Vaccine in pre-term infants

Rota-022 final protocol synopsis: A phase II, double-blinded, randomized, placebo-controlled study to assess the safety, reactogenicity and immunogenicity of -------- doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine (RIX4414 at ----- CCID50) administered to human immunodeficiency virus (HIV) infected infants at ---------- of age in South Africa

<u>Submitted July 13, 2007</u>
Module 5.3.5.1 Study Report Rota-060
Module 5.3.5.1.3 Study Report Body

<u>Submitted July 20, 2007</u>
Module 5.3.5.4 Study Report Kawasaki: Analysis of Kawasaki reports following Rotarix
Module 5.3.5.4.3 Study Report Body

<u>Submitted October 3, 2007</u>
Module 1.14.1 Draft Labeling
Module 1.14.1.1 Draft Carton and Container Labels: Draft Inner Carton Label

Submitted October 18, 2007
Module 1.14.1 Draft Labeling
Module 1.14.1.2 Annotated Draft Labeling Text
Module 1.14.1.3 Draft Labeling Text

Submitted October 31, 2007
Module 5.3.5.1 Study Report Rota-060 Annex 1
Module 5.3.5.1.3 Study Report Body

Submitted November 30, 2007
Module 5.3.6 Study Report PSUR Rotarix – 4th report

Submitted February 1, 2008
Module 1.11.2 Safety Information Amendment
Module 1.11.3 Efficacy Information Amendment

Submitted February 11, 2008
Module 1.11.1 Quality Information Amendment

6.1.2 Literature

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6.1.3 Post-Marketing Experience

Since July 2004, Rotarix at a potency of at least $10^{6.0}$ $CCID_{50}$ per dose has been licensed in 100 countries worldwide. Between July 2004 and July 2007, 12,309,365 total doses of Rotarix have been distributed. Safety information from post-marketing surveillance and unblinded SAEs from ongoing clinical trials during the period from July 2006 to January 2007 were submitted in the BLA. Additional data from January 2007 to July 2007 were later submitted. No significant post-marketing safety issues have been identified. Please refer to section 10.4.13 for a detailed review.

6.2 Table(s) of Clinical Studies

The following clinical summary tables are provided in Appendix 1: Table 1 (Overview of study characteristics), Table 2 (Overview of safety data, Part 1), Table 3 (Overview of safety data, Part 2), Table 4 (Overview of efficacy studies, Part 1), Table 5 (Overview of efficacy studies, Part 2), Table 6 (Overview of immunogenicity studies, Part 1), and Table 7 (Overview of immunogenicity studies, Part 2).

Summary of Individual BLA studies

All studies were conducted in a double-blinded, randomized, placebo-controlled manner involving healthy infants.

Rota-004 (Finland): The primary objective was to determine if 2 doses of Rotarix could prevent RV GE over one RV season post-vaccination. Secondary objectives were to assess VE against severe RV GE during the 1st and 2nd season, VE against any RV GE during the 2nd season, combined VE over 2 seasons, and the immunogenicity, reactogenicity and safety of Rotarix. Subjects 6-12 weeks of age received either two doses of $10^{5.3}$ $CCID_{50}$ of Rotarix or placebo on a 0, 2-month schedule. Co-administration of routine vaccinations and feeding 1 hour pre-vaccination were prohibited.

Rota-005 (US, Canada): The primary objective was to assess the reactogenicity and immunogenicity of 2 doses of Rotarix at different potencies. Secondary objectives were to assess safety of Rotarix, explore the effect of unrestricted feeding (breast vs formula, 60 minutes pre- vs 30 minutes post-vaccination) on immunogenicity, determine the rate of RV GE, and to evaluate immunogenicity of co-administered routine vaccinations. Subjects 6-12 weeks of age received 2 doses of Rotarix ($10^{5.6}$ $CCID_{50}$ or $10^{6.6}$ $CCID_{50}$) or placebo on a 0, 2-month schedule. DTaP, Hib, IPV, and 7-valent *S. pneumoniae* vaccines were co-administered. Pre-dose feeding was allowed.

Rota-006 (Brazil, Mexico, and Venezuela): The primary objective was to determine if 2 doses of Rotarix at different potencies could prevent RV GE during the 1st efficacy follow-up period. Secondary objectives were to assess VE against severe RV GE during the 1st follow-up period, VE against RV types during the 1st follow-up period, VE against any and severe RV GE during the 2nd follow-up period, to assess immunogenicity, reactogenicity, and safety of Rotarix, and to explore the immunogenicity of co-administered routine vaccinations, and the effect of unrestricted feeding (breast vs formula, 60 minutes pre- vs 30 minutes post-vaccination) on the immune response to Rotarix. Subjects 6-12 weeks of age received 2 doses of Rotarix $10^{5.3}$ $CCID_{50}$, Rotarix $10^{5.6}$ $CCID_{50}$, Rotarix $10^{6.6}$ $CCID_{50}$ or placebo on a 0, 2-month schedule. In addition, a subset of 121 subjects received a 3rd dose of vaccine or placebo. All subjects were followed during the 1st efficacy period for 12 months, with a subset of subjects followed for an additional 6 to 12 months. DTwP-HepB and Hib were co-administered, while OPV was administered 2 weeks apart from study vaccines. Pre-vaccination feeding was allowed.

Rota-007 (Singapore): The primary objective was to determine if 2 doses of Rotarix could prevent RV GE during the 1st efficacy follow-up period. Secondary objectives were to assess safety, reactogenicity, and immunogenicity of Rotarix at 3 potencies, and to explore the immunogenicity of co-administered routine vaccinations and effect of unrestricted feeding (breast vs formula, 60 minutes pre- vs 30 minutes post-vaccination) on the immune response to Rotarix. Subjects 11-17 weeks of age received 2 doses of Rotarix $10^{5.3}$ $CCID_{50}$, Rotarix $10^{5.6}$ $CCID_{50}$, Rotarix $10^{6.6}$ $CCID_{50}$ or placebo on a 0, 1-month schedule. All subjects were followed until approximately 18 months of age. DTaP, IPV and Hib were co-administered. Pre-vaccination feeding was allowed.

Rota-014 (South Africa): The primary objective was to demonstrate that co-administration of Rotarix did not decrease poliovirus immune response 1 month after the 3rd dose of OPV. Secondary objects were to assess the safety, reactogenicity, and immunogenicity of Rotarix when co-administered with OPV or IPV. The study was conducted in 2 parts. Subjects 5-10 weeks of age (Part 1) or 8-17 weeks of age (Part 2) received one of the following regimens on a 0, 1-month schedule: Rotarix $10^{5.6}$ $CCID_{50}$ + OPV + DTaP/Hib, Rotarix $10^{5.6}$ $CCID_{50}$ + DTaP-IPV/Hib, or placebo + OPV + DTaP/Hib. Subjects were followed until 18 months of age. Co-administration of routine vaccines according to local recommendations and unrestricted feeding were allowed.

Rota-023 (Latin America – Efficacy study; Latin America + Finland – Safety Study): The primary objectives were to 1) to determine the safety of Rotarix with respect to the risk of intussusception (IS) within 31 days post-vaccination after each dose and 2) determine if Rotarix can prevent severe RV GE up to 12 months of age. The primary clinical case definition for severe GE was an episode that required hospitalization and/or rehydration therapy (equivalent to WHO plan B or C) in a medical facility. Secondary objectives were to VE against different RV types, VE in the second year of life, vaccine immunogenicity in a subset of subjects, and vaccine safety throughout the study period. Subjects 6-12 weeks of age (6-13 weeks in Chile) received 2 doses of Rotarix $10^{6.5}$ $CCID_{50}$ or placebo on a 0, 1-month or 0, 2-month schedule. All 63,225 enrolled subjects were followed up to 30-90 days after Dose 2 (safety study). A subset of 20,169 subjects was followed until 12 months of age (efficacy study). A subset of 15,183 subjects was followed until 24 months of age (efficacy study). Co-administration of routine vaccines and unrestricted feeding were allowed.

Rota-033 (Columbia, Mexico, Peru): The primary objective was to demonstrate lot-to-lot consistency of Rotarix by assessing immunogenicity 2 months post-Dose 2. Secondary objectives were to assess the lot-to-lot consistency of Rotarix in terms of reactogenicity and to assess the safety, reactogenicity, and immunogenicity of the HRV vaccine compared to placebo. Subjects 6-12 weeks of age received 2 doses of Rotarix $10^{6.5}$ $CCID_{50}$ from one of 3 consecutive production lots (A, B, or C) or placebo on a 0, 2-month schedule. DTwP, HepB and Hib were co-administered, while OPV was administered 2 weeks apart from study vaccines. Unrestricted feeding was allowed.

Rota-036 (Czech Republic, Finland, France, Germany, Italy, Spain): The primary objective was to determine if Rotarix can prevent RV GE of any severity up until the end of the 1st RV season. Secondary objectives were to assess VE against severe RV GE, RV GE requiring any medical attention, RV GE causing hospitalization, and any and severe RV GE caused by different types during the 1st efficacy follow-up period, as well as VE in the 2nd efficacy and combined follow-up periods. Other secondary objectives were to assess vaccine safety in all subjects, reactogenicity and immunogenicity of Rotarix, the effect of unrestricted feeding (breast for ≥ one dose vs at none of the doses) on the immune response to Rotarix, and immunogenicity of co-administered routine vaccinations. Subjects 6-14 weeks of age received 2 doses of Rotarix $10^{6.5}$ $CCID_{50}$ or placebo on a 0, 1-month or 0, 2-month schedule. Co-administration of routine vaccines was allowed.

Rota-039 (Thailand): The primary objective was to compare the immunogenicity between Rotarix reconstituted without buffer (with or without feeding) and Rotarix reconstituted with buffer (with or without feeding), measured by vaccine take at 2 months post-Dose 2. Other objectives were to assess the immunogenicity of Rotarix when stored at 37°C for 7 days instead of the recommended temperature of 2° to 8°C, and to assess vaccine reactogenicity and safety under the different reconstitution and storage conditions. In addition, an exploratory assessment of the effect of feeding on the immunogenicity of Rotarix reconstituted without buffer was performed, as feeding immediately before vaccine administration was expected to have a buffering effect. Subjects 6-12 weeks of age received one of the following regimens on a 0, 2-month schedule: Rotarix $10^{6.5}$ $CCID_{50}$ reconstituted with buffer, Rotarix $10^{6.5}$ $CCID_{50}$ reconstituted without buffer, Rotarix $10^{6.5}$ $CCID_{50}$ stored at 37°C for 7 days and reconstituted with buffer, placebo reconstituted with buffer, or placebo reconstituted without buffer. Co-administration of routine vaccines was allowed. Feeding was controlled as part of the study design.

Rota-048 (Finland): The primary objective was to compare the immunogenicity between the lyophilized formulation of Rotarix and a new liquid formulation of Rotarix, as measured by vaccine take. In addition, safety and reactogenicity of the formulations was assessed. Subjects 6-12 weeks of age received one of the following regimens on a 0, 1-month schedule: Rotarix $10^{6.5}$ $CCID_{50}$ liquid formulation, Rotarix $10^{6.5}$ $CCID_{50}$ lyophilized formulation, placebo liquid formulation, or placebo lyophilized formulation. Co-administration of routine vaccines was not performed. Unrestricted feeding was allowed.
Rota-060 (US): The primary objective was to demonstrate that co-administration with Rotarix did not impair the immune response to all antigens contained in each of the routine infant vaccines (Pediarix, Prevnar and ActHIB). In addition, safety (SAEs) and immunogenicty were assessed. Subjects 6-12 weeks of age received one of the following regimens on a 0, 2-month Rotarix schedule: Rotarix $10^{6.5}$ $CCID_{50}$ co-administered with routine vaccines or administered one month apart from routine vaccines. All subjects received 3 doses of routine vaccines on a 0, 2, 4-month schedule. Unrestricted feeding was allowed.

6.3 Review Strategy

This clinical review of Rotarix began with the review of the Clinical Overview (m2.5), Summary of Clinical Efficacy (m2.7.3), Summary of Clinical Safety (m2.7.4), and the Tabular Listing of All Clinical Studies (m5.2). Detailed reviews were then performed on the 4 BLA studies containing efficacy data: Rota-023, Rota-036, Rota-004, and Rota-006. All efficacy, immunogenicity, and safety reports from each of these studies were reviewed in detail. The reviewer also analyzed demographic, dropout, and safety datasets provided by the applicant for these 4 studies using the statistical software program JMP Version 6. In general, the design, conduct, and data analysis for each trial appeared consistent and acceptable, and demographic and safety data obtained using JMP were consistent with data presented in the study reports.

The Summary of Clinical Efficacy was then reviewed again to provide an overview of efficacy and immunogenicity across all studies. This was followed by a second review of the Summary of Clinical Safety which contained 2 integrated safety analyses based on data from 10 of the 11 BLA trials. During these reviews, individual study reports from Rota-005 and Rota-060 were reviewed because both trials involved U.S. subjects. The individual study report from Rota-033 was also reviewed because this was a lot consistency study. For Rota-005, Rota-033, and Rota-060, safety and immunogenicity were reviewed, and demographic, dropout, and safety datasets were reviewed using JMP 6. For Rota-005 and Rota-033, virus shedding datasets were reviewed using JMP 6. Overall, the integrated efficacy, immunogenicity, and safety reports were adequately presented, with no data inconsistencies across studies. Rota-005, Rota-033, and Rota-060 also appeared to have been designed and conducted in an acceptable manner. During the overview of clinical efficacy and clinical safety, the reviewer also referred to specific information in the reports of the other BLA studies (Rota-007, Rota-014, Rota-039, Rota-048) when needed.

Next, post-marketing safety data was reviewed in the Periodic Safety Update Report (PSUR) (m5.3.6). A list of SAEs from non-BLA studies (m5.3.5.3) was also reviewed, as was an analysis of Kawasaki reports following Rotarix (m5.3.5.4).

The Rotarix United States Risk Management Plan (m1.16) was then reviewed. As part of the review, protocols for the PASS study in Mexico, Rotavirus Surveillance in Europe, Rota-022, Rota-054, and Rota-056 were also reviewed.

In general, all study reports adequately referenced published literature to support efficacy, immunogenicity, and safety findings.

The package insert and patient information sheet was then reviewed with several other CBER reviewers, and revisions and comments were forwarded to the applicant during the review cycle.

6.4 Good Clinical Practices (GCP) and Data Integrity

All studies were conducted by experienced investigators in accordance with standard operating procedures of the GSK Group of Companies, which comply with the principles of GCP, and in accordance with the Declaration of Helsinki of 1996. All studies were also conducted with the approval of Ethics Committees or Institutional Review Boards (IRBs). Regulatory approval was obtained from the relevant health authority when required. All laboratory assays were performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standard, validated procedures with adequate controls. Adherence to protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of CRF/eCRF completion and source documents/data.

Informed consent
Written Informed consent was obtained from the parent or guardian of each subject prior to the performance of any study-specific procedures.

Protocol violations, Site-specific issues, Data integrity
Bioresearch monitoring (BIMO) inspections at six sites (1 site each in Mexico, Honduras, and Brazil; 3 sites in Finland) did not reveal any major violations or other site-specific issues that would have affected data integrity of the studies. Please refer to CBER's BIMO reports for more details.

6.5 Financial Disclosures

A Financial Disclosure Statement (m1.3.4), including form FDA 3454, was submitted with the BLA. The applicant stated that none of the clinical investigators had any financial interests or arrangements in any of the studies or the applicant itself. A list of investigators with no disclosable financial interests/arrangements was provided for each study. In addition, a list of investigators whose updated financial interests/arrangements could not be obtained was provided for each study. Information could not be obtained from these investigators mainly because they could not be located. However, several refused to provide this information.

7 Human Pharmacology (Immunogenicity, Pharmacology, Pharmacokinetics)

Overall, Rotarix at the proposed licensing potency was highly immunogenic, as demonstrated by anti-RV IgA seroconversion rates and GMCs and vaccine take. Please refer to section 8.1 for review of immunogenicity data from Rota-023 (8.1.1), Rota-036 (8.1.2), Rota-004 (8.1.3), and Rota-006 (8.1.4) of this review. Please also refer to section 9.1 for an overview of immunogenicity data across the BLA studies

No clinical pharmacology studies are relevant to this BLA.

8 Clinical Studies

8.1 Indication # I : Prevention of rotavirus gastroenteritis caused by G1 and non-G1 types

8.1.1 Rota-023

8.1.1.1 Protocol 444563/023 (rota-023): A phase III, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants

8.1.1.1.1 Objective/Rationale

Primary Objectives
1. In subset A (N = 20,000), to determine if 2 doses of Rotarix can prevent severe RV GE caused by circulating wild-type RV strains during the period starting from 2 weeks post-Dose 2 until 1 year of age (rationale: disease burden of severe RV is maximal between 5-11 months of age)
2. In all subjects (N = 60,000), to determine the safety of Rotarix with respect to intussusception (IS) within 31 days (Days 0-30) after each dose (rationale: vaccine-related IS is expected to occur when vaccine virus replication and host responses are maximal)

Secondary Efficacy Objectives, Subset A
1. To assess if 2 doses of Rotarix can prevent severe wild G1 RV GE during the period starting from 2 weeks post-Dose 2 until 1 year of age
2. To assess if 2 doses of Rotarix can prevent severe non-G1 RV GE during the period starting from 2 weeks post-Dose 2 until 1 year of age
3. To assess if 2 doses of Rotarix can prevent severe non-G1 RV GE, for each serotype, during the period starting from 2 weeks post-Dose 2 until 1 year of age
4. To assess if 2 doses of Rotarix can prevent severe wild RV GE after Dose 1
5. To assess if 2 doses of Rotarix can prevent severe wild RV GE with a score of ≥ 11 on the 20-point Vesikari scale during the period starting from 2 weeks post-Dose 2 until 1 year of age

Secondary Efficacy Objectives, Subset B (N = 13,000)
1. To assess if 2 doses of Rotarix can prevent severe RV GE during 2nd efficacy follow-up period
2. To assess if 2 doses of Rotarix can prevent severe RV GE during 2 consecutive efficacy follow-up periods

Secondary Safety Objectives
1. For all subjects, to assess the safety of Rotarix in terms of occurrence of SAEs throughout the study period
2. For subset A, to assess the safety of Rotarix in terms of occurrence of definite IS during the period starting from Dose 1 until 1 year of age
3. For subset B, to assess the safety of Rotarix in terms of occurrence of definite IS during the period starting from Dose 1 until 2 years of age

Secondary Immunogenicity Objectives
1. In a subset of 100 subjects per country (except Finland), to assess the immunogenicity of Rotarix in terms of anti-RV IgA antibody concentrations 1 or 2 months post-Dose 2

8.1.1.1.2 Design Overview

Rota-023 was a double-blind, randomized, placebo-controlled, multi-country and multi-center study. Healthy subjects 6-12 weeks of age (6-13 weeks in Chile) at the time of Dose 1 were randomized to receive 2 doses of either Rotarix ($10^{6.5}$ $CCID_{50}$) or placebo (1:1 ratio) on a 0, 1-month or 0, 2-month schedule. Subjects were randomized and administered Dose 1 of Rotarix or placebo on the same day (i.e. Day 0). The intended study duration was 2-4 months for subjects in the IS safety cohort, 9-10 months for subjects in subset A (Year 1 efficacy cohort), and 21-22 months for subjects in subset B (Year 2 efficacy cohort). The study was subject-blinded only during Year 2 follow-up.

8.1.1.1.3 Population

Inclusion Criteria
1. Parents/guardians of subject can and will comply with protocol requirements
2. Male or female 6-12 weeks or 6-13 weeks (Chile only) of age at the time of Dose 1
3. Written informed consent obtained from parent/guardian prior to study procedures
4. Free of obvious health problems as established by medical history and clinical examination prior to entering the study

5. Parents/guardians of subject can and will comply with protocol requirements

Exclusion Criteria
1. Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days before Dose 1, or planned use during the study
2. Chronic administration (> 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed)
3. Subject unlikely to remain in the study area for the duration of the study
4. Any immunosuppressive or immunodeficient condition, including HIV infection
5. History of allergic disease or reaction likely to be exacerbated by any vaccine component
6. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period
7. Any clinically significant history of chronic gastrointestinal disease, including any uncorrected congenital malformation of the GI tract or other serious medical condition

Procedures Allowed
1. Co-administration of routine vaccinations, except for OPV which was given at least 2 weeks apart from Rotarix vaccination
2. Hepatitis B, BCG and OPV vaccination at birth according to local Expanded Program of Immunization (EPI)
3. Complimentary Hepatitis A vaccination at Visit 5 and Visit 6 for subjects in subset B
4. Unrestricted feeding pre- and post-vaccination

Participating Countries
1. IS Safety Cohort: Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela
2. Year 1 Efficacy Cohort: Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela
3. Year 2 Efficacy Cohort: Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Venezuela

8.1.1.1.4 Products mandated by the protocol

Rotarix
Each dose of Rotarix consists of a lyophilized preparation of ------ $CCID_{50}$ of the RIX4414 HRV strain together with DMEM, sucrose, dextran, sorbitol, and amino acids, reconstituted in GSK's calcium carbonate buffer consisting of calcium carbonate and xanthane ----------.

Vaccine	Formulation	Presentation	Volume
GSK Biologicals. HRV vaccine	RIX4414 HRV strain ----- $CCID_{50}$ Dulbecco's Modified Eagle Medium (DMEM) ------ Sucrose ---- Dextran ----- Sorbitol ------- Amino acids ----	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals. Placebo for HRV vaccine	DMEM ------- Sucrose ---- Dextran ----- Sorbitol ------- Amino acids ----	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals. calcium carbonate buffer	Calcium carbonate ----- Xanthane ---------- --------- ml	Liquid buffer in pre-filled syringe	---- ml

(Source: Study Report Body Rota-023 Protocol or Amendment, pg 72)

Doses of Rotarix will be administered orally at 0, 1-month or 0, 2-month schedules. Lots RVC018A42, RVC019A43 and RVC021A44 were used for the lyophilized vaccine. Lots DD05A002A, DD05A002B, DD05A002C, DD05A003B, DD05004A, DD05A004B and DD05A004C were used for the diluent.

Placebo
The placebo consisted of all components of Rotarix, but without any RV particles; lot RVC020A41PL was used. Lots DD05A002A, DD05A002B, DD05A002C, DD05A003B, DD05004A, DD05A004B and DD05A004C were used for the diluent.

Concomitant routine vaccines
Co-administration of any of the following routine vaccines was allowed, with the choice of vaccines determined according to national recommendations in each country: DTPw, DTPa, HBV, Hib, IPV, MMR, and BCG. OPV was administered 2 weeks apart from study vaccine/placebo.

Hepatitis A vaccine
Two doses of Havrix 720 Junior (GSK) were offered to subset B subjects at Visits 5 and 6.

8.1.1.1.5 Endpoints

Primary Endpoints
1. Occurrence of severe RV GE caused by wild RV strains during the period starting from 2 weeks post-Dose 2 until 1 year of age
2. Occurrence of definite IS cases within 31 days (Days 0-30) after each Rotarix dose (amended on May 16, 2003, before study initiation in August 2003)

Secondary Efficacy Endpoints
1. Occurrence of severe RV GE due to wild G1 serotype RV strains during the period starting from 2 weeks post-Dose 2 until 1 year of age
2. Occurrence of severe RV GE due to non-G1 serotypes during the period starting from 2 weeks post-Dose 2 until 1 year of age
3. Occurrence of severe RV GE due to each non-G1 serotype during the period starting from 2 weeks post-Dose 2 until 1 year of age
4. Occurrence of severe RV GE due to circulating wild-type RV strains, wild G1 serotype RV strains, non-G1 serotypes, and each non-G1 serotype, from Dose 1 until 1 year of age
5. Occurrence of severe RV GE due to circulating wild-type RV strains with a score of ≥ 11 on the Vesikari scale during the period starting from 2 weeks post-Dose 2 until 1 year of age (amended on January 23, 2004, before date of last Visit 3 in July 2004)
6. Occurrence of severe RV GE due to wild G1 serotype RV strains in subset B during the 2nd year of follow-up
7. Occurrence of severe RV GE due to wild G1 serotype RV strains in subset B during 2 years of follow-up

Secondary Safety Endpoints
1. For all subjects, occurrence of SAEs throughout the study period
2. For subset A, occurrence of definite IS from Dose 1 until 1 year of age
3. For subset B, occurrence of definite IS from Dose 1 until 2 years of age (amended on May 19, 2004, before the last Visit 3 in July 2004)

Secondary Immunogenicity Endpoints
1. Serum RV IgA antibody concentrations in a subset of 100 subjects per country (except Finland at Visits 1 and 3 (Amended September 26, 2003)

Definitions
Definite IS: IS diagnosis confirmed by intestinal invagination at surgery or autopsy, or by radiologic techniques (gas/liquid contrast enema or abdominal ultrasound)

Diarrhea: ≥ 3 looser than normal stools (loose or watery stools) within a day
Vomiting: ≥ 1 episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding with a day
GE episode: occurrence of diarrhea, with or without vomiting
Severe GE: GE episode requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility
Severe RV GE for primary efficacy analysis: an episode of severe RV GE occurring at least 2 weeks after the full vaccination course, in which RV other than vaccine strain was identified in a stool sample collected no later than 7 days after admission to the hospital or medical facility (amended on May 16, 2003 and January 23, 2004, both before the last Visit 3 in July 2004 and therefore before the beginning of Year 1 efficacy follow-up)
RV seropositivity: anti-RV IgA titer ≥ cut-off value of 20 U/ml
RV seronegativity: anti-RV IgA titer < cut-off value of 20 U/ml
Seroconversion: appearance of serum (anti-RV IgA) antibodies ≥ 20 U/ml in subjects seronegative before vaccination

Summary of Significant Protocol Amendments

1. Amendment 1 – May 16, 2003
   a. OPV administration deferred from study vaccine administration by ≥ 2 weeks
   b. ------- Rotarix ---------- to be used instead of ----------
   c. Immunogenicity of Rotarix to be assessed in a subset of subjects at Visits 1 & 3
   d. Method of power computation for primary safety objective changed to PASS 2000 leading to 90% power to conclude
2. Amendment 2 – January 23, 2004
   a. Severe GE cases to be collected through active hospital surveillance and complemented, when needed, by subject surveillance
   b. IS surveillance to be done similarly to severe GE surveillance and complemented by SERO-EPI-204 or similar local IS surveillance programs
   c. Interval window for stool collection widened to 7 days after admission to a medical facility/hospital
   d. Costa Rica not participating in study
   e. Statistical analysis section on safety adapted to reflect recommendation from IDMC statistician
   f. Upper age limit for Dose 1 extended to 13 weeks in Chile (Country-specific amendment for Chile, August 28, 2003)
   g. Finland added as a participating country for safety only (Country-specific amendment for Finland, September 26, 2003)
3. Amendment 3 – May 19, 2004
   a. Sample size for subset B calculated based on attack rate observed in the recently completed 2nd year efficacy follow-up in study Rota-006
   b. Criteria for primary safety endpoint revised, based on the actual number of IS cases (in Rota-023) exceeding the expected number used for power calculations. Revision was needed because the higher observed IS incidence would lead to a larger CI width on Risk Difference, resulting in the initially proposed criteria being no longer appropriate
   c. Subjects to complete Visit 3 by August 1, 2004
   d. Three additional visits/contacts (age 15, 18, 21 months) included during 2nd year follow-up
4. Amendment 4 – September 17, 2004
   a. An interim analysis to be available during the 4th quarter of 2004 in order to reply to a requirement from health authorities from Latin America; interim analysis to pertain to final safety data up to Visit 3 for entire cohort
   b. Results of primary safety objective analysis provided in this study

8.1.1.1.6 Surveillance

Follow-up visits
The table below summarizes the follow-up visits or contacts for safety and efficacy

	Visit 1 Day 0	Visit 2 Month 1-2	Visit 3 Month 2-4	Visit 4 Month 9-10	Contact 1 Month 12-13	Visit 5 Month 15-16	Contact 2 Month 18-19	Visit 6 Month 21-22
Safety cohort (40,000)	X	X	X					
Subset A (20,000)	X	X	X	X				
Subset B (13,000)					X	X	X	X

Visits 1 & 2 – days of vaccination Subset A – safety and Year 1 efficacy cohort

Subset B (subset of subset A) – safety and Year 2 efficacy cohort

Contact – site visit, telephone contact, or home visit by investigator, study nurse, or qualified health worker

All subjects were followed for SAEs at Visits 2 and 3. Subjects in subset A were monitored also for SAEs at Visit 4 and severe GE episodes at Visits 2, 3, and 4. Subset B subjects were further monitored for SAEs and severe GE episodes at Contacts 1 and 2 and Visits 5 and 6.

Subjects received a physical examination at each visit. Prior/concomitant medications and vaccinations will be recorded at Visits 1, 2, and 3.

Pre-vaccination blood samples were obtained from a subset of subjects (approximately 100 per country except Finland) at Visit 1. A subset of subjects also provided post-vaccination blood samples at Visit 3.

Severe GE Case Ascertainment

Follow-up of severe GE episodes for efficacy assessment was performed from Dose 1 until the last planned visit. Parents/guardians/caretakers of subjects were instructed to seek medical advice at the nearest hospital/medical facility if symptoms of severe GE developed, and to contact the investigator.

In addition, study personnel performed hospital or medical facility surveillance for severe GE cases by contacting or visiting each medical facility at least twice per week. Furthermore, subject surveillance by telephone, home visit, or other method was performed by non-medical study personnel, at minimum intervals of 4 days, to identify severe GE cases not initially been identified by medical facility surveillance (e.g. subjects treated in facilities outside the surveillance system).

Severe GE cases were also ascertained by medical history at planned study visits and contacts (see table above). Cases elicited by medical history but not by hospital surveillance were confirmed by review of medical facility records.

All identified cases of severe GE were included in the final analysis.

Severe GE Case Follow-Up

Subjects hospitalized or treated for re-hydration at a medical facility for a GE episode were followed by study personnel. For each severe GE episode, a GE diary card should be completed daily by parent/guardian, nurse, and/or health care worker until 2 days after loose stools and vomiting have disappeared. The GE diary card allowed assessment of severe GE intensity using a 20-point (Vesikari) scale that graded duration and frequency of diarrhea and vomiting, degree of fever, dehydration and hospitalization. When counting episodes of looser than normal stools or vomiting, a missing value on a specific day was considered as absence of episodes for that day. Also, in classifying the degree of dehydration, a subject was considered 1-5% dehydrated if oral rehydration was received, and ≥ 6% if hospitalized occurred and/or IV rehydration was received.

For each severe GE episode, a stool sample was collected as soon as possible and no later than 7 days after admission to a medical facility for re-hydration treatment. A second stool sample was collected if the first sample was insufficient. Stool samples were submitted, aliquoted and stored per standard protocols.

Stool samples were analyzed by ELISA at the GSK laboratory (Belgium) to determine the presence of RV. If RV was detected, specimens were analyzed by RT-PCR for serotype determination. If G1 RV was detected, differentiation of vaccine from wild type virus was done using sequence analysis and/or hybridization ----------. Fresh stool samples were also tested locally for bacterial and parasitic enteric pathogens to identify mixed infections.

IS Case Ascertainment

SAEs were recorded throughout the study period, starting from the administration of Dose 1. Parents/guardians/caretakers of subjects were instructed to contact the investigator and to seek medical advice at the nearest hospital if the following sign/symptoms of IS developed: severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating, fever up to 41°C). IS cases were ascertained by medical history at planned study visits and contacts. All hospitals were aware of the trail, with relevant departments advised to contact study personnel for each case of IS.

All IS cases were re-captured independently from this study by means of a GSK sponsored prospective IS study (SERO-EPI-IS-204) or similar country-specific surveillance programs. The objective of this study was to estimate background incidence of IS among children less than 2 years of age in the population where the vaccine study took place. Study personnel/health workers performed hospital surveillance for IS by contacting or visiting hospitals qualified to provide IS treatment in the study area at least twice per week (weekly in Finland). This GSK surveillance program gradually concluded after all Visit 4s were completed.

A check for consistency was performed regularly between the two ascertainment methods (medical history and hospital surveillance). All definite IS cases identified by either system were included in the final analysis.

IS Case Review and Follow-Up

All cases of IS were evaluated according to standard procedures (Appendix L, Rota-023 Visit 1-3 protocol). The diagnosis of IS was to have been documented by radiography, with documentation by ultrasonography dependent on available expertise. Several biological samples were collected for all IS cases, including stool samples, rectal swabs, and throat swabs for RV, enteroviruses and adenoviruses, acute and convalescent serum samples for immune response to RV and other pathogens as needed, surgical specimens (if available). Testing was conducted at the following external and independent designated laboratories via GSK laboratory: Laboratory ---------- (PCR for RV, enteroviruses, adenoviruses), ---------- (PCR for shigella, salmonella, campylobacter), Centers for Disease Control and Prevention (PCR and ---------- on surgical biopsies for RV, enteroviruses, adenoviruses), and Delft Diagnostic Laboratory, Netherlands (RT-PCR for RV G type, hybridization assay to differentiate RV vaccine vs wild-type). In addition, fresh stool samples were also tested locally for bacterial and parasitic enteric pathogens.

The case definitions for definite, probable, possible and suspected IS developed by the Brighton Collaboration Intussusception Working group were applied (Appendix I, Rota-023 Visit 1-3 protocol). The definition of a definite case of IS was as follows:

Level 1 of Evidence (Definite)

Surgical criteria

The demonstration of invagination of the intestine at surgery,

AND/OR

Radiological criteria

The demonstration of invagination of the intestine by either gas 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 post-reduction ultrasound

AND/OR

Autopsy criteria
The demonstration of invagination of the intestine.

* target sign or doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section.
(Source: Rota-023 Protocol or Amendment Year 1, pg 134)

In order to capture all IS events, IS cases were reported irrespective of whether or not the Brighton Case Definition was met.

In the protocol, it was originally specified that a Clinical Events Review Committee (CEC), consisting of physicians acting as consultants with particular expertise, would perform blinded objective reviews of all IS cases, independent from the IDMC. CEC members were not study investigators or medical care providers to study subjects. However, as stated in the Year 1 Study Report, a GSK physician rather than the CEC reviewed IS cases diagnosed after Visit 3 up to Visit 4 using the same case definition for definite IS mentioned above.

Other AE/SAE Monitoring
Parents/guardians of each subject were instructed to contact the investigator immediately for any perceived serious signs or symptoms. Subjects hospitalized for an SAE were followed by study personnel. SAEs were ascertained by medical history at planned study visits and contacts. In addition, all AEs leading to subject withdrawal or drop out will be recorded.

Intensity and causality were evaluated for all SAEs and AEs leading to subject withdrawal or drop out using standard criteria. Follow-up of these subjects continued until the AE resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up. SAEs were reported by the investigators to GSK within 24 hours of awareness of the events.

Because many study fatalities had more than one SAE, an independent Safety Review Committee performed blinded reviews of all fatalities that occurred during the study period, and assessed the cause of death (primary cause of death, secondary diagnoses, underlying diagnoses). The primary cause of death was used for all mortality analyses.

Signs, symptoms, and diagnoses of SAEs were coded and summarized according to Medical Dictionary for Regulatory Activities (MedDRA) classification. System Organ Class (SOC) and Preferred Terms (PT) obtained from the verbatim of the investigators were used for SAE analyses, including IS and fatal cases.

Serology Analysis
Sera were collected from a subset of 100 subjects per study country (except Finland) at Visit 1 (pre-Dose 1) and Visit 3 (post-Dose 2). Anti-RV IgA antibody concentrations were measured by ELISA at a GSK designated laboratory. The assay cut-off was 20 U/ml. Geometric Mean Concentrations (GMCs) calculations were also performed.

Forms
1. GE diary card: completed daily (by parent/guardian, nurse, and/or health care worker) until 2 days after loose stools and vomiting have disappeared, for each severe GE episode during the study period
2. Electronic Case Report Form (CRF): included all reviewed severe GE cases, information from GE diary cards, local laboratory results of stool analysis, IS/SAEs, AEs leading to withdrawal or drop out, prior/concomitant medications or vaccinations
3. SAE Report Form
4. Standard Verbal Autopsy Questionnaire

Independent Data Monitoring Committee (IDMC)
An IDMC was charged with monitoring the safety aspects of the Rotarix clinical development. The IDMC conducted unblinded reviews of all SAEs and other relevant safety data, including

withdrawals due to AEs. A safety boundary, applied to definite IS cases reported within 31 days post-vaccination, was established to recommend a clinical study hold if necessary (Table 1 in Rota-023 Visit 1-3 protocol).

8.1.1.1.7 Statistical Considerations

Power Considerations - Primary Efficacy Objective
Assuming a true VE of 70% and an incidence rate of severe RV GE of 1.5% during the 1st efficacy period (Year 1), and 9,000 subjects in each treatment arm, the study had 83.3% power to observe a lower limit of the VE 95% CI > 50%.

Power Considerations - Primary Safety Objective
An overall IS incidence rate of 1/10,000 vaccinees, which was based on a consensus estimate of Rotashield attributable risk, was revised based on the total observed IS cases that occurred during Rota-023. Therefore, the overall definite IS incidence rate, which was further substantiated by data from active IS surveillance in the same 11 Latin American countries participating in Rota-023, was revised to 3-5/10,000. This subsequently led to revision of criteria for meeting the following primary safety objective:

- The upper limit of the 95% CI of the risk difference for definite IS should be <6/10,000
- There should be no statistically significant increase in the incidence of definite IS (the lower limit of the 95% of the risk difference should be < 0)

Assuming a definite IS incidence rate of 3-5/10,000 in the placebo group and 30,000 subjects in each treatment arm, the study had >86% power to meet its primary objective if the risk difference was truly 0. (Amended May 19, 2004, before the last Visit 3 in July 2004)

Power Considerations – 2nd Efficacy Follow-up Objectives
Assuming a true VE of 60% and an incidence rate of severe RV GE of 1% during the second efficacy period (Year 2), and 5,600 subjects in each treatment arm, the study had 95.2% power to observe a LL of the VE 95% CI > 0%, and 89.9% power for a LL >10%.

Study Cohorts
Total vaccinated cohorts (TVCs) consisted of all subjects in the IS Safety study, Year 1 Efficacy study, and Year 2 Efficacy study, that were administered at least one vaccine/placebo, and underwent the following analyses:

- IS and SAE safety analysis from Dose 1 to Visit 3
- Secondary efficacy analyses for Year 1 (TVC, 1st year efficacy subset)
- Secondary efficacy analyses for Year 2 (TVC, 2nd year efficacy subset)
- Efficacy from Dose 1 to Visit 6 (TVC, 1st year efficacy subset)
- Analysis of definite IS from Dose 1 to Visit 4 (TVC, 1st year efficacy subset)
- Analysis of definite IS from Dose 1 to Visit 6 (TVC, 2nd year efficacy subset)
- Safety analysis for Year 1 (TVC subset Year 1)
- Safety analysis for Year 2 (TVC subset Year 2)

The TVC for immunogenicity included vaccinated subjects in the TVC who had immunogenicity data.

The ATP safety cohort consisted of vaccinated subjects who 1) received at least 1 dose of vaccine/placebo, 2) did not have their randomization codes broken, 3) did not receive a vaccine forbidden by or not specified in the protocol, and 4) did not receive a replacement vial. The ATP safety cohort was to be performed if needed.

The ATP efficacy cohort consisted of all subjects from the ATP safety cohort who 1) belonged to subsets A and/or B, 2) received 2 doses of vaccine/placebo, 3) entered the first efficacy (subset A) and second efficacy (subset B) follow-up periods, 4) did not have their randomization codes broken before the end of Year 1 efficacy follow-up, and 5) did not have rotavirus other than vaccine strain in GE stool samples collected between Day 0 (Dose 1) and 2 weeks post-Dose 2. (Amended on

September 14, 2004, date of last Visit 4) The ATP efficacy cohort was used for the primary efficacy analysis for the Year 1 efficacy follow-up period (2 weeks post-Dose 2 to Visit 4), Year 2 efficacy follow-up period (after Visit 4 up to Visit 6), and the combined efficacy follow-up period (2 weeks post-Dose 2 to Visit 6).

The ATP immunogenicity cohort consisted of all subjects from the ATP safety cohort who 1) did not receive forbidden medications per protocol 2) did not have underlying medical conditions forbidden per protocol 3) had no protocol violations of demographics 4) complied with study vaccination schedule 5) complied with blood sampling schedule 6) had immunogenicity data at pre- and post-sampling time points 7) had no rotavirus other than vaccine strain in GE stool samples collected up to Visit 3 8) had no concomitant infections unrelated to the vaccine which may have influenced the immune response and 8) were negative for serum anti-RV IgA antibodies on the day of Dose 1. The ATP immunogenicity cohort was used for the primary immunogenicity analysis.

Final Analyses

The final statistical analysis for the primary safety objective was performed after all subjects completed Visit 3. Final analysis for primary efficacy and other objectives involving the period from Visit 1 to Visit 4 was performed after all subjects completed Visit 4. Data analysis from the end of the 1st efficacy follow-up period to the end of the 2nd efficacy follow-up period was later performed.

SAEs corresponding to the primary safety objective (i.e. IS) were not unblinded until all subjects completed their Visit 3. At the time of the final safety analysis for data reported from Dose 1 to Visit 3, all subjects from the safety cohort only (~40,000), all subjects in the safety/efficacy cohort (subset A) who reported an SAE during this period, and all fatal subjects (up to the September 2004 lock point) were unblinded for analysis. Drop-outs due to non-SAEs were not unblinded.

Investigators were unblinded to subjects that reported SAEs from Dose 1 to Visit 3 after receiving a copy of the final safety report for this period on November 18, 2004. Data up to Visit 4 were reviewed and frozen before unblinding of subjects with SAEs from Dose 1 up to Visit 3 for this safety report.

For the final analysis of data up to Visit 4, only efficacy subset subjects who reported an SAE after Visit 3 up to Visit 4 and fatal cases (up to the December 2004 lock point) were unblinded. Access to individual unblinding for the remaining subjects in subset A was limited to the statistician and database administrator until completion of the 2nd year of efficacy follow-up. The study was subject-blinded only during Year 2 efficacy follow-up.

The following analyses were performed:

1. Demographics: age (mean, median, range, and SD per group) at specific time points, racial and gender composition; length of intervals between specific time points; drop-outs at Visit 4 and Visit 6 by reason
2. Efficacy:
    a. VE against severe wild-type RV GE from 2 weeks post-Dose 2 until 1 year of age
    b. VE against severe G1 wild-type RV GE from 2 weeks post-Dose 2 until 1 year of age
    c. VE against severe non-G1 RV GE from 2 weeks post-Dose 2 until 1 year of age
    d. VE against severe RV GE due to each non-G1 serotype from 2 weeks post-Dose 2 until 1 year of age
    e. VE against severe wild-type RV GE with a score of ≥ 11 on the 20-point Vesikari scale from 2 weeks post-Dose 2 until 1 year of age
    f. VE against severe wild-type RV GE in a subset of subjects during Year 2 follow-up
    g. VE against severe wild-type RV GE in a subset of subjects during Year 2 follow-up

VE after Dose 1 was also calculated for the 6 endpoints noted above. Other supportive and exploratory analyses were performed (e.g. VE by country, VE against severe GE, time-to-event analysis – Cox proportional hazard model, sub-analyses for 2nd year efficacy).

For all VE analyses, a GE episode without a stool sample or available result was not considered as a RV GE episode.

3. Safety
   a. Asymptotic standardized 95% CI for group difference and 2-sided asymptotic score test for the null hypothesis of identical incidence in both groups for:
      - SAEs between groups throughout the study, including fatal cases and SAEs/non-SAEs leading to drop-out
   b. Asymptotic standardized 95% CI for treatment group difference for:
      - % difference in subjects with definite IS within 31 days after any dose between vaccine and placebo groups
      - % difference in subjects with definite IS within 31 days after each dose between vaccine and placebo groups
      - % difference in subjects with definite IS from Visit 1 to Visit 3
      - % difference in subjects with definite IS from Visit 1 to Visit 4 (subset A)
      - % difference in subjects with definite IS from Visit 1 to Visit 6 (subset B)

   Asymptotic standardized 95% on the relative risk was also calculated for Endpoints 1 and 2 above. Of note, p-values were be adjusted for the number of safety endpoints. Multiplicity adjustment was not performed.

4. Immunogenicity (for each country and pooled countries, at each time point):
   a. Seroconversion rates and 95% CI, by group
   b. GMCs and 95% CIs, by group

Immunogenicity analysis will not be performed before final efficacy analysis of the 1st efficacy follow-up period in order to avoid unblinding. Immunogenicity analyses excluded subjects with missing or non-evaluable measurements.

Interim Analyses

For regulatory purposes, an interim safety analysis (which also served as the final analysis of the primary safety objective) for SAEs up to Visit 3 was performed on the entire study cohort when all subjects completed Visit 3. The same analytical methodologies described above in section 3a were used. Definite IS cases diagnosed within 31 days after any Rotarix/placebo dose were unblinded after all subjects completed Visit 3.

A second interim safety analysis, which also served as the final analysis of SAEs from Dose 1 to Visit 3 and fatal cases up to the data lock point (September 10, 2004), was performed for regulatory purposes. All subjects from the safety-only cohort, all subjects in the efficacy cohort who had an SAE during the stated interval, and all fatal cases were unblinded.

An interim efficacy analysis was performed on data from Nicaragua for regulatory purposes. Precautions were taken to maintain blinding during this analysis. No study report was written.

Additional analyses/changes

The following analyses that were not part of the final protocol and analysis plan were added:

- For ATP efficacy cohort, seasonal distributions of severe GE and RV GE episodes from 2 weeks post-Dose 2 to Visit 4 displayed by country
- For ATP efficacy cohort, VE against hospitalization due to RV GE caused by circulating wild-type RV strains form 2 weeks post-Dose 2 to Visit 4
- For ATP efficacy cohort, VE against severe RV GE due to main G serotypes with a score of ≥ 11 on the Vesikari scale from 2 weeks-post Dose 2 to Visit 4
- For ATP efficacy cohort, VE against severe RV GE with a score ≥ a specific value on the Vesikari scale from 2 weeks post-Dose 2 to Visit 4
- Safety analyses after Visit 3 up to Visit 4 using subjects in the TVC (1st year efficacy subset) that had a contact during this interval

- 2-sided asymptotic 90% CI for group difference for % of subjects reporting definite IS cases diagnosed within 31 days after any dose between treatment groups (to assess original criteria of UL of 90%CI <2/10,000 for primary safety objective)
- 2-sided exact p-value (because for few events, the asymptotic p-value is an underestimation of the true p-value)
- Analysis on specific pooled MedDRA PTs
- Sub-group analysis according to age at dose 1 (<57 days, 57-84 days, >84 days), country, gender, and time following vaccination
- Differences in hospitalization rates due to SAEs between groups
- Safety analyses after Visit 4 up to Visit 6 using subjects in the TVC (2nd year efficacy subset) that had a contact during this interval
- For ATP cohorts (2nd year efficacy subset), VE against hospitalization due to RV GE and against hospitalization due to all cause GE, during each efficacy follow-up period
- For ATP cohorts (2nd year efficacy subset), VE against severe RV type G GE with a score of ≥ 11 on the Vesikari scale, during each efficacy follow-up period
- For ATP cohorts (2nd year efficacy subset), VE against severe RV GE with a score ≥ a specific value on the Vesikari scale during the combined efficacy follow-up period
- For the TVC (1st year efficacy subset), VE from Dose 1 to Visit 6

8.1.1.2 Results, by Trial (Objective information)

Study initiation date: August 5, 2003
Date of last Visit 3: July 23, 2004 (Date of data lock point: August 9, 2004)
Date of first Visit 4 for 2nd year efficacy subset: May 20, 2004
Date of last Visit 4: October 14, 2004
Date of last Visit 6: October 20, 2005
Data lock point for fatal cases: September 10, 2004 (for Visits 1-3)
December 21, 2004 (for period after Visit 3 to Visit 4)
Date when safety database archived for analysis: October 8, 2004
Date of report on final safety data from Dose 1 up to Visit 3: November 18, 2004
(Note: at this time, all investigators were unblinded with respect to subjects who reported an SAE from Dose 1 to Visit 3, and fatal cases up to September 10, 2004).
Date of report on final efficacy data from Visit 1 to Visit 4,
Final immunogenicity data from Visit 1 to Visit 3, and
Safety follow-up data after Visit 3 up to Visit 4 in efficacy subset: March 31, 2005
Date of report on efficacy data during each efficacy period,
Efficacy data from Dose 1 up to Visit 6
Safety follow-up data after Visit 4 up to Visit 6: March 2006

8.1.1.2.1 Populations enrolled/analyzed

Year 1 Efficacy Subset (subset A)

Study population by country
A total of 20,169 subjects were enrolled in the TVC for 1st year efficacy. Distribution by treatment group among the 11 participating countries is summarized below.

	HRV	Placebo	Total	
Country	**n**	**n**	**n**	**%**
Argentina	737	727	1464	7.3
Brazil	328	325	653	3.2
Chile	271	220	491	2.4
Colombia	954	943	1897	9.4
Dominican Republic	621	618	1239	6.1
Honduras	956	948	1904	9.4

Mexico	2656	2642	5298	26.3
Nicaragua	927	904	1831	9.1
Panama	589	577	1166	5.8
Peru	1357	1350	2707	13.4
Venezuela	763	756	1519	7.5
All countries	10159	10010	20169	100

Source: Study Report Body Rota-023 Year 1, pg 76

Drop-outs at Visit 4

As depicted in the table below, 17,882 out of 20,169 (88.7%) subjects in the TVC for 1st year efficacy subset completed Visit 4.

	Rotarix	**Placebo**	**Total**
Number of subjects enrolled and vaccinated	10159	10010	20169
Number of subjects who completed Visit 4	9027	8855	17882
Number of subjects dropped out at Visit 4	1132	1155	2287
Reasons for drop-out			
Serious Adverse Event	30	33	63
Non-serious adverse event	19	19	38
Protocol violation§	2	2	4
Consent withdrawal (not due to an adverse event)	202	220	422
Migrated/moved from study area	298	322	620
Lost to follow-up (subjects with incomplete vaccination course)	164	144	308
Lost to follow-up (subjects with complete vaccination course)	417	414	831
Other*	0	1	1

§Protocol violation: administration of immunoglobulin, age of patient not according to protocol, congenital malformation, and error when the informed consent was taken

*The reason was congenital disease

(Source: Study Report Body Rota-023 Year 1, pg 77)

Protocol deviations – TVC for 1st year efficacy subset

- 1 subject did not receive any dose of Rotarix; therefore, 20,169 subjects were included in this subset

Protocol deviations – TVC for 1st year safety

- 1,895 (Rotarix-926, placebo-969) subjects did not have a follow-up contact beyond Visit 3; therefore, 18,274 subjects were included in this subset

Protocol deviations – ATP cohort for 1st year efficacy

The following is a summary of protocol deviations leading to exclusion from the ATP cohort:

- 475 (Rotarix-239, placebo-236) received OPV within 2 weeks of study dose
- 11 (Rotarix-2, placebo-9) had randomization code broken due to IS (placebo-5) within 31 days after study dose and due to vaccine-related AE (Rotarix-2, placebo-4)
- 13 (Rotarix-8,placebo-5) received study dose not administered per protocol
- 1573 (Rotarix-797, placebo-776) did not receive Dose 2
- 218 (Rotarix-101, placebo-117) did not enter into the surveillance period for efficacy follow-up (i.e. 2 weeks post-Dose 2)
- 12 (Rotarix-3, placebo-9) had GE stool samples positive for non-vaccine RV strain between Dose 1 and 2 weeks post-Dose 2

Therefore, 17,867 subjects were included in the 1st year ATP efficacy cohort.

Protocol deviations – ATP cohort for immunogenicity

The following is a summary of protocol deviations that led to subject exclusion from this ATP cohort (number of subjects originally planned for this cohort = 1013):

- 147 (Rotarix-61, placebo-76) were positive for serum anti-RV IgA at Dose 1 or their IgA status was unknown at Dose 1
- 2 (Rotarix-1, placebo-1) received a medication forbidden by the protocol

- 2 (Rotarix-0, placebo-2) had GE stool samples positive for non-vaccine RV strain between Visit 1 to Visit 3
- 4 (Rotarix-1, placebo-3) were non-complaint with vaccination schedule (received Dose 2 outside 21-90 day interval between vaccinations)
- 27 (Rotarix-12, placebo-15) were non-compliant with blood sampling schedule
- 91 (Rotarix-46, placebo-45) were missing post-vaccination serology results (mainly because of invalid results or no blood sample collected)
- 6 (Rotarix-3, placebo-3) did not complete vaccinations but had serological data at Visit 3

Therefore, 734 subjects were included in the ATP immunogenicity cohort.
Subjects with SAEs from Visits 1 to 3 were not excluded from ATP cohorts for randomization code broken (because codes weren't broken before Visit 4).

A few minor protocol deviations were observed with respect to vaccine administration in the subset A efficacy cohort, and are mentioned in section 8.1.1.2.3 of this report. None of these subjects reported SAEs between Dose 1 and Visit 4.

Study demographics – ATP efficacy cohort (N=17,867)
Demographic characteristics are included in the table below. The median ages at Dose 1 (8 weeks), Dose 2 (16 weeks), and Visit 4 (12 months) were the same between groups. Most of the subjects in either group were Hispanic. The female-to-male ratios were comparable between groups.

Demographic characteristics – ATP efficacy cohort

		HRV (N = 9009)		**Placebo (N = 8858)**		**Total (N = 17867)**	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at the first dose (weeks)	Mean	8.4	-	8.4	-	8.4	-
	SD	2.38	-	2.37	-	2.4	-
	Median	8.0	-	8.0	-	8.0	-
	Minimum	5	-	2	-	2	-
	Maximum	13	-	13	-	13	-
Age at the second dose (weeks)	Mean	16.3	-	16.3	-	16.3	-
	SD	3.74	--	3.77	--	3.8	--
	Median	16.0		16.0		16.0	
	Minimum	10	-	9	-	9	-
	Maximum	36	-	30	-	36	-
Age at visit 4 or at last contact if visit	Mean	11.9		11.9		11.9	
	SD	1.54		1.55		1.5	
	Median	12.0		12.0		12.0	
	Minimum	3		3		3	
	Maximum	15	--	15	--	15	--
Gender	Female	4999	49.9	4251	48.0	8750	49.0
	Male	4510	50.1	4607	52.0	9117	51.0
Race	African	95	1.1	96	1.1	191	1.1
	White/Caucasian	729	8.1	686	7.7	1415	7.9
	Hispanic	7728	85.8	7599	85.8	15327	85.8
	Arabic/North African	0	0.0	1	0.0	1	0.0
	East/South East Asian	0	0.0	0	0.0	0	0.0
	South Asian	1	0.0	0	0.0	1	0.0
	Other*	456	5.1	476	5.4	932	5.2

Source: Study Report Body Rota-023 Year 1, pg 83

Dose/Visit intervals – ATP efficacy cohort

The median number of days between Doses 1 and 2, Dose 2 and Visit 3, Dose 1 and Visit 3, and Visits 3 and 4 were the same or similar between groups. The median duration of follow-up from Visit 3 up to Visit 4 was 207 days.

Parameters	HRV Value	Placebo Value	Total Value
Number of days between Dose 1 and Dose 2			
N	9009	8858	17867
Mean	55.9	55.8	55.8
Minimum	18.0	24.0	18.0
Q1	39.0	39.0	39.0
Median	56.0	56.0	56.0
Q3	68.0	68.0	68.0
Maximum	167.0	138.0	167.0
Number of days between Dose 2 and Visit 3			
N	8799	8636	17435
Mean	55.4	55.1	55.3
Minimum	19.0	11.0	11.0
Q1	36.0	36.0	36.0
Median	50.0	49.0	49.0
Q3	66.0	66.0	66.0
Maximum	211.0	204.0	211.0
Number of days between Dose 1 and visit 3 or last contact at visit 3			
N	9009	8858	17867
Mean	112.0	111.5	111.8
Minimum	31.0	30.0	30.0
Q1	89.0	90.0	89.0
Median	110.0	110.0	110.0
Q3	129.0	129.0	129.0
Maximum	291.0	302.0	302.0
Number of days between Visit 3 and Visit 4*			
N	8646	8481	17127
Mean	206.1	206.3	206.2
Minimum	1.0	1.0	1.0
Q1	182.0	183.0	183.0
Median	207.0	207.0	207.0
Q3	232.0	231.0	232.0
Maximum	330.0	371.0	371.0

N for between Dose 1 and Dose 2: N = Number of subjects with two doses administered
N for between Dose 2 and Visit 3: N = Number of subjects with Dose 2 administered and Visit 3 done
N for between Dose 1 and Visit 3 or last contact: N = Number of subjects vaccinated at dose 1
N for between Visit 3 and Visit 4: N = Number of subjects with a follow-up contact after Visit 3 to Visit 4
*If Visit 3/Visit 4 has not been performed then last contact at Visit 3/Visit 4
Q1 = 25th percentile; Q3 = 75th percentile

Source: Study Report Body Rota-023 Year 1, pg 123

Dose distribution – TVC 1st year efficacy subset (N=20,169)

The table below summarizes the numbers and percentages of subjects in each group that received 1 or 2 doses.

Total number of doses received	HRV (N = 10159)		Placebo (N = 10010)		Total (N = 20169)	
	n	%	n	%	n	%
1	803	7.9	787	7.9	1590	7.9
2	9356	92.1	9223	92.1	18579	92.1
Any	10159	100	10010	100	20169	100

Source: Study Report Body Rota-023 Year 1, pg 231

Dose distribution – TVC for safety (N=18,274)
The table below summarizes the numbers and percentages of subjects in each group that received 1 or 2 doses.

Total number of doses received	HRV (N = 9233)		Placebo (N = 9041)		Total (N = 18274)	
	n	%	n	%	n	%
1	354	3.8	330	3.7	684	3.7
2	8879	96.2	8711	96.3	17590	96.3
Any	9233	100	9041	100	18274	100

Source: Study Report Body Rota-023 Year 1, pg 96

Study demographics – TVC for safety
The median ages at Dose 1 (8 weeks) and Dose 2 (16 weeks), gender and race distributions were the same or similar between groups.

Study demographics and Dose/Visit intervals – TVC 1st year efficacy subset
The median ages at Dose 1 (8 weeks) and Dose 2 (16 weeks), gender and race distributions were the same or similar between groups. The median number of days between Doses 1 and 2, Dose 2 and Visit 3, Dose 1 and Visit 3, and Visits 3 and 4 were the same or similar between groups; these figures were also similar to those of the ATP efficacy cohort. The median duration of follow-up from Visit 1 to Visit 4 was 10.5 months in each group; the median duration from Visit 3 to Visit 4 was 7 months in each group.

Study demographics – ATP immunogenicity cohort (N=734)
The median ages at Dose 1 (9 weeks), Dose 2 (16 weeks) and gender and race distribution and Visit 4 (12 months) were similar between groups.

Concomitant and intercurrent vaccinations – ATP efficacy cohort
Only 7.8% of subjects from each group received routine vaccinations with Dose 1; less than 3% in each group received routine vaccinations with Dose 2. The percentages of subjects receiving intercurrent vaccinations (i.e. vaccinations given from birth until Visit 3, excluding vaccines given at Dose 1 and Dose 2) were similar between groups; 89% of subjects in each group received at least one routine vaccination between Dose 1 and Dose 2.

Concomitant and intercurrent vaccinations – TVC efficacy cohort
The figures for the concomitant and intercurrent vaccinations for the TVC efficacy subset were similar to those of the ATP efficacy cohort.

Year 2 Efficacy Subset (subset B: after Visit 4 to Visit 6) & Combined Efficacy Subset (2 weeks post-Dose 2 to Visit 6)

Study population by country
The total number of subjects in the TVC for 2nd year efficacy subset by treatment group among the 10 participating countries is summarized below.

	HRV N = 7669		Placebo N = 7514		Total N = 15183	
Country	n	%	n	%	n	%
Argentina	637	8.3	632	8.4	1269	8.4
Brazil	319	4.2	311	4.1	630	4.1
Chile	235	3.1	180	2.4	415	2.7
Colombia	861	11.2	847	11.3	1708	11.2
Dominican Republic	569	7.4	560	7.5	1129	7.4
Honduras	773	10.1	772	10.3	1545	10.2
Mexico	2178	28.4	2157	28.7	4335	28.6

Nicaragua	874	11.4	853	11.4	1727	11.4
Panama	535	7.0	522	6.9	1057	7.0
Venezuela	688	9.0	680	9.0	1368	9.0

Source: Study Report Body Rota-023 Annex Year 2, pg 56

Drop-outs at Visit 6

Of the 15,183 subjects in the TVC for 2nd year efficacy subset, 14,615 (96%) completed Visit 6. The numbers of drop-outs per reason were similar between study groups.

	Rotarix	Placebo	Total
Number of vaccinated subjects in 2nd year efficacy subset	**7669**	**7514**	**15183**
Number of subjects who completed Visit 6	**7397**	**7218**	**14615**
Number of subjects who did not return at Visit 6	**272**	**296**	**568**
Reasons for drop-out :			
Serious Adverse Event	6	7	13
Non-serious adverse event	1	2	3
Protocol violation§	0	2	2
Consent withdrawal (not due to an adverse event)	15	18	33
Migrated/moved from study area	117	132	249
Lost to follow-up (subjects with incomplete vaccination course)	6	11	17
Lost to follow-up (subjects with complete vaccination course)	126	124	250
Others*	1	0	1

Vaccinated = subjects who received at least one dose of HRV vaccine/placebo
§Protocol violation: Error when the informed consent was taken and adoption of the subject was in process.
*The reason was HIV positive.

Source: Study Report Body Rota-023 Annex Year 2, pg 57

Protocol deviations – TVC for 2nd year efficacy subset

- Of the 20,170 subjects enrolled in the 1st year efficacy subset, 4,987 subjects (Rotarix-2491, placebo-2496) did not satisfy eligibility criteria for the 2nd year efficacy subset; thus 15,183 subjects were included in the TVC for 2nd year efficacy subset

Protocol deviations – TVC for 2nd year safety

- Of 15,183 subjects in the TVC for 2nd year efficacy subset, 54 subjects (Rotarix-33, placebo-24) did not have a follow-up contact beyond Visit 4 and were therefore excluded from the TVC for safety follow-up after Visit 4 up to Visit 6. Therefore, 15,129 subjects were included in the TVC for 2nd year safety.

Protocol deviations – ATP cohort for efficacy during combined efficacy period

- 3851 (Rotarix-1804, placebo-1777) from the ATP cohort during the 1st year efficacy period did not satisfy eligibility criteria for the 2nd year efficacy subset and were excluded from the ATP cohort for efficacy during the combined period. Therefore, 14,286 subjects were included in this cohort.

Protocol deviations – ATP cohort for efficacy during 2nd efficacy period

- 49 (Rotarix-30, placebo-19) did not enter the 2nd efficacy follow-up period and were excluded from this cohort

Subjects with SAEs from after Visit 3 to Visit 4 were not excluded from ATP cohorts for randomization code broken.

Study demographics – ATP efficacy cohort during 2nd period (N=14,237)

Demographic characteristics are included in the table below. The median ages at Dose 1 (8 weeks), Dose 2 (15 weeks), Visit 4 (12 months), and Visit 6 (24 months) were similar between groups. Most of the subjects in both groups were Hispanic.

Follow-up duration – ATP efficacy cohort 2nd efficacy period & ATP efficacy cohort for combined period
The median number of months of follow-up for the 2nd efficacy period (11.96) and the combined efficacy period (20.26) the same between groups.

Dose distribution – TVC for safety
The table below summarizes the numbers and percentages of subjects in each group that received 1 or 2 doses for the safety follow-up after Visit 4 up to Visit 6.

	HRV N = 7636		Placebo N = 7493		Total N = 15129	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	263	3.4	246	3.3	509	3.4
2	7373	96.6	7247	96.7	14620	96.6
At least one	7636	100	7493	100	15129	100

Source: Study Report Body Rota-023 Annex Year 2, pg 80

Study demographics – TVC for safety
The median ages at Dose 1 (8 weeks), Dose 2 (15 weeks), Visit 4 (12 months), and Visit 6 (24 months), and gender and race distributions were the same or similar between groups.

Study demographics and Dose/Visit intervals – TVC for 2nd year efficacy subset,
The median ages at Dose 1 (8 weeks), Dose 2 (15 weeks), Visit 4 (12 months), and Visit 6 (24 months), and gender and race distributions were the same or similar between groups.

Duration of follow-up – TVC for 1st year efficacy subset, Dose 1 to Visit 6
The median duration of follow-up from Dose 1 to Visit 6 was 1.855 years in the Rotarix group and 1.852 years in the placebo group.

8.1.1.2.2 Efficacy endpoints/outcomes

Year 1 Efficacy Study (2 weeks post-Dose 2 to Visit 4) – ATP efficacy cohort

Summary of reported severe GE and severe RV GE episodes
The median duration of follow-up during the Year 1 efficacy period was 8 months in each group. Numbers of severe GE and severe RV GE episodes, as well as numbers of subjects, are depicted for each group in the table below. Among Rotarix and placebo recipients, RV was detected in 12 and 77 severe GE episodes, respectively. No subject had more than one RV GE episode.

		HRV N= 9009		Placebo N= 8858	
Event	**Total number of episode reported**	**n**	**%**	**n**	**%**
Severe GE	1	173	1.9	280	3.2
	2	10	0.1	18	0.2
	3	0	0.0	1	0.0
	4	0	0.0	1	0.0
	Any	183	2.0	300	3.4
Severe RV GE	1	12	0.1	77	0.9
	Any	12	0.1	77	0.9

(Source: Study Report Body Rota-023 Year 1, pg 154)

Stool test results were available for 171 (88.6%) severe GE episodes in Rotarix recipients and 278 (86.1%) in placebo recipients. The percentages of unavailable stool sample results were similar between the groups (table below).

	HRV	**Placebo**

	N'= 193		N'= 323	
Category	**n**	**%**	**n**	**%**
No stools collected	20	10.4	36	11.1
Stools collected but no results available*	2	1.0	9	2.8
No stool results available	22	11.4	45	13.9

(Source: Study Report Body Rota-023 Year 1, pg 155)

Serotype G and P distribution is summarized in the table below. No vaccine strain was detected in the stools collected. G1P8 was the most prevalent circulating type.

	HRV N'= 12		Placebo N'= 77	
Serotype	**n**	**%**	**N**	**%**
G1 wt and P8wt	2	16.7	33	42.9
G1 wt and P8	0	0.0	1†	1.3
G2 and P4	6	50.0	9	11.7
G3 and P8wt	1	8.3	8	10.4
G4 and P8wt	1	8.3	2	2.6
G9 and P8wt	1	8.3	19	24.7
G9 and G1wt, P8wt	1	8.3	1	1.3
G2, G9 and G1wt, P4, P8wt	0	0.0	1	1.3
GX and P6	0	0.0	1	1.3
Negative‡	0	0.0	1	1.3
Unknown	0	0.0	1*	1.3

† = one stool sample from a placebo recipient at 258 days after dose 2 of placebo had an initial testing result showing wild-type G1 and G1 vaccine strain. Repeated testing of the sample and of a back-up sample confirmed the presence of only wild-type G1 strain. It is not known whether P8 genotype was vaccine or wild-type.
‡ = positive by RotaClone but negative by RT-PCR
* = one RV GE was not tested by RT-PCR due to insufficient quantity
(Source: Study Report Body Rota-023 Year 1, pg 87)

Clinical characteristics of severe RV GE episodes

Clinical characteristics of severe RV GE episodes (duration/maximum # of loose stools, duration/maximum # of vomiting episodes, maximum fever, treatment, % dehydration), between treatment groups were similar overall.

Enteric pathogens testing

Although the protocol did not require enteric pathogen testing of stool specimens, 3 (Rotarix) and 38 (placebo) RV-positive stool specimens were tested. Enterotoxigenic E. coli was detected in 1 Rotarix specimen and 2 placebo specimens; E. histolytica was detected in 1 Rotarix specimen.

Vaccine efficacy against severe RV GE – Year 1 (Primary endpoint)

VE of Rotarix against severe RV GE caused by circulating wild-type RV during Year 1 follow-up was 84.7%. The primary efficacy objective was reached because the lower limit of the 95% CI was greater than 50% (refer to section 8.1.1.1.7 of this report on power considerations). VE was also 84.8% (95%CI: 72.0-91.7%) using the Cox proportional-hazard model.

			n/N	95% CI		VE	95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	9009	12	0.1	0.1	0.2	84.7	71.7	92.4	<0.001
Placebo	8858	77	0.9	0.7	1.1				

(Source: Study Report Body Rota-023 Year 1, pg 88)

VE against severe RV GE by main RV serotypes – Year 1 (Secondary endpoint)

VE against severe RV GE by serotype is presented below. VE against G1 severe RV GE was 91.8%; VE using Cox proportional hazard model was also significant (91.8%: 95%CI 73.5-97.5). VE

against G3, G9, and all non-G1 types pooled together reached statistical significance. VE against pooled non-G1 types was 75.5% (95% CI: 51.0-87.6%) using the Cox proportional hazard model. Although fewer G2 episodes occurred in the Rotarix group, VE did not reach statistical significance. VE against G4 type was not evaluated due to limited subjects (Rotarix-1, placebo-2).

Group (wild type)	n	% (n/N)	VE %	95%CI		P-value
				LL	UL	
G1						
Rotarix	3†	0.0	91.8	74.1	98.4	<0.001
placebo	36†	0.4				
G2						
Rotarix	6	0.1	41.0	-79.2	82.4	0.328
placebo	10†	0.1				
G3						
Rotarix	1	0.0	87.7	8.3	99.7	0.020
placebo	8	0.1				
G9						
Rotarix	2†	0.0	90.6	61.7	98.9	<0.001
placebo	21†	0.1				
Pooled non-G1(G2, G3, G4, G9)						
Rotarix	10†	0.1	75.4	50.0	89.0	<0.001
placebo	40†	0.5				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one specified severe RV GE episode in each group
Not included in table = subjects with G4 (Rotarix-1, placebo-2)
†Subject(s) appears in more than one category if more than one G-type was identified in the stool sample.
One subject from HRV group counted in G1 and G9 categories
One subject from placebo group counted in G1 and G9 categories
One subject from placebo group counted in G1, G2 and G9 categories
(Source: Study Report Body Rota-023 Year 1, pg 90)

VE against severe RV GE with a Vesikari score ≥ 11 – Year 1 (Secondary endpoint)
VE against severe RV GE defined as a Vesikari score ≥ 11 was 84.8%, nearly identical to the VE calculated against severe RV GE using the primary efficacy clinical case definition. VE against G1, G2, G3, G9, and pooled non-G1 types were also consistent with VE figures using the primary clinical case definition (see table above).

			n/N 95% CI			Vaccine Efficacy 95% CI			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	9009	11	0.1	0.1	0.2	84.8	71.1	92.7	<0.001
Placebo	8858	71	0.8	0.6	1.0				

(Source: Study Report Body Rota-023 Year 1, pg 91)

Furthermore, VE increased with increasing Vesikari scores >11; VE reached 100% (95% CI: 74.5-100%) for a score of ≥ 19 points.

VE against hospitalized RV GE – Year 1 (Exploratory endpoint)
Among the 68 subjects who required hospitalization for severe RV GE, 9 (0.1%) were Rotarix recipients compared to 59 (0.7%) placebo recipients; VE was 85.0% (95% CI: 69.6-93.5%).

VE against all cause severe GE – Year 1 (Exploratory endpoint)
VE against severe GE of any etiology was 40.0% (95% CI: 27.7-50.4).

VE against severe RV GE, by country – Year 1 (Exploratory endpoint)
VE against severe RV GE was greater than 50% in all countries except Chile, the country with the smallest study population where 1 subject in each group reported an episode. VE reached statistical significance for the countries below; four of the countries (Colombia, Mexico, Nicaragua, Peru) had the largest study populations.

Country	VE	95% CI LL	UL
Colombia	100%	42.1	100
Mexico	91.8	44.4	99.8
Nicaragua	100	18.2	100
Panama	100	40.2	100
Peru	87.6	47.1	98.6

(Source: Study Report Body Rota-023 Year 1, pg 193)

Year 1 Efficacy Study (Dose 1 to Visit 4) – TVC 1st year efficacy subset

Summary of reported severe RV GE episodes
A total of 112 subjects in the TVC efficacy subset reported one episode of severe RV GE from Dose 1 to Visit 4; 18 (0.2%) occurred in Rotarix recipients and 94 (0.9%) occurred in placebo recipients. No subject in either group had more than one RV GE episode. Stool results were not available for 29 (11.7%) Rotarix and 67 (15.9%) recipients who reported severe GE episodes during this interval.

VE against severe RV GE – Dose 1 to Visit 4
VE against severe RV GE occurring from Dose 1 to Visit 4 was 81.1% (95% CI: 68.5-89.3%), indicating that Rotarix was protective from Dose 1 onwards. This figure is comparable to the VE estimate for the primary endpoint in the ATP cohort (84.7%). VE using the Vesikari scale definition for severe RV GE (≥ 11 points) was 80.5% (95%CI: 67.0- 89.2%).

Similar to the ATP cohort, VE against wild-type G1, G3, G9, and pooled non-G1 types reached statistical significance (86.6%, 73.7%, 91.0%, and 73.9%, respectively).

VE against severe RV GE was statistically significant in Colombia (100%), Honduras (100%), Mexico (80.1%), Nicaragua (86.1%), Panama (100%), Peru (88.3%), and Venezuela (67.0%).

VE against all cause severe GE – Dose 1 to Visit 4
VE against severe GE of any cause was 40.8% (95%CI: 30.2-49.9%).

Year 1 Efficacy Study (Dose 1 to 14 days post-Dose 2) – TVC 1st year efficacy subset

VE against severe RV GE – Dose 1 to 14 days post-Dose 2
VE against severe RV GE occurring from Dose 1 to 14 days post-Dose 2 was 60.6% (95% CI: -7.5-87.5%). As indicated by the 95% CI, VE for this period did not reach statistical significance, although fewer Rotarix than placebo recipients reported episodes (6 vs 15).

Year 1 Efficacy Study (Dose 1 to pre-Dose 2) – TVC 1st year efficacy subset

VE against severe RV GE – Dose 1 to pre-Dose 2
Similar to the VE during Dose 1 to 14 days post-Dose 2, VE during Dose 1 to pre-Dose 2 did not reach statistical significance (50.7% (95% CI: -41.8-84.8), despite episodes occurring less in Rotarix recipients (6 vs 12).
Year 1 Immunogenicity – ATP immunogenicity cohort

Anti-RV IgA immunogenicity was evaluated for both the ATP (N=734) and TVC cohorts. Due limited numbers of subjects, correlation between seroconversion rates and protection against severe RV GE could not be assessed.

Immunogenicity – ATP immunogenicity cohort
Anti-RV IgA seropositive rates and GMCs at both pre-Dose 1 and Visit 3 (1-2 months post-Dose 2) are presented below. Post-Dose 2 seropositive rates and GMCs were significantly greater in the Rotarix group compared to placebo.

Group	Timing	N	≥ 20 U/ml			GMC (U/ml)	
					95% CI	Value	95% CI

			n	%	LL	UL		LL	UL
HRV	Pre	393	0	0.0	0.0	0.9	<20.0	-	-
	PII (M2-4)	393	302	76.8	72.4	80.9	102.6	86.3	122.0
Placebo	Pre	341	0	0.0	0.0	1.1	<20.0	-	-
	PII (M2-4)	341	33	9.7	6.8	13.3	<20.0	-	-

PII(M2-4) = blood sample taken one to two months after dose 2 of HRV vaccine or placebo (Visit 3)
(Source: Study Report Body Rota-023 Year 1, pg 103)

Immunogenicity – TVC immunogenicity cohort

The median number of days between the last administered dose and post-vaccination blood sampling was 44.0 and 46.5 days in Rotarix and placebo groups, respectively. Seropositive rates and GMCs in the Rotarix group were similar to those for the ATP cohort.

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV	Pre	495	20	4.0	2.5	6.2	<20.0	-	-
	PII M2-4)	457	356	77.9	73.8	81.6	113.0	96.2	132.9
Placebo	Pre	432	15	3.5	2.0	5.7	<20.0	-	-
	PII (M2-4)	398	60	15.1	11.7	19.0	<20.0	-	-

(Source: Study Report Body Rota-023 Year 1, pg 297)

Year 2 Efficacy Subset & Combined Efficacy Subset – ATP cohort for 2nd year efficacy& ATP cohort for combined efficacy period

Summary of reported severe GE and severe RV GE episodes – ATP cohorts for 2nd year efficacy and combined efficacy

Numbers of severe GE and severe RV GE episodes, as well as numbers of subjects, by efficacy period, are summarized below.

Event	Total number of episode reported	HRV n	HRV %	Placebo n	Placebo %
Second efficacy period		**N= 7175**		**N= 7062**	
Severe GE	1	193	2.7	317	4.5
	2	14	0.2	14	0.2
	3	1	0.0	1	0.0
	Any	208	2.9	332	4.7
Severe RV GE	1	22	0.3	103	1.5
	Any	22	0.3	103	1.5
Combined efficacy period		**N = 7205**		**N = 7081**	
Severe GE	1	304	4.2	501	7.1
	2	35	0.5	42	0.6
	3	3	0.0	8	0.1
	Any	342	4.7	551	7.8
Severe RV GE	1	32	0.4	161	2.3
	Any	32	0.4	161	2.3

Source: Study Report Body Rota-023 Annex Year 2, pg 116

Percentages of unavailable stool sample results for each period are summarized below.

Category	HRV n	HRV %	Placebo n	Placebo %
Second efficacy period	**N'= 224**		**N'= 348**	
No stools collected	30	13.4	57	16.4
Stools collected but no results available*	1	0.4	5	1.4
No stool results available	31	13.8	62	17.8
Combined efficacy period	**N'= 383**		**N'= 609**	
No stools collected	45	11.7	91	14.9
Stools collected but no results available*	1	0.3	13	2.1

No stool results available	46	12.0	104	17.1

Source: Study Report Body Rota-023 Annex Year 2, pg 117

The distribution of severe RV GE by serotype is summarized below. For the second efficacy period, G9P8 was the most prevalent circulating type.

	HRV		**Placebo**	
Serotype	**n**	**%**	**n**	**%**
Second efficacy period	**N'= 22**		**N'= 103**	
P4 and G2	1	4.5	1	1.0
P6 and G3	0	0.0	1	1.0
P8wt and G1wt	6	27.3	24	23.3
P8wt and G3	2	9.1	6	5.8
P8wt and G4	6	27.3	15	14.6
P8wt, G4 and G9	0	0.0	1	1.0
P8wt and G9	6	27.3	54	52.4
P8wt, G9 and G1wt	1	4.5	1	1.0
Combined efficacy period	**N'= 32**		**N'= 161**	
P4 and G2	5	15.6	8	5.0
P6 and G3	0	0.0	1	0.6
P6 and GX	0	0.0	1	0.6
P8wt and G1wt	8	25.0	53	32.9
P8wt and G3	3	9.4	13	8.1
P8wt and G4	7	21.9	17	10.6
P8wt, G4 and G9	0	0.0	1	0.6
P8wt and G9	7	21.9	63	39.1
P8wt, G9 and G1wt	2	6.3	2	1.2
Unknown	0	0.0	2*	1.2

n/% = number/percentage of severe RV GE episodes reported in each group, by G and P types; wt = wild type; GX = G type unknown, but not vaccine strain; * = one RV GE was not tested by RT-PCR due to quantity not sufficient and another was not typable
Source: Study Report Body Rota-023 Annex Year 2, pg 68

Clinical characteristics of severe RV GE episodes

The duration of vomiting and diarrhea, as well as the proportion of hospitalizations for RV GE episodes, were lower in the Rotarix group compared to placebo.

Enteric pathogens testing

Percentages of severe RV GE episodes with other detected pathogens are summarized below.

	HRV		**Placebo**	
Mixed infection	**n**	**%**	**N**	**%**
Second efficacy period	**N'= 22**		**N'= 103**	
Unknown*	10	45.5	55	53.4
Negative	10	45.5	45	43.7
At least one mixed infection	2	9.1	3	2.9
Enterotoxigenic E.coli	1	4.5	1	1.0
Giardia	1	4.5	1	1.0
Other**	1	4.5	1	1.0
Combined efficacy period	**N'= 32**		**N'= 161**	
Unknown*	17	53.1	78	48.4
Negative	12	37.5	78	48.4
At least one mixed infection	3	9.4	5	3.1
Enterotoxigenic E.coli	2	6.3	3	1.9
Giardia	1	3.1	1	0.6
Other**	2	6.3	1	0.6

n/% = number/percentage of mixed severe RV GE episodes reported in each group, among all severe RV GE episodes reported
* = not tested or unknown result; ** = ENTAMOEBA HISTOLYTICA
Source: Study Report Body Rota-023 Annex Year 2, pg 128

VE against severe RV GE – Year 2 and Combined Period (Secondary endpoints)
VE of Rotarix against severe RV GE caused by circulating wild-type RV was 79.7% during the second efficacy follow-up period and 80.5% for the combined efficacy period.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Second efficacy period									
HRV	7175	22	0.3	0.2	0.5	79.0	66.4	87.4	<0.001
Placebo	7062	103	1.5	1.2	1.8	-	-	-	-
Combined efficacy period									
HRV	7205	32	0.4	0.3	0.6	80.5	71.3	87.1	<0.001
Placebo	7081	161	2.3	1.9	2.6	-	-	-	-

Source: Study Report Body Rota-023 Annex Year 2, pg 69

VE against severe RV GE by main RV serotypes – Year 2 (Secondary endpoint)
VE against severe RV GE by serotype is presented below. Compared to placebo recipients, Rotarix recipients reported significantly less episodes caused by G1 wild-type strains (VE=72.4%). VE against G4, G9, and all non-G1 types pooled together reached statistical significance. Although fewer G3 episodes occurred in the Rotarix group, VE did not reach statistical significance.

Second Efficacy Period

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	UL	
G1						
Rotarix	7†	0.1	72.4	34.5	89.9	<0.001
placebo	25†	0.4				
G2						
Rotarix	1	0.0	1.6	-7626.1	98.7	1.000
placebo	1	0.0				
G3						
Rotarix	2	0.0	71.9	-47.7	97.1	0.107
placebo	7	0.1				
G4						
Rotarix	6†	0.1	63.1	0.7	88.2	0.033
placebo	16†	0.2				
G9						
Rotarix	7†	0.1	87.7	72.9	95.3	<0.001
placebo	56†	0.8				
Pooled non-G1(G2, G3, G4, G9)						
Rotarix	16†	0.2	80.1	65.6	89.1	<0.001
placebo	79†	1.1				

N Rotarix recipients=7175, N placebo recipients=7062
†Subject(s) appears in more than one category if more than one G-type was identified in the stool sample.
One subject from HRV group counted in G1 and G9 categories
One subject from placebo group counted in G1 and G9 categories
One subject from placebo group counted in G4 and G9 categories
Source: Study Report Body Rota-023 Annex Year 2, pg 72

VE against severe RV GE by main RV serotypes –Combined Period (Secondary endpoint)
VE against severe RV GE by serotype is presented below. Compared to placebo recipients, Rotarix recipients reported significantly less episodes caused by G1 wild-type strains (VE=82.1%). VE against G3, G4, G9, and all non-G1 types pooled together reached statistical significance. Although fewer G2 episodes occurred in the Rotarix group, VE did not reach statistical significance.

Combined Efficacy Period

Group (wild type)	n	% (n/N)	VE %	95%CI		P-value
				LL	UL	
G1						
Rotarix	10†	0.1	82.1	64.6	91.9	<0.001
placebo	55†	0.8				
G2						
Rotarix	5	0.1	38.6	-112.9	84.2	0.420
placebo	8	0.1				
G3						
Rotarix	3	0.0	78.9	24.5	96.1	0.007
placebo	14	0.2				
G4						
Rotarix	7†	0.1	61.8	4.1	86.5	0.028
placebo	18†	0.3				
G9						
Rotarix	9†	0.1	86.6	73.0	94.1	<0.001
placebo	66†	0.9				
Pooled non-G1(G2, G3, G4, G9)						
Rotarix	24†	0.3	77.5	64.7	86.2	<0.001
placebo	105†	1.5				

N Rotarix recipients=7205, N placebo recipients=7081
Unknown G type for 2 subjects: one RV GE was not tested by RT-PCR due to insufficient quantity of sample and one was not typable
†Subject(s) appears in more than one category if more than one G-type was identified in the stool sample.
Two subjects from HRV group counted in G1 and G9 categories
Two subjects from placebo group counted in G1 and G9 categories
One subject from placebo group counted in G4 and G9 categories
Source: Study Report Body Rota-023 Annex Year 2, pg 74

VE against severe RV GE with a Vesikari score ≥ 11 – Year 2 and Combined Period
VE against severe RV GE defined as a Vesikari score ≥ 11 was 81.5% during Year 2 and 82.1% during the combined period, comparable to the VE calculated against severe RV GE using the primary efficacy clinical case definition. For Year 2, VE against G1 (75.4%), G3 (85.9%), G4 (63.1%), G9 (89.3%), and pooled non-G1 types (82.3%) reached statistical significance. Comparable results were observed for the combined efficacy period.

Group	N	n	n/N 95%CI			Vaccine Efficacy 95%CI			P-value
			%	LL	UL	%	LL	UL	
Second efficacy period									
HRV	7175	19	0.3	0.2	0.4	81.5	69.6	89.3	<0.001
Placebo	7062	101	1.4	1.2	1.7	-	-	-	-
Combined efficacy period									
HRV	7205	28	0.4	0.3	0.6	82.1	73.1	88.5	<0.001
Placebo	7081	154	2.2	1.8	2.5	-	-	-	-

Source: Study Report Body Rota-023 Annex Year 2, pg 76

Furthermore, during the combined efficacy period, VE increased with increasing Vesikari scores >11; VE reached 100% (95% CI: 60.8-100%) for a score of ≥ 20 points.

VE against hospitalized RV GE – Year 2 and Combined Period (Exploratory endpoint)
During Year 2, 15 (0.2%) Rotarix recipients required hospitalization for RV GE compared to 80 (1.1%) placebo recipients; VE was 81.5% (95% CI: 67.7-90.1%). During the combined period, 22 (0.3%) Rotarix recipients required hospitalization compared to 127 (1.8%) placebo recipients; VE was 83.0% (95% CI: 73.1-89.7)

VE against all cause severe GE – Year 2 and Combined Period (Exploratory endpoint)
VE against severe GE of any etiology was 38.3% (95% CI: 26.4-48.4%) for Year 2 and 39.0% (95% CI: 30.1-46.9%) for the combined period.

VE against hospitalization for all cause severe GE – Year 2 and Combined Period (Exploratory endpoint)
VE against hospitalized severe GE of any etiology was 37.8% (95% CI: 23.5-49.
5%) for Year 2 and 39.3% (95% CI: 29.1-48.1%) for the combined period.

VE against severe RV GE, by country – Year 2 and Combined Period (Exploratory endpoint)
VE against severe RV GE was greater than 50% in all countries during Year 2 and the combined period. During Year 1, VE reached statistical significance for the Brazil, Colombia, Mexico, Panama, and Venezuela. During the combined period, VE reached statistical significance for Brazil, Colombia, Honduras, Mexico, Nicaragua, Panama, and Venezuela.

		95% CI	
Country	**VE**	**LL**	**UL**
Year 2			
Brazil	70.5	28.9	89.3
Colombia	74.0	18.5	93.7
Mexico	100	55.6	100
Panama	100	75.7	100
Venezuela	100	16.4	100
Combined period			
Brazil	68.8	32.0	87.0
Colombia	83.0	50.3	95.7
Honduras	79.9	28.9	96.3
Mexico	95.3	70.7	99.9
Nicaragua	77.6	18.5	95.9
Panama	100	83.3	100
Venezuela	91.8	44.4	99.8

Source: Study Report Body Rota-023 Annex Year 2, pgs 138-139

Dose 1 to Visit 6 Efficacy Subset – TVC for 1st year efficacy subset (N=20,169)

A total of 2430 subjects in the TVC 1st year efficacy subset reported at least one episode of severe RV GE from Dose 1 to Visit 6; 41 (0.4%) occurred in Rotarix recipients and 202 (2.0%) occurred in placebo recipients. Stool results were not available for 59 (12.1%) Rotarix and 134 placebo (17.0%) recipients.

VE against severe RV GE – Dose 1 to Visit 6 (using Cox regression model)
VE for the TVC for the 1st year efficacy subset during the period from Dose 1 to Visit 6 was 80.3% (95% CI: 72.4-85.9%). This figure was comparable to VE for the ATP efficacy cohort for the combined period. VE against severe RV GE reached statistical significance in Argentina (61.8%), Brazil (70.8%), Colombia (83.9%), Honduras (83.5%), Mexico (88.6%), Nicaragua (67.7%), Panama (100%), Peru (88.5%), and Venezuela (79.3%).

VE against wild-type G1, G3, G4, G9, and pooled non-G1 types reached statistical significance (81.9%, 74.4%, 60.9%, 88.9%, and 77.9%, respectively).

VE using the Vesikari scale definition for severe RV GE (≥ 11 points) was 81.3% (95%CI: 73.4-86.8%). VE increased with increasing total points, reaching 100% (95% CI: 72.5-100%) for severity ≥ 20 points. For severe RV GE ≥ 11 points, VE against wild-type G1, G3, G4, G9, and pooled non-G1 types reached statistical significance (81.7%, 76.7%, 60.9%, 90.0%, and 79.4%, respectively).

VE against hospitalized RV GE was 81.3% (95% CI: 72.3-87.3%).

VE against all cause severe GE was 40.1% (95% CI: 32.5-46.8%). VE against all cause hospitalized GE was 41.0% (95% CI: 32.4-48.5%).

8.1.1.2.3 Safety outcomes

IS Safety Study

General study population characteristics
General characteristics of the total safety cohort from Visit 1 to Visit 3 are summarized below. The numbers of subjects that were enrolled and vaccinated (i.e. TVC), received 2 doses, and completed Visit 3 were similar between groups. The median ages at Dose 1 and Dose 2, male-to-female ratio and proportion of Hispanics and Caucasians were also similar between groups. In addition, 6% and 3% of subjects were co-administered routine vaccinations with Dose 1 and Dose 2, respectively. Mexico and Peru enrolled the largest numbers of subjects (20.9% and 19%, respectively).

Overview of total safety cohort

Treatment Group	# Enrolled & vaccinated (TVC)	#/ % Received 2 doses	# Completed Visit 3	Median age (weeks)		M/F ratio	Ethnicity	Median Interval (days)			% with ≥ 31 days f/u after each dose	
				D1	D2			D1 to D2	D2 to V3	D1 to V3	D1	D2
Total	63,225	59,081/ 93.4%	59,308	7	15	1.04	81.3% Hisp 10.9% Cau	55	45	100	98.0	98.3
Rotarix	31,673	29,616/ 93.5%	29,753	7	15	1.03	81.2% Hisp 11.0% Cau	55	45	100	98.0	98.4
Placebo	31,552	29,465/ 93.4%	29,555	7	15	1.05	81.3% Hisp 10.9% Cau	55	45	99	98.1	98.2

D1 = Dose 1; D2 = Dose 2; V3 = Visit 3
Source: Study Report Body Rota-023 Visit 1-3, pgs 71, 76, 78, 152, 182

Overall numbers of subjects that dropped out at Visit, as well as numbers of drop-outs for each reason, are fairly balanced between treatment groups as depicted below.

Counts of drop-outs at Visit 3, by reason - TVC

	Rotarix	Placebo	Total
Number of subjects enrolled and vaccinated	31673	31552	63225
Number of subjects who completed Visit 3	29753	29555	59308
Number of subjects dropped out at Visit 3	1920	1997	3917
Reasons for drop-out:			
Serious Adverse Event	61	48	109
Non-serious adverse event	57	56	113
Protocol violation§	5	6	11
Consent withdrawal (not due to an adverse event)	541	538	1079
Migrated/moved from study area	431	448	879
Lost to follow-up (subjects with incomplete vaccination course)	398	437	835
Lost to follow-up (subjects with complete vaccination course)	427	459	886
Other*	0	5	5

§Protocol violation: administration of immunoglobulins or gammaglobulins (before enrollment in the study), age not within protocol range, congenital malformation (before enrollment in the study) and error when the informed consent was taken or signed
*Other: subject enrolled twice, information of Visit 3 not retrievable, blood transfusion and protocol deviation
Source: Study Report Body Rota-023 Visit 1-3, pg 71

Protocol deviations
A few minor protocol deviations were observed with respect to vaccine administration. None of the subjects with deviation reported IS or SAE between Dose 1 and Visit 3. No adjustments were made in the analyses. A summary of deviations are as follows:

							(Rotarix – Placebo)			(Rotarix/ Placebo)			
	Rotarix			Placebo			difference/ 10,000	95% CI		RR	95% CI		
31 days after	N	n	n/ 10,000	N	n	n/ 10,000		LL	UL		LL	UL	p-value
Any dose	31,673	6	1.9	31,552	7	2.2	-0.32	-2.91	2.18	0.85	0.30	2.42	0.776
Dose 1	31,673	1	0.3	31,552	2	0.6	-0.32	-2.03	1.20	0.50	0.07	3.80	0.561
Dose 2	29,616	5	1.7	29,465	5	1.7	-0.01	-2.48	2.45	0.99	0.31	3.21	0.994

N = # of subjects in the cohort; n = # with definite IS
(Source: Study Report Body Rota-023 Visit 1-3, pg 79)

When the original criterion for the primary safety objective was used, i.e. the upper limit of the 2-sided 90% CI of the Risk Difference below 2/10,000, the primary objective was still met (UL = 1.71/10,000); the risk difference was -0.32/10,000 with a lower limit of -2.41.

There were no apparent differences in onset interval from vaccination or median age at the time of IS diagnosis between the groups (table below). Onset interval from 1-15 days was observed in 2 Rotarix and 2 placebo recipients; all pertained to Dose 2. Onset interval from 16-30 days was observed in 4 Rotarix (1 after Dose 1) and 5 placebo recipients (2 after Dose 1). The most common symptoms in both groups were vomiting, bloody stools and abdominal distension. One of the 3 cases diagnosed after Dose 1 received Dose 2 without subsequent problems, with the other 2 remained in the study. One of the 13 subjects dropped out of the study at Visit 3. Nine of the 13 cases underwent surgery; all 13 cases made complete recoveries.

Characteristics of 13 definite IS cases diagnosed during 31 days after any dose - TVC

Treatment Group	Country	Male-to-Female Ratio	# cases occurring after each dose	Median age/ range at diagnostic day (months)	Median Interval/ range from vaccination to onset (diagnostic day) (days)	Treatment
Total	Chile - 1 Colombia - 1 Mexico - 1 Nicaragua - 2 Panama - 4 Peru - 2 Venezuela - 2	5:8	Dose 1 - 3 Dose 2 - 10	4/ 2-5	17/ 3-28	Surgery - 9 Hydrostatic enema - 4
Rotarix	Chile - 1 Colombia - 0 Mexico - 1 Nicaragua - 0 Panama - 3 Peru - 1 Venezuela - 0	3:3	Dose 1 - 1 Dose 2 - 5	4/ 2-5	16.5/ 3-25	Surgery -4 Hydrostatic enema - 2
Placebo	Chile - 0 Colombia - 1 Mexico - 0 Nicaragua - 2 Panama - 1 Peru - 1 Venezuela - 2	2:5	Dose 1 - 2 Dose 2 - 5	3.5/ 2-5	18/ 6-28	Surgery - 5 Hydrostatic enema - 2

Source: Study Report Body Rota-023 Visit 1-3, pg 81

Test results of biological specimens obtained from the 13 IS cases are summarized below. Of note, shigella was detected in 11 cases (Rotarix-5, placebo-6). Detection of at least 2 pathogens (including RV vaccine or RV wild-type strains) was observed in 9 cases (Rotarix-5, placebo-4). Vaccine virus was detected in 3 Rotarix recipients (1 of which was detected by lymph node biopsy); RV (wild-type vs vaccine not specified) was detected by bowel biopsy in 2 Rotarix recipients (one

who also had G1 vaccine strain detected in stool). G1 wild type RV was detected by throat swab in 1 placebo recipient.

Rotarix or Placebo	post-Dose	Interval (days)	Rectal swab	Stool	Biopsy bowel	Biopsy lymph node	Throat
r1	2	3	G1 vaccine	G1 vaccine, entero, shigella	RV	neg	neg
r2	2	25	not done	entero, shigella	not done	not done	entero
r3	2	16	not done	shigella	not done	G1 vaccine, polio type 3	neg
r4	1	18	G1 vaccine, entero	G1 vaccine, entero, shigella, adeno	not done	not done	neg
r5	2	17	adeno	shigella, adeno, campy	RV	?not done	neg
r6	2	3	entero	not done	not done	neg	neg
p1	1	16	not done	entero, shigella	not done	not done	neg
p2	2	28	not done	entero, shigella	polio type 3, adeno 2 or 6	?not done	G1 wild type
p3	2	18	not done	entero, shigella	not done	not done	neg
p4	2	9	neg	shigella	?not done	neg	neg
p5	2	6	neg	not done	not done	not done	neg
p6	2	24	not done	shigella	not done	not done	neg
p7	1	22	not done	shigella, campy	not done	not done	neg

Source: Study Report Body Rota-023 Visit 1-3, pgs 266-278

Reviewer Note: One definite IS case had an onset on Day 29 but was confirmed diagnostically on Day 31. If this case is included in the Days 0-30 analysis, then there would be 7 out of 31,673 Rotarix cases (versus to 7 out of 31,552 placebo cases). The statistical reviewer calculated a risk difference of -8.48 $x10^{7}$ with a 95% CI of -2.63/10,000 to 2.61/10,000, and a 90% CI of -2.14/10,000 to 2.12/10,000. Incidence of IS post-vaccination in different onset intervals would be as follows:

Onset interval (days)	Rotarix IS	Rotarix N*	Incidence (per 10,000)	Placebo IS	Placebo N	Incidence (per 10,000)
1 to 7	2	31673	0.63	1	31552	0.32
8 to 14	0	31673	0	1	31552	0.32
15 to 21	3	31673	0.95	2	31552	0.63
22 to 30	2	31673	0.63	3	31552	0.95
1 to 14	2	31673	0.63	2	31552	0.63
1 to 21	5	31673	1.58	4	31552	1.27
1 to 30	7	31673	2.21	7	31552	2.22

*onset date used rather than diagnosis date

Secondary Safety Endpoint – IS (Dose 1 until Visit 3)

A total of 25 definite IS cases adjudicated by the CEC were diagnosed from Dose 1 until Visit 3 (Rotarix – 9, placebo – 16). As depicted in the table below, there was no statistically significant difference between Rotarix and placebo groups in the % of subjects diagnosed with definite IS during this time period.

Differences in % of subjects diagnosed with definite IS from Dose 1 to Visit 3 - TVC

	Study group						Risk Difference (Rotarix – Placebo)			Relative Risk (Rotarix/ Placebo)			
	Rotarix			Placebo			difference/ 10,000	95% CI		RR	95% CI		
Interval	N	n	n/ 10,000	N	n	n/ 10,000		LL	UL		LL	UL	p-value
Dose 1 to Visit 3	31,673	9	2.8	31,552	16	5.1	-2.23	-5.70	0.94	0.56	0.25	1.24	0.159

Source: Study Report Body Rota-023 Visit 1-3, pg 85; N = # of subjects in the cohort; n = # with definite IS

Of the 25 cases, 12 (Rotarix – 3, Placebo – 9) were diagnosed beyond Day 30 after vaccine or placebo until Visit 3. There were no apparent differences in onset interval from vaccination or

median age at the time of IS diagnosis between the groups (table below). Onset interval from 31-60 days was observed in 2 Rotarix and 5 placebo recipients, onset interval from 61-90 days was observed in 0 Rotarix and 3 placebo recipients, and onset interval > 90 days was observed in 1 Rotarix and 1 placebo recipient. The most common symptoms in both groups were vomiting and bloody stools. Two of the 7 cases diagnosed after Dose 1 received Dose 2 without subsequent problems. Ten of the 12 cases underwent surgery; 12 cases made complete recoveries and 1 case recovered with sequelae (jejunum/distal ileum resection). One of the subjects dropped out.

Characteristics of 12 definite IS cases diagnosed beyond 31 days after any dose until Visit 3 - TVC

Treatment Group	Country	M/F ratio	# cases occurring after each dose	Median age/ range at diagnostic day (months)	Median Interval/ range from vaccination to onset (diagnostic day) (days)	Treatment
Total	Argentina - 1 Colombia - 2 Honduras - 1 Mexico - 5 Panama - 1 Venezuela - 2	6:6	Dose 1 - 7 Dose 2 - 5	4/ 2-7	53.5/ 31-107	Surgery - 10 Hydrostatic enema - 2
Rotarix	Colombia - 1 Mexico - 1 Panama - 1	2:1	Dose 1 - 2 Dose 2 - 1	4/ 2-7	54/ 31-145	Surgery - 3 Hydrostatic enema - 0
Placebo	Argentina - 1 Colombia - 1 Honduras - 1 Mexico - 4 Venezuela - 2	4:5	Dose 1 - 5 Dose 2 - 4	4/ 3-6	53 /35-107	Surgery - 7 Hydrostatic enema - 2

Source: Study Report Body Rota-023 Visit 1-3, pg 86

Test results of biological specimens obtained from the 12 IS cases showed that shigella was detected in 9 of the cases (Rotarix-2, placebo-7). Detection of at least 2 pathogens (including RV vaccine and wild-type strains) was observed in 9 cases (Rotarix-2, placebo-7). Vaccine virus was detected in 1 Rotarix recipient, while G1 wild type RV was found in 2 placebo cases (both in stool and bowel biopsy specimens).

Of note, two other IS cases occurred that were not included in the IS analyses. The first case, a Rotarix recipient who was diagnosed on Day 22 post-Dose 2, was adjudicated by the CEC as a probable case due to a normal ultrasound and clinical improvement without treatment. Clinical signs and symptoms of this patient consisted of vomiting, bloody mucous stools, abdominal pain, irritability, and decreased bowel sounds; stool cultures were negative for shigella, salmonella, E. coli, and campylobacter.

The second case, also a Rotarix recipient, was adjudicated by the CEC as a definite IS case, but was not included in the analysis because the date of diagnosis occurred after Visit 3. Symptom onset occurred 56 days after Dose 2, with the diagnosis of IS made 2 days later.

Secondary Safety Endpoint - All SAEs (Dose 1 to Visit 3)

The number of subjects who experienced at least 1 SAE from Dose 1 to Visit 3 was significantly less in the Rotarix group compared to the placebo group (table below). The reported SAEs were coded to 24 MedDRA SOCs and 265 PTs. None of the SAE PTs were reported at a rate ≥ 1% in the Rotarix group.

Number of total subjects with SAEs from Dose 1 to Visit 3 classified by MedDRA SOCs and PTs – TVC

	Rotarix N = 31673				Placebo N = 31552				Risk Difference (Rotarix - Placebo)			
			95% CI*				95% CI*			95% CI**		
Primary SOC (CODE) / Selected PTs	n	Per 10000	LL	UL	n	Per 10000	LL	UL	Per 10000	LL	UL	P-Value

N = number of subjects in the considered cohort; n = number of subjects reporting at least once the specified symptom
Per 10 000 = number of subjects per 10 000 reporting at least once the specified symptom
At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA SOC
(Source: Study Report Body Rota-023 Visit 1-3, pg 89, 90, 91)

Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained the following figures in the table below, with differences from the applicant highlighted in bold italics. Because the numbers and percentages did not differ substantially from those provided by the applicant, and the software programs used in the analyses of AEs may elicit some minor differences between CBER and the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

	Rotarix N = 31673	**Placebo N = 31552**
Primary SOC (CODE) / Selected PTs	**n (%)**	**n (%)**
At least one SAE	***933 (2.95)***	***1049 (3.32)***
SOC: Congenital, familial and genetic disorders (10010331)	***9 (0.03)***	***8 (0.03)***
SOC: Gastrointestinal disorders (10017947)	***48 (0.15)***	***76 (0.24)***
PT: Diarrhoea (10012735)	***16 (0.05)***	37 (0.12)
SOC: General disorders and administration site conditions (10018065)	20 (0.06)	***22 (0.07)***
SOC: Infections and infestations (10021881)	***747 (2.36)***	***863 (2.74)***
PT: Gastroenteritis (10017888)	***134 (0.42)***	***227 (0.72)***
SOC: Injury, poisoning and procedural complications (10022117)	***29 (0.09)***	32 (0.10)
SOC: Metabolism and nutrition disorders (10027433)	23 (0.07)	***51 (0.16)***
SOC: Respiratory, thoracic and mediastinal disorders (10038738)	***97 (0.31)***	***87 (0.28)***
SOC: Skin and subcutaneous tissue disorders (10040785)	12 (0.04)	***3 (0.01)***

Primary SOCs g*astrointestinal disorders, infections and infestations, metabolism and nutrition,* and *vascular disorders* were reported significantly less in the Rotarix group compared to the placebo group. PTs *diarrhea, vomiting*, *gastroenteritis* and *dehydration* were also reported significantly less in the Rotarix group than the placebo group. These favorable SOCs were primary driven by these PTs (also *hypovolemic shock* which did not reach statistical significance), reflecting efficacy of Rotarix against GE-related symptoms and complications.

The Primary SOC *Skin and subcutaneous tissue disorders* was reported significantly more in the Rotarix group compared to the placebo group. This imbalance was driven by the PT *Urticaria*, which was also significantly higher in the Rotarix group (5 subjects) compared to placebo group (0 subjects). Four of the 5 subjects developed urticaria between 15 and 82 days after Dose 1; 1 subject developed urticaria after intake of an unspecified medication, while 2 developed urticaria within 4 and 16 days after receiving DTPw vaccination. Moreover, these 4 subjects did not develop urticaria after receiving Dose 2. The remaining fifth subject had onset 4 days after Dose 2. All 5 were judged as not being related to vaccination, and made complete recoveries. Based on these individual case reviews and post-hoc analyses, the applicant concluded that the observed imbalance was likely a chance finding and not clinical relevant.

The PT *Convulsions* was also reported significantly more in the Rotarix group (16) compared to the control group (6), despite no imbalance for the SOC *Nervous system disorders*. Upon further review, the applicant found that SAEs coded to multiple PTs related to convulsive disorders were reported for different subjects and in some instances the same subject. After the convulsion disorder-related PT terms *Convulsions, Epilepsy, Grand mal convulsion, Status epilepticus,* and *Tonic convulsion* were combined, no statistical difference between groups was found (Rotarix – 20 subjects, placebo – 12 subjects; p=0.219). There was also no evidence of imbalances by age, gender, and country. All episodes were assessed as not related to vaccination.

Among the subjects who experienced a convulsion-related episode within 31 days after any dose, 7 were Rotarix recipients (2 hours to 29 days after vaccination) and 9 were placebo recipients. Ten cases occurred after Dose 1 (Rotarix – 5, placebo – 5); 1 Rotarix recipient had previous neonatal hypoxia (and developed convulsions 2 hours after receiving Dose 1) and 2 had current conditions

(pneumonia/anemia/family history of epilepsy, hypocalcemia/hyponatremia). Six subjects had onset after Dose 2 (Rotarix – 2, placebo – 4); 1 Rotarix recipient had previous neonatal hypoxia, 2 convulsion episodes 3 and 27 days post-Dose 2, and 1 grand mal convulsion 58 days post-Dose 1, while the other Rotarix recipient (onset 6 days post-Dose 2) also had chronic malnutrition and gastroenteritis.

Among the subjects with onsets beyond 31 days after any dose until Visit 3, 14 were in Rotarix recipients (32 to 144 days after vaccination) and 3 were placebo recipients. Eleven subjects developed convulsion occurred after Dose 1 (Rotarix – 10, placebo – 1); 5 Rotarix recipients had a concurrent medical condition (anemia, Down's syndrome, cellulitis, GE plus receiving metoclopromide before convulsions). One Rotarix recipient had 2 episodes (46 and 56 days post-Dose 1). Six subjects had an episode after Dose 2 (Rotarix – 4, placebo – 2); 2 Rotarix recipients had otitis media and 2 other Rotarix recipients had previously experienced multiple episodes of convulsions.
Reviewer Note: The reviewer also explored rates of convulsion-related SAEs within the first 43 days after vaccination in each group. A significant imbalance was not observed (Rotarix – 12 [0.04%], placebo – 9 [0.03%]).
Based on these post-hoc analyses, the applicant concluded that the originally observed imbalance of PT *Convulsions* was likely a chance finding and not clinical relevant.

Results of the SAE analyses for each country were in line with the overall SAE analyses.

Reviewer Note: The reviewer explored rates of SAE bronchitis in each group. After PTs *Bronchitis* and *Bronchitis acute* were combined*,* an imbalance not favoring the Rotarix group was not observed within 31 days post-vaccination (Rotarix- 24 [0.08%], placebo - 24 [0.08%]) or within 43 days post-vaccination (Rotarix – 34 [0.11%], placebo – 30 [0.10%]).

Reviewer Note: The reviewer explored rates of non-fatal SAE pneumonia in each group. After PTs *Pneumonia*, *Bronchopneumonia*, *Pneumonia cytomegalovirus*, and *Pneumonia viral* were combined*,* imbalances were not observed within 31 days post-vaccination (Rotarix- 148 [0.48%], placebo - 154 [0.49%]) or within 43 days post-vaccination (Rotarix – 193 [0.61%], placebo – 194 [0.61%]).

Reviewer Note: The reviewer explored rates of GI bleeding not related to IS in each group. After PTs *Diarrhoea haemorrhagic*, *Gastritis haemorrhagic*, *and Upper gastrointestinal haemorrhage* were combined*,* 4 Rotarix recipients compared to 0 placebo recipients reported at least one of these PTs (*Diarrhoea haemorrhagic*: Rotarix – 2, placebo – 0). Of the 4 subjects, 3 were in the analysis dataset provided by the applicant; all 3 had onset of illness within 31 days post-vaccination (7 days, 20 days).

Secondary Safety Endpoint - SAEs leading to hospitalization (Dose 1 to Visit 3)
Results from a post-hoc analysis demonstrated that the number subjects with SAEs leading to hospitalization from Dose 1 to Visit 3 were significantly less in the Rotarix group than the placebo group (886 vs 1003, p=0.005). When hospitalized GE-related events were excluded from SOC *Infections and infestations*, there was no major imbalance in the number of subjects hospitalized for SAEs between groups (Rotarix -627, placebo – 654).
Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained totals of 888 Rotarix and 1005 placebo recipients who were hospitalized for SAEs from Dose 1 to Visit 3. In addition, although the applicant did not specifically state which GE-related events were excluded from SOC *Infections and infestations*, the reviewer attempted to obtain numbers for hospitalized non-GE-related events by excluding all PTs with "gastroenteritis," "dysentery," "amoebiasis," "ascariasis," "enterocolitis," "gastrointestinal infection," "giardiasis," and "parasitic infection intestinal." By excluding these PTs, the reviewer obtained a total of 627 Rotarix and 656 placebo recipients who were hospitalized for non-GE-related SAEs during this interval. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

Secondary Safety Endpoint - SAEs related to vaccination (Dose 1 to Visit 3)
The number of subjects that reported at least 1 SAE that was assessed as related to vaccination from Dose 1 to Visit 3 were not significantly different among the groups (Rotarix – 21, placebo – 14, p=0.241). These SAEs included 9 definite IS cases (Rotarix-5, placebo-4); 1 case in the Rotarix group was diagnosed beyond 31 days after vaccination. There were also no significant differences between groups when subject numbers were assessed by SOC and PT categories. Of the SAEs in the Rotarix group not including IS, 9 of 15 were classified under PT *Gastroenteritis* (onset 0-34 days after previous dose).
Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained totals of 20 Rotarix and 14 placebo recipients who reported at least 1 vaccine-related SAE during this interval. The reviewer obtained a total of 16 non-IS vaccine-related SAEs reported in the Rotarix group, the same figure reported by the applicant.

Secondary Safety Endpoint - Deaths
A total of 99 deaths (Rotarix – 56, placebo – 43; p=0.198; table below) occurred up to September 10, 2004 (approximately 1.5 months after the last Visit 3); 84 had symptom onset before Visit 3 (Rotarix – 51, placebo 33; p=0.051) and 83 died before Visit 3. One death had symptom onset before Dose 1 of Rotarix. Ninety of the 99 deaths had primary cause of deaths assigned with definite/possible evidence (Rotarix – 52, placebo – 38; p=0.145). None of the fatalities were assessed as related to vaccination.

Number of deaths according to different time windows for the date of death - TVC

Time window	HRV					Placebo					Risk Difference (HRV minus Placebo)			P-value
				95% CI*					95% CI*			95% CI**		
	n	N	Per 10000	LL	UL	n	N	Per 10000	LL	UL	Per 10000	LL	UL	
All	56#	31673	17.68	13.36	22.95	43	31552	13.63	9.86	18.35	4.05	-2.15	10.4	0.198
All before visit 3	51#	31673	16.10	11.99	21.17	32	31552	10.14	6.94	14.31	5.96	0.32	11.86	0.039
Post Dose 1														
All	44#	31673	13.89	10.10	18.64	26	31552	8.24	5.38	12.07	5.65	0.48	11.11	0.033
Within 31 days	22#	31673	6.95	4.35	10.51	11	31552	3.49	1.74	6.24	3.46	-0.11	7.39	0.057
Post Dose 2														
All	7	29616	2.36	0.95	4.87	6	29465	2.04	0.75	4.43	0.33	-2.36	3.08	0.789
Within 31	2	29616	0.68	0.08	2.44	5	29465	1.70	0.55	3.96	-1.02	-3.37	0.95	0.254

N = number of subjects in the considered cohort; n = number of subjects who died within the specified time window
Per 10 000 = number of subjects per 10 000 with death date within the specified time window
#For 1 HRV subject the onset of the primary CoD was before vaccination (Dose 1).
(Source: Study Report Body Rota-023 Visit 1-3, pg 287)

Reviewer Note: The reviewer obtained the same “n” for each category in the table above. However, subcategory “All” under Post Dose 1 and Post Dose 2 should be “All before visit 3.”

Among the 99 deaths, there was no significant difference between groups in the number of subjects classified under each MedDRA SOC. Of the PT terms, *Pneumonia* was reported significantly more in the Rotarix group than the placebo group (14 vs 5, p=0.04). Of these 19 PT *Pneumonia* deaths, 7 (Rotarix-5, placebo-2) had symptom onset within 31 days following study dose. Upon further review, it was noted that 2 other pneumonia-related PTs, *Bronchopneumonia* and *Pneumonia cytomegalovirus*, were reported under the same SOC *Infections and infestations.* Because the etiologic pathogen was not recovered in all pneumonia-related deaths, the applicant conducted an ad-hoc analysis by pooling these 3 PTs. When pooled, the number of deaths due to pneumonia disease was not significantly different between groups (Rotarix – 16, placebo – 6; p=0.054). Of the pooled pneumonia deaths with symptom onset occurring within 31 days after vaccination/placebo, 7 were in Rotarix (4-25 days post-vaccination) and 3 in placebo (2-25 days post-dose) recipients; 6 of 7 Rotarix and 2 of 3 placebo deaths were reported after Dose 1. A temporal association was not clearly established when analyzing pneumonia onset by week for each group (Rotarix/placebo): week 1 – 2/2, week 2 – 2/0, week 3 - 2/0, week 4 – 1/1. Of the pooled pneumonia deaths with

symptom onset occurring beyond 31 days after vaccination/placebo, 9 were in Rotarix (31-199 days post-vaccination) and 3 in placebo (46-83 days post-dose) recipients; 5/9 Rotarix and 2/3 placebo deaths were reported after Dose 1. None of the 22 pooled pneumonia deaths were assessed as related to vaccination/placebo.
Reviewer Note: As discussed in the Executive Summary (section 3), the applicant appeared to incorrectly calculate the p-value (p=0.054) for the difference in pneumonia-related PTs between treatment groups. The CBER statistical reviewer obtained an exact p-value of 0.0345 and 0.0354 using two methodologies. Also, of the pooled pneumonia deaths with symptom onset occurring within 43 days after vaccination/placebo, 8 were in Rotarix and 3 in placebo recipients.

Additional exploratory analyses of SAE hospitalizations coded under the pooled pneumonia category based on all pneumonia-containing PTs (within SOC *Infections and infestations*) showed that there were no significant differences between groups in the number of subjects hospitalized for pneumonia from Dose 1 to Visit 3 (Rotarix-277, placebo-273; p=0.90). Significant differences when stratified by dose (post-Dose 1 vs post-Dose 2) and timing of hospitalization (within 31 days vs beyond 31 days after each dose) were also not observed.
Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained totals of 278 Rotarix and 274 placebo recipients who reported at least 1 PT pneumonia-related hospitalization during this interval. Other discrepancies included totals for post Dose 2 (applicant: Rotarix-92, placebo-96; reviewer: Rotarix-92, placebo-97), post-Dose 2 within 31 days (applicant: Rotarix-49, placebo-56; reviewer: Rotarix-49, placebo-57). Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

In addition, there were no significant differences in the number of subjects with pooled pneumonia SAEs from all pneumonia-containing PTs (within SOC *Infections and infestations*) between groups when stratified by dose (post-Dose 1 vs post-Dose 2) and timing of onset (within 31 days vs beyond 31 days after each dose).
Reviewer Note: Discrepancies in numbers of Rotarix/placebo subjects for pneumonia-related PT SAEs between the applicant's and reviewer's calculations are noted below. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

Dose 1 to Visit 3	Applicant: Rotarix-280, placebo-277
	Reviewer: Rotarix-284, placebo-280
Within 31 days post-Dose 2	Applicant: Rotarix-49, placebo-57
	Reviewer: Rotarix-49, placebo-58
Beyond 31 days post-Dose 2	Applicant: Rotarix-43, placebo-41
	Reviewer: Rotarix-45, placebo-43

Based on these individual reviews and post-hoc analyses, the applicant concluded that the originally observed imbalance of PT *Pneumonia* was likely not clinical relevant due to the lack of significant difference between groups when pneumonia-related PTs were pooled, the absence of a clear temporal association between Rotarix and pneumonia, and lack of significant differences between groups for pneumonia hospitalizations and non-fatal pneumonia SAEs.

Secondary Safety Endpoint - SAEs and non-serious AEs leading to drop-out

There were no significant differences between treatment groups in the frequencies of subjects who dropped out at Visit 3 due to SAEs or non-SAEs. There were also no significant differences in the frequencies of SAEs or non-SAEs leading to drop-out, among SOCs and PTs.

Visits 1-3	**Rotarix N = 31,673**				**Placebo N = 31,552**				**Risk Difference (Rotarix – Placebo)**			
			95% CI				**95% CI**			**95% CI**		
	n	**n/10,000**	**LL**	**UL**	**n**	**n/10,000**	**LL**	**UL**	**n/10,000**	**LL**	**UL**	**p-value**
SAE dropout	61	19.3	14.7	24.7	48	15.2	11.2	20.2	4.05	-2.46	10.69	0.220
Non-SAE dropout	57	18.0	13.6	23.3	56	17.7	13.4	23.0	0.25	-6.45	6.94	0.941

Source: Study Report Body Rota-023 Visit 1-3, pgs 72 & 74

Additional analyses

The applicant performed analyses of deaths by age and gender at dose 1. The trend toward higher mortality in Rotarix recipients was seen primarily in female infants who received Dose 1 at 57-84 days of age (Rotarix – 10, placebo – 2; p=0.023). The range of symptom onset interval from vaccination in the Rotarix group was 13-199 days. However, for this particular stratum, there were no significant differences between Rotarix and placebo groups in deaths with symptom onset that occurred within 31 days of Dose 1 (2 vs 0, p=0.161). Deaths in this stratum were largely due to non-enteric infectious causes, especially pneumonia (Rotarix-6/10). No differences by country were observed. Hospitalizations were also significantly less in females Rotarix than placebo recipients (360 vs 419), as well as 57-84 day-old (at Dose 1) Rotarix recipients compared to the same aged placebo recipients (282 vs 331).
Reviewer Note: The reviewer obtained the following figures below which differed from those provided by the applicant. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the applicant's results.
Deaths

Female, 57-84 days, Dose 1-within 31 days	Rotarix-3, placebo-0

Hospitalizations

Female, hospitalization	Rotarix-361, placebo-420
Hospitalization, 57-84 days at Dose 1	Rotarix-283, placebo-464

Follow-up safety – TVC, Year 1 efficacy period

The TVC for safety (N=18,274) was used for the safety analysis after Visit 3 up to Visit 4. The TVC for efficacy subset (N=20,169) was used for the IS analysis from Dose 1 to Visit 4.

SAEs – After Visit 3 up to Visit 4
The number of subjects who experienced at least 1 SAE after Visit 3 up to Visit 4 was significantly less in the Rotarix group compared to the placebo group (468 vs 521; p=0.038). The reported SAEs were coded to 19 different MedDRA SOCs and 164 PTs were analyzed for potential imbalances between groups. All SAEs during this interval were assessed as not related to vaccination. The only PTs reported at ≥ 1% in the Rotarix group were gastroenteritis (1.3%) and pneumonia (1.1%).
Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained totals of 473 Rotarix subjects and 523 placebo subjects with at least 1 SAE from Visit 3 up to Visit 4, and SAEs coded to 165 PTs. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the applicant's analysis.

Among the SOCs, a significant risk difference between groups was only observed for the SOC *Infections and infestations* (Rotarix-352 subjects, placebo-444 subjects), in which the SAE risk in the Rotarix group minus the placebo group was -110 per 10,000 subjects (p=0.000). This difference was driven by the SAE risk difference under PT *Gastroenteritis* which favored the Rotarix group (126.7/10,000 vs 214.6/10,000, p<0.001).
Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained totals of 356 Rotarix subjects and 445 placebo subjects who reported at least 1 SAE in the SOC *Infections and infestations.* Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the applicant's results.

Among the other PTs, a significant risk difference was observed for PT *Pyrexia* (Rotarix- 8.7/10,000 vs 1.1/10,000, p=0.021). Individual review of these 9 cases by the applicant physician provided no evidence that this difference was of clinical relevance; all occurred between 55 and 188 days post-Dose 2. No significant differences were observed for pneumonia-related, convulsion-related, or skin-related PTs.

Four subjects who did not return for Visits 3 and 4 reported SAEs beyond their last contact; these subjects were excluded from safety analyses.

Deaths – After Visit 3 up to Visit 4
Among subjects followed for efficacy, 4 deaths were reported beyond the September 10, 2004 lock date (the date up until which time reported deaths were included in the report of the final safety data for

Visits 1 to 3), two in each group. The deaths in Rotarix recipients were coded to the PTs *Postoperative infection* and *Road traffic accident*. Three of the subjects died after Visit 4. All deaths were assessed as not related to vaccination.
Reviewer Note: The reviewer noted that one of the three cases that died after Visit 4 was included in the Visit 3-Visit 4 category, while the other two cases were included in the Visit 4- Visit 6 category. In addition, the reviewer noted that one SAE (PT *Congestive cardiomyopathy*) in a placebo recipient who died after Visit 4 was included in the Visit 3-Visit 4 category.

Fourteen of the 15 deaths leading to drop-out at Visit 4 were reported before the September 10, 2004 lock date, and were therefore not described in this section.

SAEs and non-serious AEs leading to drop-out – After Visit 3 up to Visit 4
There were no significant differences between treatment groups in the frequencies of non-serious AEs in the TVC for safety who dropped out after Visit 3 up to Visit 4. Only one subject (placebo) withdrew due to a non-serious AE classified by MedDRA (PT – nasopharyngitis). There were also no significant differences in the number of SAEs during this time period between the groups (table below). Of the 16 subjects who dropped out due to SAEs, 15 were fatal. All fatal cases were assessed as not related to vaccination. The one non-fatal case reported acute lymphocytic leukemia that was also not related to vaccination.

After Visit 3-Visit 4	Rotarix N = 9,233				Placebo N = 9,041				Risk Difference (Rotarix – Placebo)			
			95% CI				95% CI			95% CI		
	n	n/10,000	LL	UL	n	n/10,000	LL	UL	n/10,000	LL	UL	p-value
SAE dropout	6	6.5	2.4	14.1	10	11.1	5.3	20.3	-4.56	-14.6	4.49	0.297
Non-SAE dropout	0	0.0	0.0	4.0	1	1.1	0.0	6.2	-1.11	-6.26	3.05	0.312

Source: Study Report Body Rota-023 Year 1, pgs 119-122

Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained 9 placebo subjects with at least 1 SAE resulting in dropout. The reviewer was not able to capture 1 placebo subject (PT *Acute lymphocytic leukaemia*) because this SAE occurred 81 days post-Dose 2 and therefore occurred before Visit 3. Also, the reviewer was not able to capture a reported death of a Rotarix subject (PT *Ependymoma*) because the onset of this SAE was on Day 0 post-Dose 1, therefore occurring before Visit 3.

Definite IS – After Visit 3 up to Visit 4 (TVC for safety)
During this interval, three Rotarix recipients and 4 placebo recipients were diagnosed with definite IS; the risk difference was not statistically significant (see table below). All IS cases were assessed as not related to vaccination.

	Study group						Risk Difference (Rotarix – Placebo)			Relative Risk (Rotarix/ Placebo)			
	Rotarix			Placebo			difference/ 10,000	95% CI		RR	95% CI		
Interval	N	n	n/ 10,000	N	n	n/ 10,000		LL	UL		LL	UL	p-value
After Visit 3 to Visit 4	9233	3	3.2	9041	4	4.4	-1.18	-8.48	5.63	0.73	0.18	2.93	0.685

(Source: Study Report Body Rota-023 Year 1, pg 101)

A summary of the seven IS cases is presented below.

Country	Gender	Age at dose 1 (Weeks)	Age at dose 2 (Weeks)	Age at diagnostic day (Months)	Previous dose	Onset day (Start date of the symptom)	Onset day (Diagnostic date)
Rotarix							
Mexico	F	7	15	5	2	68	68
Argentina	M	11	15	6	2	86	86
Mexico	F	8	17	11	2	231	231
Argentina	M	11	16	7	2	126	127

Placebo							
Honduras	M	6	11	6	2	127	128
Mexico	M	11	15	10	2	222	222
Honduras	M	12	D2 NA	10	1	224	227

D2 NA = Dose 2 not administered
(Source: Study Report Body Rota-023 Year 1, pg 102)

Test results of biological specimens obtained from the 7 IS cases showed that shigella was detected in 3 cases (Rotarix-1, placebo-2) and adenovirus in 3 cases (Rotarix-2, placebo-1). Detection of at least 2 pathogens (including RV vaccine and wild-type strains) was observed in 4 cases (Rotarix-2, placebo-2). G1 wild type RV was detected in stool in 1 Rotarix and 1 placebo recipient each.

Definite IS – Dose 1 to Visit 4 (TVC for efficacy subset)
During this interval, there was no increased risk of definite IS in the Rotarix group compared to the placebo group.

	Study group						**Risk Difference (Rotarix – Placebo)**			**Relative Risk (Rotarix/ Placebo)**			
	Rotarix			**Placebo**			**diff/ 10,000**	**95% CI**		**RR**	**95% CI**		
Interval	**N**	**n**	**n/ 10,000**	**N**	**n**	**n/ 10,000**		**LL**	**UL**		**LL**	**UL**	**p-value**
Dose 1 to Visit 4	10,159	4	3.9	10,010	14	14.0	-10.05	-19.95	-2.02	0.28	0.10	0.81	0.017

(Source: Study Report Body Rota-023 Year 1, pg 101)
Follow-up safety – TVC, Year 2 efficacy period

The TVC for 2nd year safety (N=15,129) was used for the safety analysis after Visit 4 up to Visit 6. The TVC for 2nd year efficacy subset (N=15,183) was used for the IS analysis from Dose 1 to Visit 6.

SAEs – After Visit 4 up to Visit 6
The number of subjects who experienced at least 1 SAE after Visit 4 up to Visit 6 was significantly less in the Rotarix group compared to the placebo group (518 vs 590; p=0.010). The reported SAEs were coded to 22 different MedDRA SOCs and 196 PTs were analyzed for potential imbalances between groups. All SAEs during this interval were assessed as not related to vaccination. The only SAE PTs reported in ≥ 1% of the Rotarix group were gastroenteritis (2.1%) and pneumonia (1.3%).

Among the SOCs, a significant risk difference between groups was only observed for the SOC *Infections and infestations*, in which the SAE risk in the Rotarix group minus the placebo group was -119 per 10,000 subjects (p=0.001). This difference was driven by the SAE risk difference under PT *Gastroenteritis* (213.5/10,000 vs 336.3/10,000, p<0.001) and PT *Dengue fever* (0/10,000 vs 6.7/10,000, p=0.024), both which favored the Rotarix group. Borderline significant difference was observed for SOC *Gastrointestinal disorders* favoring the Rotarix group (risk difference= -17.8/10,000, p=0.050), although there were no significant PTs in this SOC.

Among the other PTs, a significant risk reduction favoring the Rotarix group was observed for PT *Lymphadenopathy* (Rotarix- 0/10,000 vs 5.3/10,000, p=0.043). No significant differences were observed for pneumonia-related, convulsion-related, or skin-related PTs.

Of note, PT *Kawasaki's disease* was reported in one Rotarix recipient. As described in the SAE report, the patient was a 2 year-old female from Mexico who developed fever, skin spots, irritability and seizure 19 months post-Dose 2. Her clinical course was notable for persistence of fever and seizures, and she developed respiratory failure. Aside from fever, typical clinical features of Kawasaki's disease were not described in the report.

Deaths – After Visit 4 up to Visit 6
Eleven deaths were reported during this interval (Rotarix-5, placebo-6). The deaths Rotarix recipients were coded to the PTs *Death, Aspiration/Asphyxia, Pneumonia aspiration, Gastroenteriris/Septic shock, Skull fracture/Hepatic rupture, Meningitis bacterial, Road traffic*

accident, and Congestive cardiomyopathy/Cardiac failure congestive. All deaths were assessed as not related to vaccination.

Definite IS – After Visit 4 up to Visit 6 (TVC for 2nd year safety)
No IS cases were reported during this interval.

Definite IS – Dose 1 to Visit 6 (TVC for 2nd year efficacy subset)
During this interval, there was no increased risk of definite IS in the Rotarix group compared to the placebo group.

	Study group						Risk Difference (Rotarix – Placebo)			Relative Risk (Rotarix/ Placebo)			
	Rotarix			Placebo			diff/ 10,000	95% CI		RR	95% CI		
Interval	N	n	n/ 10,000	N	n	n/ 10,000		LL	UL		LL	UL	p-value
Dose 1 to Visit 4	7669	4	5.2	7514	11	14.6	-9.4	-21.6	0.6	0.36	0.12	1.06	0.065

Source: Study Report Body Rota-023 Annex Year 2, pg 86

SAEs and non-serious AEs leading to drop-out – After Visit 4 up to Visit 6
There were no significant differences between treatment groups in the frequencies of non-serious AEs in the TVC for safety who dropped out after Visit 4 up to Visit 6. Among the non-serious AEs, 1 Rotarix recipient reported PT *Asthma*, while 1 placebo recipient each reported PT *Tonsillitis* and PT *Varicella*. There were also no significant differences in the number of SAEs during this interval by SOC and PTs. Of the 13 subjects who dropped out due to SAEs, 11 were fatal (Rotarix-5, placebo-6). All fatalities were assessed as not related to vaccination.

After Visit 4-Visit 6	Rotarix N = 7636				Placebo N = 7493				Risk Difference (Rotarix – Placebo)			
			95% CI				95% CI			95% CI		
	n	n/10,000	LL	UL	n	n/10,000	LL	UL	n/10,000	LL	UL	p-value
SAE dropout	6	7.9	2.9	17.1	7	9.3	3.8	19.2	-1.5	-12.3	8.9	0.755
Non-SAE dropout	1	1.3	0.0	7.3	2	2.7	0.3	9.6	-1.4	-8.5	5.0	0.533

Source: Study Report Body Rota-023 Annex Year 2, pg 99

Individual report forms reviewed

Individual International Event Report (i.e. SAE) report forms were reviewed for all IS cases, all (i.e. one) Kawasaki's Disease cases, and all vaccine-related SAEs and deaths in the Rotarix group.

8.1.1.3 Comments & Conclusions

In Rota-023, two doses of Rotarix at a potency of $10^{6.5}$ $CCID_{50}$ per dose, administered to children 6 to 13 weeks of age at 1-month or 2-month intervals, were efficacious (>84%) against severe RV GE during the period from 2 weeks post-Dose 2 until 1 year of age. Efficacy results were consistent using either of two case definitions for severe RV GE. Rotarix was also efficacious against G1 and G9 wild-type strains (>90%). When all non-G1 types were pooled together, VE was over >75%. Efficacy was also high from Dose 1 to 1 year of age (>80%), and remained high during the second year of follow-up (79%).

An increased risk in definite IS was not seen within 31 days after any dose, nor during the first and second year efficacy follow-up periods. Statistically significant differences in frequencies of SAEs not favoring the Rotarix group were observed for non-fatal PT *Convulsions* and fatal PT *Pneumonia*. When five convulsion-related PTs were pooled, a statistically significant difference was not observed. When three pneumonia-related PTs were combined, the increase in frequency of death in the Rotarix group remained statistically significant. However, less than half of the pneumonia-related deaths had symptom onset within 31 days post-vaccination.

The validity of the results was strengthened by the double-blinded, placebo-controlled, multi-center study design. Efficacy, safety, and immunogenicity endpoints, case definitions, and study cohorts were clearly defined and appropriate. There were no significant efficacy or safety differences by country, although population sizes were limited in some countries. Overall, the study was well-conducted without major sources of biases. Data quality was acceptable, and appropriate data analyses were conducted protocol and amendments. Protocol deviations were minor, occurred infrequently, and did not lead to any SAEs. Subject dropouts and missing data were handled appropriately and according to protocol.

The applicant stated that the proposed indication for Rotarix is the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, G9). Results from Rota-023 support the use of Rotarix in the prevention of severe RV GE only. Efficacy data supports the use of Rotarix in the prevention of severe RV GE caused by G1 types; VE was statistically significant for Year 1, Year 2, and the combined efficacy periods. Efficacy data also supports the use of Rotarix in the prevention of severe RV GE caused by non-G1 types when pooled together. However, when VE was assessed for each type individually, Rotarix demonstrated statistically significant efficacy against G9 types during all three study periods. Statistically significant efficacy against G3 types was demonstrated during Year 1 and combined efficacy periods. However, the lower limits of the 95% CIs were very low. Efficacy against G4 types was not assessed during Year 1 due to limited numbers of severe G4 RV GE; efficacy estimates during Year 2 and the combined efficacy periods were 63.1% (LL of the 95% CI: 0.7) and 61.8% (LL of the 95% CI: 4.1%). Statistically significant efficacy was not demonstrated against G2 types for any study period.

8.1.2 Rota-036

8.1.2.1 Protocol 102247/036 (rota-036): A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines

8.1.2.1.1 Objective/Rationale

Primary Objectives

1. To determine the efficacy of two doses of Rotarix given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the 1st efficacy follow-up period (i.e. 2 weeks post-Dose 2 to Visit 5)

Secondary Efficacy Objectives – 1st efficacy follow-up period

1. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild RV strains
2. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any and severe RV GE due to wild G1 RV strains
3. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any and severe RV GE due to wild non-G1 RV strains
4. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against hospitalization for RV GE due to wild RV strains
5. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE due to wild RV strains
6. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any and severe wild-type RV GE from Dose 1 to Visit 5
7. To assess VE of 2 doses of Rotarix against any and severe RV GE during the 1st efficacy follow-up period in subjects who completed the 2-dose course before the RV epidemic season vs those who were vaccination during the RV epidemic season

Secondary Efficacy Objectives – 2nd efficacy follow-up period (i.e. Day after Visit 5 to Visit 7)

1. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild RV strains
2. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild G1 RV strains
3. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild non-G1 RV strains
4. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against hospitalization for RV GE due to wild RV strains
5. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE due to wild RV strains

Secondary Efficacy Objectives – Combined efficacy follow-up period

1. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild RV strains
2. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild G1 RV strains
3. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against severe RV GE due to wild non-G1 RV strains
4. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against hospitalization for RV GE due to wild RV strains
5. To assess VE of 2 doses of Rotarix given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE due to wild RV strains

Secondary Immunogenicity Objectives (immunogenicity-reactogenicity subset)

1. To assess the immunogenicity of Rotarix in terms of serum anti-RV IGA antibody concentrations at 1 to 2 months after Dose 2
2. To explore the effect of Rotarix on the immune response to all antigens contained in each of the co-administered childhood vaccines

Secondary Safety Objectives

1. In the immunogenicity-reactogenicity subset, to assess the reactogenicity of 2 doses of Rotarix given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms
2. In all subjects, to assess the safety of 2 doses of Rotarix given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days post-dose) and SAEs during the entire study period

8.1.2.1.2 Design Overview

Rota-036 was a double-blind, randomized, placebo-controlled, multi-country and multi-center study. Healthy subjects 6 to 14 weeks of age at the time of Dose 1 were randomized to receive 2 doses of either Rotarix ($10^{6.5}$ $CCID_{50}$) or placebo (2:1 ratio) on a 0, 1-month or 0, 2-month schedule. Subjects were randomized and administered Dose 1 of Rotarix or placebo on the same day (i.e. Day 0). The intended study duration was 22 to 24 months.

A total enrollment of 3990 subjects was targeted, of which 2490 were to have come from Finland, with 300 subjects to have been enrolled in each of the remaining 5 countries.
For Finland, 300 subjects enrolled at specific centers comprised the immunogenicity- reactogenicity subset, while in each of the other countries, the 300 enrolled subjects were part of this subset.

Rotarix/placebo and co-administered childhood vaccines were given according to national plans of immunization in each country as follows:

- Czech Republic: 3, 4, 5 months

- Finland: 3, 5, 11-12 months (Amended June 7, 2005)
- France, Germany: 2, 3, 4 months
- Italy: 3, 5, 11 months
- Spain: 2, 4, 6 months

8.1.2.1.3 Population

Inclusion Criteria
1. Male or female 6-14 weeks (42-104 days) of age at the time of Dose 1
2. Birth weight > 2000g
3. Written informed consent obtained from parent/guardian prior to study procedures
4. Free of obvious health problems as established by medical history and clinical examination prior to entering the study

Reviewer Note: Inclusion Criteria #3 and #4 were the same as for Rota-023.

Exclusion Criteria
1. History of use of experimental rotavirus vaccine
2. Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine and ending 14 days after
3. History of diphtheria, tetanus, pertussis, Hib disease and/or hepatitis B disease; also, for subjects in Spain: history of meningococcal group C disease, for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*
4. Previous vaccination against diphtheria, tetanus, pertussis, *H. flu* type b; also, for subjects in Spain: previous vaccination against of meningococcal group C disease, for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*
5. Acute disease at the time of enrolment (presence of moderate or severe illness with/without fever)
6. Gastroenteritis within 7 days before Dose 1 (warrants deferral of vaccination)
7. Family history of congenital or hereditary immunodeficiency
8. History of any neurologic disorders or seizures
9. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening
10. Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days before Dose 1, or planned use during the study
11. Chronic administration (> 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed)
12. Any immunosuppressive or immunodeficient condition, including HIV infection
13. History of allergic disease or reaction likely to be exacerbated by any vaccine component
14. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period
15. Any clinically significant history of chronic gastrointestinal disease, including any uncorrected congenital malformation of the GI tract, IS, or other medical condition

Reviewer Note: Exclusion criteria #10-15 were also included in Rota-023.

Procedures Allowed
1. Co-administration of the following routine vaccinations was allowed: Infanrix Hexa®, Infanrix Polio Hib®, Meningitec® (or other *N. meningitidis C* vaccine) , Prevnar® (or other *S. pneumoniae* vaccine)
2. Unrestricted feeding pre- and post-vaccination

Participating Countries
1. Czech Republic, Finland, France, Germany, Italy, Spain

8.1.2.1.4 Products mandated by the protocol

Rotarix
The formulation was the same as in Rota-023. Lot RVC018A42 was used. Lots DD05A003A and DD05A003C were used for the diluent.

Placebo
The formulation was the same as in Rota-023. Lot RVC020A41PL was used. Lots DD05A003A and DD05A003C were used for the diluent.

Concomitant routine vaccines
GSK's Infanrix Hexa® (DTaP-Hib-HepB-IPV) were co-administered with each Rotarix or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, Infanrix Hexa® was co-administered with Dose 1 of Rotarix or placebo, while GSK's Infanrix Polio Hib® (DTaP-Hib-IPV) was co-administered with Dose 2 of Rotarix or placebo; Infanrix Hexa® was used for Dose 3 to complete the series.

In addition, a *N. meningitidis* C vaccine (e.g. Meningitec®) will be co-administered in Spain, and a *S. pneumoniae* vaccine (e.g. Prevnar®) will be co-administered in France and Germany.

8.1.2.1.5 Endpoints

Primary Endpoints
1. Occurrence of any wild-type RV GE during the 1st efficacy follow-up period

Secondary Efficacy Endpoints – 1st efficacy follow-up period
1. Occurrence of severe RV GE due to wild RV strains
2. Occurrence of any and severe RV GE due to wild G1 RV strains
3. Occurrence of any and severe RV GE due to wild non-G1 RV strains
4. Occurrence of hospitalizations for RV GE due to wild RV strains
5. Occurrence of any medical attention for RV GE due to wild RV strains
6. Occurrence of any and severe RV GE due to wild RV strains from Dose 1 to Visit 5
7. Occurrence of any and severe RV GE due to wild RV strains in subjects who completed the 2-dose vaccination course before the RV epidemic season
8. Occurrence of any and severe RV GE due to wild RV strains in subjects who were vaccinated during the RV epidemic season

Secondary Efficacy Endpoints – 2nd efficacy follow-up period
1. Occurrence of severe RV GE due to wild RV strains
2. Occurrence of severe RV GE due to wild G1 RV strains
3. Occurrence of severe RV GE due to wild non-G1 RV strains
4. Occurrence of hospitalizations for RV GE due to wild RV strains
5. Occurrence of any medical attention for RV GE due to wild RV strains

Secondary Efficacy Endpoints – Combined efficacy follow-up period
1. Occurrence of severe RV GE due to wild RV strains
2. Occurrence of severe RV GE due to wild G1 RV strains
3. Occurrence of severe RV GE due to wild non-G1 RV strains
4. Occurrence of hospitalizations for RV GE due to wild RV strains
5. Occurrence of any medical attention for RV GE due to wild RV strains

Secondary Immunogenicity Endpoints – subset of subjects
1. Serum RV IgA antibody concentrations expressed as GMC at Visit 1 and Visit 3
2. Seroconversion rates to anti-RV IgA antibody at Visit 3

3. Serum levels of antibodies, expressed as GMC/Ts, and seroprotection status, to all antigens contained in each of the routine childhood vaccines at Visit 3 and Visit 4 or Visit 6 (see section 8.1.2.1.6)

Secondary Safety and Reactogenicity Endpoints
1. For subset of subjects, occurrence of each type of solicited symptoms Day 0-7 post-dose
2. For all subjects, occurrence of unsolicited symptoms Day 0 - Day 30 post-dose
3. For all subjects, occurrence of SAEs throughout entire study period

Definitions
***GE*:** same as in Rota-023
Diarrhea: same as in Rota-023
RV GE: an episode of GE in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after GE symptom onset
Severe RV GE: an episode of RV GE with a Vesikari score ≥ 11 points
RV seropositivity: same as in Rota-023
RV seronegativity: same as in Rota-023
Seroconversion: same as in Rota-023
Seroprotection against routine vaccine antigens:
- Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
- Anti-tetanus antibody concentrations ≥ 0.1 IU/ml
- Anti-polio type 1, 2, and 3 antibody titers ≥ 8 each
- Anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
- Anti-HBs antibody concentrations ≥ 10 mIU/ml
- *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
- Anti-*N. meningitidis* antibody concentrations (ELISA) ≥ 0.3 mcg/ml (amended June 7, 2005)
- Antibody concentrations to *S. pneumoniae* serotypes 4, 9V, 14, 18C, 23F, 6B, 19F ≥ 0.05 mcg/ml

Seropositivity against routine vaccine antigens:
- anti-PT antibody concentrations ≥ 5 EL.U/ml
- anti-FHA antibody concentrations ≥ 5 EL.U/ml
- anti-PRN antibody concentrations ≥ 5 EL.U/ml

Summary of Significant Protocol Amendments
1. Amendment 1 – June 7, 2005
   a. Specify measurement of anti-*N. meningitidis* antibody concentrations by ELISA for subset from Spain
   b. Specify details of the reactogenicity interim analysis
   c. Implement administrative changes (update SAE contact information, study contact information, applicant information)

8.1.2.1.6 Surveillance

Follow-up visits
The table below summarizes the follow-up visits for safety/efficacy/immunogenicity.

	Visit 1 Day 0	**Visit 2 Month 1-2**	**Visit 3 Month 3-4**	**Visit 4 Month 5 (Spain only)**	**Visit 5 mid-June to end-July 2006**	**Visit 6 Month 9 (Italy only) Month 10 (Finland only)**	**Visit 7 mid-June to end-July 2006**
Rotarix (N=2660)	X	X	X	X	X	X	X
Placebo (N=1330)	X	X	X	X	X	X	X

Vaccination with Rotarix or placebo took place at Visits 1 and 2. Subjects received a physical examination at Visits 1, 2, and 3 (plus Visits 4 and 6 if requested). Prior/concomitant medications and vaccinations will be recorded at Visits 1, 2, 3, and 5 (plus Visits 4 and 6). Feeding practices will be recorded at Visits 1 and 2.

Reactogenicity diary cards were collected at Visits 2 and 3. GE diary cards were collected at Visits 2 to 7 as needed.

Pre-vaccination blood samples were obtained from a subset of subjects (approximately 1800) at Visit 1, while post-vaccination blood samples were drawn at Visit 3. For subjects in countries (Finland, Italy, Spain) where Dose 3 of the routine vaccinations did not coincide with Visit 3, an additional study visit for a 1 month post-Dose 3 blood sampling was performed if necessary as follows (amended June 7, 2005):

- Finland: Visit 6 (13 months of age)
- Italy: Visit 6 (12 months of age)
- Spain: Visit 4 (7 months of age)

GE Case Ascertainment

Active case ascertainment for any GE episodes was conducted throughout the study. From Day 7 post-Dose 1 until the end of May 2005, each parent/guardian of a subject was contacted weekly by telephone, short message service using cellular phone, an Independent Calling Center or other convenient means. From June 2005 until December 1, 2005, contact occurred bi-weekly. From December 2005 to the end of May 2006 (2^{nd} RV epidemic season), weekly contact was resumed. From June 2006 to the end of the study, bi-weekly contact was conducted.

GE Case Follow-Up

For each GE episode, a GE diary card should be completed daily by parents/guardians until the end of the GE symptoms, and returned to the investigator at the following study visit. The GE diary card allowed assessment of severe GE intensity using a 20-point (Vesikari) scale that graded duration and frequency of diarrhea and vomiting, degree of fever, rehydration and other medication. Procedures for categorizing dehydration status and handling of missing values of loose stools/vomiting episodes were the same as in Rota-023. The diary card also allowed recording of medical attention (medical provider contact/advice/visit, emergency room contact/visit, hospitalization) and behavioral symptoms (normal, less playful/irritable, lethargic/listless, seizure) and their duration.

In addition to the Vesikari scale, a 24-point Clark scoring system was used as an exploratory measure of severe RV GE. This scale assigned points according to duration/intensity of diarrhea, vomiting, and fever, and on intensity/duration of behavioral symptoms. A score of >16 points was defined as severe GE.

For each GE episode, a stool sample was collected as soon as possible after onset but not later than 7 days after illness onset. Samples were returned to the investigator on an ongoing basis.

Stool samples were tested for wild-type and vaccine RV strains using the same methods as in Rota-023.

AE/SAE Monitoring, including IS

Solicited symptoms (fever, fussiness/irritability, loss of appetite, vomiting, diarrhea, cough/runny nose) occurring from Day 0 to Day 7 after each dose were monitored in a subset of subjects using diary cards.

Unsolicited symptoms occurring from Day 0 to Day 30 after each dose were recorded for all subjects. SAEs occurring throughout the study period were recorded for all subjects.

For each solicited and unsolicited symptom, receipt of medical attention (defined as hospitalization, an emergency room visit, or a visit to or from medical personnel)

Parents/guardians of each subject were instructed to contact the investigator immediately in case of SAEs or IS during the study. SAEs were also ascertained by medical history at planned study visits and contacts. Parents/guardians were informed of the signs and symptoms of IS: severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. They were also instructed to seek medical advice at the nearest hospital in case of IS symptom onset.

Procedures for grading the intensity of unsolicited AEs/SAEs, assessing causality of AEs/SAEs to vaccination, follow-up of AEs/SAEs, and SAE reporting were the same as in Rota-023.

Occurrences of unsolicited symptoms after each Rotarix or placebo dose were coded according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Every verbatim term from safety reports was matched with an appropriate Preferred Term (PT).

IS Case Ascertainment and Follow-up

Follow-up diagnostic procedures for IS cases were similar to that in Rota-023. The diagnosis of IS was to have been documented by radiography, with documentation by untrasonography dependent on available expertise. Several biological samples were collected for all IS cases, including 1) stool samples, rectal swabs, and throat swabs for RV, enteroviruses and adenoviruses, 2) acute and convalescent serum samples, and 3) for surgical resections, any enlarged mesenteric lymph nodes and specimens from resected bowel or appendix for ----------, or ------ testing. Fresh stool samples were also tested locally for enteric pathogens.

Serology Analysis

Sera were collected from a subset of 300 subjects per study country at Visit 1 (pre-Dose 1) and Visit 3 (post-Dose 2). Anti-RV IgA antibody concentrations were measured by ELISA at GSK's central laboratory or a validated GSK-designated laboratory.

Sera were also collected Post-Dose 3 of routine vaccines for antibody measurements to 1) D, T, PT, HFA, PRN, HBs, PRP, meningococcal C, and pneumococcal capsular polysaccharide (7 serotypes) by -------- ELISA and 2) poliovirus (1, 2, 3) by ---------- test.

Other Laboratory testing

Anti-meningococcal C bactericidal activity was performed using an in-house serum test.

Forms

1. GE diary card
2. Reactogenicity diary card
3. Electronic Case Report Form (CRF)
4. SAE Report Form

Independent Data Monitoring Committee (IDMC)

An IDMC consisting of clinical experts and a biostatistician was charged with monitoring the safety aspects of the Rotarix clinical development. The IDMC conducted unblinded reviews of each SAE/IS case and each fatal case.

8.1.2.1.7 Statistical Considerations

Power Considerations - Primary Efficacy Objective

Assuming a true VE of 70% and an incidence rate of any RV GE of 10% in the placebo group during the 1st efficacy period, 2260 subjects in the Rotarix group and 1130 subjects in the placebo group, the study had 91% power to observe a LL of the VE 95% CI greater than 50%.

Power Considerations – Secondary Immunogenicity Objective

Assuming seroprotection rates of 97% for anti-diphtheria, 99% for anti-tentatus, 100% for anti-PRP, 94% for anti-HBs and 100% for antio-polio type 1,2 and 3 antibodies, and a standard deviation between 0.28 and 0.33 for anti-PT, anti-FHA and anti-PRN antibody concentrations, 160 Rotarix and 80 placebo subjects provided the following:

- at least 80% global power that all the 95% CIs on the decrease in seroprotection rates in the vaccine group compared to placebo would be below 10%
- at least 80% global power that the 95% CIs on the fold decrease in anti-PT, anti-FHA, and anti-PRN GMCs in the vaccine group vs. placebo would be below 1.5

Study Cohorts

Total vaccinated cohorts (TVCs) consisted of all subjects that were administered at least one vaccine/placebo, and underwent the following analyses:

- primary safety analysis
- secondary immunogenicity analysis for subjects with immunogenicity data (if needed)
- secondary efficacy analysis for subjects with efficacy follow-up data

The TVC for immunogenicity-reactogenicity subset included vaccinated subjects in the TVC who had planned to provide reactogenicity data and blood samples were to be collected for immunogenicity data. The immunogenicity-reactogenicity subset was used for the reactogenicity analysis and secondary immunogenicity analysis.

The ATP safety (reactogenicity) cohort consisted of subjects who 1) received at least 1 dose of vaccine/placebo, 2) did not have their randomization codes broken, and 3) did not receive a vaccine forbidden by or not specified in the protocol. The ATP safety cohort was to be performed if needed.

The ATP efficacy cohort consisted of all subjects from the ATP safety cohort who 1) received 2 doses of vaccine/placebo, 3) entered into efficacy follow-up period (1^{st} period, 2^{nd} period, combined period – had follow-up beyond 2 weeks post-Dose 2) 4) did not have their randomization codes broken before the end of Year 1 efficacy follow-up, and 5) did not receive a vaccine forbidden by or not specified in the protocol, and 6) did not have rotavirus other than vaccine strain in GE stool samples collected between the Day 0 (Dose 1) and 2 weeks post-Dose 2. The ATP efficacy cohort was used for the primary efficacy analysis, while the TVC was used for the secondary efficacy analysis. The ATP cohort for efficacy during the 1^{st} efficacy period was also used to calculate efficacy during the combined period.

Criteria for the ATP immunogenicity cohort were identical to that of Rota-023. The ATP immunogenicity cohort was used for the primary immunogenicity analysis.

Final Analyses

Final analyses for efficacy, safety and immunogenicity were performed after subjects completed Visit 5. Access to individual treatment decode was strictly controlled until the end of the 2^{nd} efficacy follow-up period.

The following analyses were performed:

1. Demographics: age and height/weight (mean, range, SD per group), race and gender, summary of feeding criteria on vaccination days, number of siblings/subject, day care attendance, by group; distribution of enrolled subjects among study centers as a whole and by group; length of intervals between specific time points; drop-outs at Visit 5, by reason
2. Efficacy – 1^{st} efficacy follow-up period:
    a. VE against any and severe RV GE due to wild-type RV strains
    b. VE against any and severe RV GE due to wild-type G1 RV strains
    c. VE against any and severe RV GE due to wild-type non-G1 RV strains
    d. VE against hospitalization for RV GE due to wild-type RV strains
    e. VE against any medical attention for RV GE due to wild-type RV strains
    f. VE against any and severe wild-type RV GE from Dose 1 to Visit 5
    g. VE against any and severe RV GE due to wild-type RV strains for subjects who completed the 2-dose vaccination course before the RV epidemic season
    h. VE against any and severe RV GE due to wild-type RV strains for subjects vaccinated during the RV epidemic season

VE against any RV GE, any G1 RV GE, and any non-G1 RV GE during the 1st efficacy follow-up period was also estimated by the Cox proportional-hazard model.

For the 2nd efficacy and combined follow-up periods, VE against severe RV GE, severe RV GE due to G1 serotypes, severe RV GE due to non-G1 serotypes, hospitalization due to RV GE and any medical attention for RV GE will be calculated.

The following additional analyses will be performed:
- VE by country
- VE against any RV GE during the 2nd efficacy period
- VE against severe GE
- VE from Dose 1 until 2 weeks post-Dose 2
- VE against hospitalization due to GE of any etiology
- VE against severe RV GE using alternative scoring systems other than the Vesikari system
- Assessment of risk factors of RV infection (age of child at first RV infection, breastfeeding, number of siblings and attendance at day care)

For all VE analyses, a GE episode without a stool sample or available result was not considered as a RV GE episode.

3. Immunogenicity (for each country and pooled countries, at each time point):
   a. Seropositivity/seroprotection/seroconversion rates and 95% CI
   b. GMCs/GMTs and 95% CIs, by group

The asymptotic standardized 95% CI for difference in seroconversion percentages between the groups at Visit 3 will be computed. Also, the difference in immune responses to childhood vaccines after Dose 2 of the primary series will be evaluated by the asymptotic standardized 2-sided 95% CI (for difference in seropositivity and seroprotection rates between groups) and the 2-sided 95% CI (for the ratio of GMCs or GMTs between groups)

Immunogenicity analyses excluded subjects with missing or non-evaluable measurements. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

4. Safety
   a. Subset of subjects- Solicited follow-up period
      - Overall incidence of any AEs (solicited and unsolicited), by group, by dose, for overall doses, by subject
      - Incidence of each solicited symptom, by group, over the follow-up period, after each dose, for all doses, by subject; same calculations for Grade 3 and vaccine-related symptoms
      - Increase in incidence of specific symptoms in Rotarix vs. placebo groups
      - Summary of reactogenicity by country
   b. All subjects
      - Signs and symptoms coded according to MedDRA; every verbatim term matched with an appropriate PT
      - % of subjects with unsolicited symptoms within 31 days, by group, by SOC and PT; similar tabulations for vaccine-related unsolicited symptoms
      - Summary of SAEs by group

Subjects with no symptoms documented were considered as subjects without symptoms.

<u>Interim Analyses</u>
An interim analysis on reactogenicity and immunogenicity was performed with available data at Visit 3 (data lock point: June 20, 2005) from the Italy and Finland subsets only. The analysis presented a descriptive summary of reactogenicity data on solicited and unsolicited symptoms, immunogenicity for

the study vaccine, and immunogenicity data for co-administered childhood vaccines. To maintain study blinding for the study applicant, subjects families and investigators, the analysis was performed by the independent data center supporting the IDMC. No study report was written, and access to the results was strictly controlled.

Additional analyses/changes
The following additions or deletions to the final protocol and reporting/analysis plan were made:

- VE in subjects who completed 2 doses before the RV epidemic season versus those vaccinated during the RV epidemic season not performed because 90.2% of subjects were vaccinated during the RV epidemic season
- Interim analysis performed on TVC for immunogenicity/reactogenicity subsets in Finland and Italy to calculate GMCs/GMTs and seropositivity/seroprotection rates for antibodies to co-administered childhood vaccine antigens post-Dose 3
- Post-hoc descriptive analysis performed to evaluate post-Dose 3 immunogenicity of co-administered childhood vaccine antigens for Center 7715 and for the German cohort excluding Center 7715; only subjects receiving 3 doses of childhood vaccinations up to 21 days before blood sampling were included
- % of subjects with ≥ one SAE from Dose 1 summarized by group, for pooled countries
- VE on the TVC calculated for the period from Dose 1 to Visit 7

8.1.2.2 Results, by Trial (Objective information)

Study initiation date: September 8, 2004
Date of last Visit 5: September 7, 2005
Date of study completion: August 10, 2006
Date of data lock point for post-Dose 3
immunogenicity of childhood vaccinations - Finland: February 15, 2006
Date of data lock point for post-Dose 3
immunogenicity of childhood vaccinations - Italy: February 28, 2006
Date of report – final efficacy & safety analyses
for 1st efficacy follow-up period,
immunogenicity analyses of Rotarix and childhood vaccines: March 2006
Date of report – efficacy analyses from Dose 1 to Visit 7,
Post-Dose 2 and 3 immunogenicity analyses from Finland and Italy,
Safety analyses from Visit 1 up to Visit 7: March 2007

a. Populations enrolled/analyzed

Efficacy - 1st Efficacy Follow-up Period (Year 1)

Study population by country
A total of 3994 subjects were enrolled in the TVC (i.e. received at least one dose of Rotarix or placebo). Distributions by treatment group and by country are summarized below.

	HRV N = 2646		**Placebo N = 1348**		**Total N = 3994**	
Country	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	199	7.5	100	7.4	299	7.5
Finland	1918	72.5	972	72.1	2890	72.4
France	95	3.6	51	3.8	146	3.7
Germany	190	7.2	99	7.3	289	7.2
Italy	15	0.6	10	0.7	25	0.6
Spain	229	8.7	116	8.6	345	8.6

Source: Study Report Body Rota-036 Year 1, pg 109

Drop-outs at Visit 5
As noted below, 3944 out of 3994 (98.7%) subjects in the TVC completed Visit 5.

	Group		
	HRV	**Placebo**	**Total**
Number of subjects enrolled and vaccinated	2646	1348	3994
Number of subjects who completed Visit 5	2613	1331	3944
Number of dropped-out subjects at Visit 5	33	17	50
Reasons for drop out :			
SAE	0	4	4
Non-serious AE	7	2	9
Protocol violation	0	0	0
Consent withdrawal (not due to an AE)	21	4	25
Migrated/moved from study area	2	5	7
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	3	2	5
Others	0	0	0

(Source: Study Report Body Rota-036 Year 1, pg 109)

Protocol deviations – ATP efficacy cohort for 1st follow-up period
The following protocol deviations led to subject exclusion from the ATP cohort:

- 10 (Rotarix-7, placebo-3) received intercurrent vaccines forbidden in the protocol
- 1 (Rotarix-1) had randomization code broken due to IS reported on Day 8 post-Dose 2
- 9 (Rotarix-6,placebo-3) received study dose not administered per protocol
- 52 (Rotarix-31, placebo-21) were initially positive for serum anti-RV IgA antibodies at Visit 1 or serological status at Visit 1 unknown (these subjects were part of the immunogenicity-reactogenicity subset)
- 35 (Rotarix-25, placebo-10) did not receive Dose 2 of Rotarix or placebo
- 3 (Rotarix-2, placebo-1) did not enter into the 1st efficacy surveillance period
- 10 (Rotarix-2, placebo-8) had non-vaccine strain RV positive GE stool samples collected between Dose 1 to 2 weeks post-Dose 2

A total of 3874 subjects were included in the ATP efficacy cohort. Of note, subjects who completed Visit 5 outside the planned time period of mid-June to the end of July 2005 were not eliminated from the ATP efficacy cohort.

Protocol deviations – ATP immunogenicity cohort
The following protocol deviations led to subject exclusion from the ATP cohort:

- 3 (Rotarix-3) received intercurrent vaccines forbidden in the protocol
- 1 (Rotarix-1) had randomization code broken due to IS reported on Day 8 post-Dose 2
- 5 (Rotarix-4, placebo-1) received study dose not administered per protocol
- 52 (Rotarix-31, placebo-21) were initially positive for serum anti-RV IgA antibodies at Visit 1 or serological status at Visit 1 unknown (these subjects were part of the immunogenicity-reactogenicity subset)
- 10 (Rotarix-5, placebo-5) had protocol violations related to inclusion/exclusion criteria
- 12 (Rotarix-3, placebo-9) had non-vaccine RV positive GE stool samples collected between Visit 1 and post-vaccination blood sampling visit to measure anti-RV IgA
- 14 (Rotarix-8, placebo-6) received Dose 2 of Rotarix or placebo outside the required interval between vaccinations
- 34 (Rotarix-20, placebo-14) were non-compliant with blood sampling schedule
- 57 (Rotarix-45, placebo-12) did not have post-vaccination serology results due to invalid results or blood sample not collected

A total of 1216 subjects were included in the ATP immunogenicity cohort.

Study demographics – ATP efficacy cohort (N=3874)

Demographic characteristics are included in the table below. The median ages at Dose 1 (12 weeks), Dose 2 (20 weeks), and Visit 5 (11 months) were the same between groups. Most of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups, as were median height, weight, and BMI measurements.

		HRV		**Placebo**		**Total**	
		N = 2572		**N = 1302**		**N = 3874**	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	Mean	11.5	-	11.5	-	11.5	-
	SD	1.77	-	1.78	-	1.77	-
	Minimum	5	-	6	-	5	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	18	-	16	-	18	-
Age at Dose 2 (weeks)	Mean	19.7	-	19.7	-	19.7	-
	SD	2.68	-	2.72	-	2.69	-
	Minimum	10	-	10	-	10	-
	Median	20.0	-	20.0	-	20.0	-
	Maximum	30	-	27	-	30	-
Age at visit 5 or at last contact if visit 5 not performed (Months)	Mean	10.3	-	10.4	-	10.3	-
	SD	1.45	-	1.44	-	1.44	-
	Minimum	3		5		3	
	Median	11.0	--	11.0	--	11.0	--
	Maximum	13	-	13	-	13	-
Gender	Female	1194	46.4	639	49.1	1833	47.3
	Male	1378	53.6	663	50.9	2041	52.7
Race	African heritage	6	0.2	5	0.4	11	0.3
	White/Caucasian	2531	98.4	1278	98.2	3809	98.3
	Arabic/north African	9	0.3	3	0.2	12	0.3
	East/south east Asian	1	0.0	1	0.1	2	0.1
	South Asian	4	0.2	1	0.1	5	0.1
	American Hispanic	12 0	0.5	5 0	0.4	17 0	0.4
	Japanese		0.0		0.0		0.0
	Other	9	0.3	9	0.7	18	0.5
Height (cm)	Mean	60.5		60.5		60.5	
	SD	2.91	--	2.92	--	2.92	--
	Median	61.0	-	61.0	-	61.0	-
	Unknown	2	-	3	-	5	-
Weight (kg)	Mean	6.0	-	6.0	-	6.0	-
	SD	0.86	-	0.84	-	0.85	-
	Median	6.0	-	6.0	-	6.0	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	Mean	16.4		16.3		16.4	
	SD	1.52	--	1.54	--	1.52	--
	Median	16.3	-	16.3	-	16.3	-
	Unknown	2	-	3	-	5	-

Source: Study Report Body Rota-036 Year 1, pg 116

The percentages of subjects (pooled across all countries) who were breastfed at the time of both doses (Rotarix-65.6%, placebo-66.7%) and one dose (Rotarix-12.4%, placebo-13.2%) were comparable between groups. The percentage of subjects who were breastfed at the time of both doses was comparable between groups for each country, differing by no more than 6.7%.

The percentage of subjects (pooled across all countries) who were vaccinated during the RV season was similar between groups (Rotarix-90.6%, placebo -90.2%). The percentage between groups was comparable for each country.

Study demographics – TVC (N=3994)
The median ages at Dose 1 (12 weeks), Dose 2 (20 weeks), Visit 5 (10 months) and Visit 7 (22 months) were the same between groups. Most of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups. Height, weight, and BMI measurements were also the same or very similar between groups. Demographic data were also comparable between groups for each country, except for some female-to-male ratio imbalances between groups in France, Germany, Spain, and Italy. The number of siblings and percentages of subjects who did not attend day care at Visits 1 through 5 (>90%) and at Visit 7 (>61%) were similar between groups.
Reviewer Note: Reviewer obtained a maximum age of 28 months at Visit 5 in the Rotarix group.

Dose distribution – TVC

Country	**Rotarix**	**placebo**	**total**
Czech Republic	199	100	299
Finland	1918	972	2890
France	95	51	146
Germany	190	99	289
Italy	15	10	25
Spain	229	116	345
Total	2646	1348	3994

Source: Study Report Body Rota-036 Year 1, pgs 505-510

Study demographics – TVC for immunogenicity-reactogenicity subset (N=1404)
The median ages at Dose 1 (11 weeks) and Dose 2 (17 weeks) were the same between groups. Most of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups. Median height, weight, and BMI measurements were also the same or very similar between groups.
Reviewer Note: Reviewer obtained a maximum age of 28 months at Visit 5 in the Rotarix group.

Study demographics – ATP immunogenicity cohort (N=1216)
The median ages at Dose 1 (11 weeks) and Dose 2 (17 weeks) were the same between groups. Most of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups. Median height, weight, and BMI measurements were also the same or very similar between groups.

The percentages of subjects (pooled across all countries) who were breastfed at the time of both doses (Rotarix-58.4%, placebo-60.4%) and one dose (Rotarix-14.2%, placebo-15.6%) were comparable between groups. The percentage of subjects who were breastfed at the time of both doses was comparable between groups for each country, differing by no more than 4.9%.

Concomitant vaccinations - TVC
Among countries, 98.5-100% of Rotarix recipients and 99-100% of placebo recipients were co-administered routine childhood vaccinations (DTPa-HBV-IPV/Hib, Prevnar, Meningitec) with Dose 1 of study vaccine. Similarly, 100% of Rotarix recipients and 99.7-100% of placebo recipients were co-administered routine vaccinations with Dose 2.
Reviewer Note: Reviewer obtained the following differences from the applicant, highlighted in bold italics (numbers in parentheses are from the applicant). Because the numbers did not differ

substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

Dose 1

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPa-HBV-IPV/Hib	199	***198 (196)***	***99.5 (98.5)***	100	***100 (99)***	***100 (99)***	299	***298 (295)***	***99.7 (98.7)***
Germany	DTPa-HBV-IPV/Hib Prevnar	190	188 188	98.9 98.9	99	99 ***99 (98)***	100 ***100 (99)***	289	287 ***287 (286)***	99.3 ***99.3 (99)***

Dose 2

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPA-HBV-IPV/HIB	198	***196 (198)***	***99.0 (100)***	100	***98 (99)***	***98.0 (99)***	298	***294 (297)***	***98.7 (99.7)***
	PREVNAR		95	100		51	100		146	100
Germany	DTPA-HBV-IPV/HIB PREVNAR	187	187 187	100 100	99	98 ***97 (98)***	99.0 ***98.0 (99)***	286	285 ***284 (285)***	99.7 ***99.3 (99.7)***

Concomitant vaccinations – ATP efficacy cohort

Among countries, 98.4-100% of Rotarix recipients and 98.9-100% of placebo recipients were co-administered routine childhood vaccinations with Dose 1 of study vaccine. Similarly, 100% of Rotarix recipients and 98.9-100% of placebo recipients were co-administered routine vaccinations with Dose 2.

Reviewer Note: Reviewer obtained the following differences from the applicant, highlighted in bold italics (numbers in parentheses are from the applicant). Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

Dose 1

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPA-HBV-IPV/HIB	193	***192 (190)***	***99.5 (98.4)***	97	***97 (96)***	***100 (99)***	290	286	98.6

Dose 2

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPA-HBV-IPV/HIB	193	***191 (193)***	***99.0 (100)***	97	***95 (96)***	***97.9 (99)***	290	***286 (289)***	***98.6 (99.7)***

Concomitant vaccinations – ATP immunogenicity cohort

Co-administration of childhood vaccinations with Dose 1 and Dose 2 of study vaccine was similar to that of the TVC.

Reviewer Note: Reviewer obtained the following differences from the applicant, highlighted in bold italics (numbers in parentheses are from the applicant). Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

Dose 1

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPA-HBV-IPV/HIB	182	***181 (179)***	***99.5 (98.4)***	90	***90 (89)***	***100 (98.9)***	272	***271 (268)***	***99.6 (98.5)***

Dose 2

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	DTPA-HBV-IPV/HIB	182	***180 (182)***	***98.9 (100)***	90	***88 (89)***	***97.8 (98.9)***	272	***268 (271)***	***98.5 (99.6)***

The percentages of subjects who received 3 doses of childhood vaccinations from Visit 1 to 21 days before post-Dose 3 blood sampling at Visit 3 (Visit 4 for Spain) was 81.3% (Infanrix Hexa) for the Czech Republic, 98.4% (2 doses of Infanrix Hexa)/100% (1 dose of Infanrix Polio Hib) and 99.2% (Prevnar) for France, 74.9% (Infanrix Hexa) and 74.1% (Prevnar) for Germany, and 100% (Infanrix Hexa, Meningitec) for Spain. The percentages of subjects who received 3 doses of childhood vaccinations from Visit 1 to 21 days before post-Dose 3 blood sampling at Visit 5/6 was 100% (Infanrix Hexa) for both Finland and Italy.
Reviewer Note: Data for 3 doses of routine vaccinations for Spain, Finland, and Italy were not included in the analysis databases.

A minimum of 21 days between Dose 2 or Dose 3 of routine vaccination and post-vaccination blood sampling was needed to elicit adequate immune responses. At Visit 3 or Visit 4 (Spain), the median number of days between Dose 3 and post-vaccination blood sampling was the same or similar for all countries: Czech Republic (Rotarix-28, placebo-29), France (both groups-32), Germany (Rotarix-31, placebo-32), and Spain (both groups-35). At Visit 3, the median number of days between Dose 2 and post-vaccination blood sampling was the same or similar for all countries: Finland (Rotarix-35, placebo-36), Italy (Rotarix-36, placebo-37), and Spain (Rotarix-54, placebo-54). At Visit 5/6, the median number of days between Dose 3 and post-vaccination blood sampling was similar for Finland (Rotarix-37, placebo-38) and Italy (Rotarix-35.5, placebo-36).

Concomitant vaccinations – TVC immunogenicity-reactogenicity subset
For Finland, 100% of Rotarix and placebo recipients were co-administered routine childhood vaccinations with Dose 1 and Dose 2 of study vaccine.
Reviewer Note: Reviewer obtained the following difference from the applicant, highlighted in bold italics (numbers in parentheses are from the applicant). Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant. Also, similar data for Italy were not provided in the study report. However, the reviewer confirmed that 100% of Italian subjects received DTPa-HBV-IPV/Hib with both Dose 1 and Dose 2 of Rotarix/placebo.

Dose 2

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Finland	DTPA-HBV-IPV/HIB	***186 (184)***	184	***98.9 (100)***	***114 (113)***	113	***99.1 (100)***	***300 (297)***	297	***99.0 (100)***

The percentages of subjects who received 3 doses of childhood vaccinations from Visit 1 to 21 days before post-Dose 3 blood sampling at Visit 3 (Visit 4 for Spain) was 80.3% (Infanrix Hexa) for the Czech Republic, 98.6% (2 doses of Infanrix Hexa)/100% (1 dose of Infanrix Polio Hib) and 99.3% (Prevnar) for France, 75.6% (Infanrix Hexa) and 74.6% (Prevnar) for Germany, and 100% (Infanrix Hexa, Meningitec) for Spain. The percentages of subjects from who received 2 doses of childhood

vaccinations from Visit 1 to 21 days before post-Dose 3 blood sampling at Visit 3 was 100% (Infanrix Hexa) for Finland and Italy.
Reviewer Note: Data for 3 doses of routine vaccinations for Spain, Finland, and Italy were not included in the analysis databases.

At Visit 3 or Visit 4 (Spain), the median number of days between Dose 3 and post-vaccination blood sampling, for each group by country, was the same or similar as in the ATP immunogenicity cohort. At Visit 3, the median number of days between Dose 2 and post-vaccination blood sampling, for each group by country, was the same or similar as in the ATP immunogenicity cohort.

Efficacy – 2nd Efficacy Follow-up Period (Year 2)

Drop-outs at Visit 7
As noted below, 3883 out of 3994 (97%) subjects in the TVC completed Visit 7.

	HRV	Placebo	Total
Number of subjects vaccinated	2646	1348	3994
Number of subjects completed	2566	1317	3883
Number of subjects withdrawn	80	31	111
Reasons for withdrawal :			
Serious Adverse Event	1	4	5
Non-serious adverse event	7	3	10
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	34	3	37
Migrated/moved from study area	21	15	36
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	17	6	23
Others	0	0	0

Source: Study Report Body Rota-036 Annex, pg 79

Protocol deviations – ATP efficacy cohort for 2nd follow-up period
The following is a summary of protocol deviations that led to subject exclusion in the ATP cohort:
- 26 (Rotarix-18, placebo-8) did not enter into the 2nd efficacy surveillance period

A total of 3848 subjects were included in the ATP efficacy cohort for the 2nd follow-up period. Subjects who completed Visit 7 outside the planned time period of mid-June to end-July 2006 were not eliminated from the ATP efficacy cohort.

Study demographics – ATP efficacy cohort during 2nd period (N=3848)
Demographic characteristics are included in the table below. The median ages at Dose 1 (12 weeks), Dose 2 (20 weeks), and Visit 5 (11 months), and Visit 7 (22 months) were the same between groups. Most of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups. Median height, weight, and BMI measurements were also the same between groups.

8.1.2.2.2 Efficacy endpoints/outcomes

Year 1 Efficacy (2 weeks post-Dose 2 to Visit 5) – ATP efficacy cohort

Summary of reported any RV GE and severe RV GE episodes – Year 1
The median duration of follow-up during the Year 1 efficacy period was approximately 6 months in each group. Among Rotarix and placebo recipients, RV was detected in 24 and 94 GE episodes, respectively; no subject had more than one RV GE episode during the 1st efficacy follow-up period.

		HRV		Placebo	
	Total number of	N = 2572		N = 1302	
Event	episode reported	n	%	n	%

GE	1	483	18.8	277	21.3
	2	66	2.6	53	4.1
	3	8	0.3	6	0.5
	4	2	0.1	3	0.2
	Any	559	21.7	339	26.0
RV GE	1	24	0.9	94	7.2
	Any	24	0.9	94	7.2

(Source: Study Report Body Rota-036 Year 1, pg 121)

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 5 Rotarix and 60 placebo recipients.

Event	Severity using Vesikari scale	HRV n	%	Placebo n	%
GE	Mild (1-6)	302	46.7	157	38.0
	Moderate (7-10)	224	34.6	124	30.0
	Severe (≥11)	120	18.5	132	32.0
	Unknown	1	0.2	0	0.0
	Any	647	100	413	100
RV GE	Mild (1-6)	8	33.3	11	11.7
	Moderate (7-10)	11	45.8	23	24.5
	Severe (≥11)	5	20.8	60	63.8
	Any	24	100	94	100

n= no. of subjects
(Source: Study Report Body Rota-036 Year 1, pg 121)

Serotype G and P distribution is summarized below. No vaccine strain was detected in the stools collected. G1P8 was the most prevalent circulating type, followed by G9P8.

	HRV N'= 24		Placebo N'= 94	
Type	**n**	**%**	**N**	**%**
G1wt and P8wt	4	16.7	45	47.9
G2 and P4	3	12.5	3	3.2
G3 and P8wt	1	4.2	5	5.3
G4 and P8wt	3	12.5	12	12.8
G9 and P8wt	13	54.2	27	28.7
G1w and G4 and P8wt	0	0.0	1	1.1
G2 and unknown P type	0	0.0	1	1.1

wt = wild type
(Source: Study Report Body Rota-036 Year 1, pg 122)

Stool test results were available for 91.7% of GE episodes in Rotarix recipients and 89.3% in placebo recipients. The percentages of unavailable stool sample results were similar between the groups (table below).

	HRV N'= 647		Placebo N'= 413	
Category	**n**	**%**	**n**	**%**
No stools collected	42	6.5	34	8.2
Stools collected but no results available*	12	1.9	10	2.4
No stool results available	54	8.3	44	10.7

N' = number of GE episodes reported
n/% = number/percentage of GE episodes within the specified category
* = due to quantity not sufficient or stool sample not tested
(Source: Study Report Body Rota-036 Year 1, pg 247)

Clinical characteristics of RV GE episodes – Year 1
The duration of looser than normal stools and vomiting were shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration, and hospitalization were also less in the Rotarix group compared to placebo.

Vaccine efficacy against any RV GE – Year 1 (Primary endpoint)
VE of Rotarix against any wild-type RV GE during the 1st efficacy follow-up period was 87.1%. The primary efficacy objective was reached because the lower limit of the 95% CI was greater than 50% (refer to section 8.1.2.1.7 of this report on power considerations). VE was also 87.4% (95%CI: 80.3-91.9%) using the Cox proportional-hazard model.

			n/N	95%CI		VE			
							95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2572	24	0.9	0.6	1.4	87.1	79.6	92.1	<0.001
Placebo	1302	94	7.2	5.9	8.8				

(Source: Study Report Body Rota-036 Year 1, pg 123)

Vaccine efficacy against severe RV GE – Year 1 (Secondary endpoint)
VE of Rotarix against severe RV GE caused by circulating wild-type RV during the 1st efficacy follow-up period was 95.8%.

			n/N 95%CI			VE			
							95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2572	5	0.2	0.1	0.5	95.8	89.6	98.7	<0.001
Placebo	1302	60	4.6	3.5	5.9				

(Source: Study Report Body Rota-036 Year 1, pg 123)
Furthermore, VE reached 100% (95% CI: 84.7-100%) for a score of ≥ 17 points.

VE against any RV GE by main RV serotypes – Year 1 (Secondary endpoint)
VE against any RV GE by serotype is presented below. VE against any G1 RV GE was 95.6%; VE using Cox proportional hazard model was also significant (95.6%: 95%CI 87.9-98.4). VE against G3, G4, G9, and all non-G1 types pooled together reached statistical significance. However, the lower level of the 95% CI for VE against G3 was low (9.5%). VE against non-G1 types using Cox proportional hazard model was also significant (79.5%: 95%CI 65.5-87.8). Although fewer G2 episodes occurred in the Rotarix group, VE did not reach statistical significance.

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	**UL**	
G1						
Rotarix	4	0.2	95.6	87.9	98.8	<0.001
placebo	46†	3.5				
G2						
Rotarix	3	0.1	62.0	-124.4	94.4	0.234
placebo	4	0.3				
G3						
Rotarix	1	0.0	89.9	9.5	99.8	0.018
placebo	5	0.4				
G4						
Rotarix	3	0.1	88.3	57.5	97.9	<0.001
placebo	13†	1.0				
G9						
Rotarix	13	0.5	75.6	51.1	88.5	<0.001
placebo	27	2.1				
Pooled non-G1(G2, G3, G4, G9)						
Rotarix	20	0.8	79.3	64.6	88.4	<0.001

placebo	49	3.8				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one specified RV GE episode in each group
†One subject from the placebo group counted in G1 and G4 categories since both RV types were isolated
(Source: Study Report Body Rota-036 Year 1, pg 125)

VE against severe RV GE by main RV serotypes – Year 1 (Secondary endpoint)
VE against severe G1 RV GE was 96.4%. VE against G3, G4, G9, and all non-G1 types pooled together reached statistical significance; the lower level of the 95% CI for VE against G3 was low (44.8%) compared to the other categories. Although fewer G2 episodes occurred in the Rotarix group, VE did not reach statistical significance.

Group (wild type)	n	% (n/N)	VE %	95%CI		P-value
				LL	UL	
G1						
Rotarix	2	0.1	96.4	85.7	99.6	<0.001
placebo	28†	2.2				
G2						
Rotarix	1	0.0	74.7	-386.2	99.6	0.263
placebo	2	0.2				
G3						
Rotarix	0	0.0	100	44.8	100	0.004
placebo	5	0.4				
G4						
Rotarix	0	0.0	100	64.9	100	<0.001
placebo	7†	0.5				
G9						
Rotarix	2	0.1	94.7	77.9	99.4	<0.001
placebo	19	1.5				
Pooled non-G1(G2, G3, G4, G9)						
Rotarix	3	0.1	95.4	85.3	99.1	<0.001
placebo	33	2.5				

N = number of subjects included in each group; n/% = number/percentage of subjects reporting at least one specified RV GE episode in each group; †One subject from the placebo group counted in G1 and G4 categories since both RV types were isolated
(Source: Study Report Body Rota-036 Year 1, pg 126)

VE against hospitalized RV GE – Year 1 (Secondary endpoint)
No Rotarix recipient was hospitalized for RV GE compared to 12 placebo recipients. VE was 100.0% (95% CI: 81.8-100%).

VE against RV GE requiring medical attention – Year 1 (Secondary endpoint)
Medical attention (defined as medical provider contact, advice, or visit; emergency room contact or visit or hospitalization) occurred significantly less in Rotarix than placebo recipients (10 vs 62, or 0.4% vs 4.8%, respectively). VE was 91.8% (95% CI: 84.0-96.3%).

VE against all cause GE – Year 1 (Exploratory endpoint)
VE against GE of any etiology was 16.5% (95% CI: 4.2-27.2%).

VE against all cause severe GE – Year 1 (Exploratory endpoint)
VE against severe GE of any etiology was 52.3% (95% CI: 38.0-63.3%).

VE against all cause GE requiring hospitalization – Year 1 (Exploratory endpoint)
VE against GE of any etiology requiring hospitalization was 74.7% (95% CI: 45.5-88.9%).

VE against any RV GE by serum IgA status at Visit 3 – Year 1 (Exploratory endpoint)
Among subjects who were seropositive for anti-RV IgA at Visit 3, 2 (0.3%) Rotarix recipients versus 2 (6.5%) placebo recipients reported any RV GE from 2 weeks post-Dose 2 to Visit 5; VE was 95.6%

(95% CI: 39.8-99.7%). The applicant concluded that it was difficult to correlate seroconversion rate and VE because immunogenicity was evaluated in only a subset of subjects.

VE against any RV GE and severe RV GE by feeding criteria – Year 1 (Exploratory endpoint)
VE against any RV GE among subjects that breastfed at the time of at least one dose was similar to VE among subjects not breastfed at any of the doses (86.0%, 95% CI: 76-91.9% vs. 90.8%, 95% CI: 72.5-97.7%, respectively). VE against severe RV GE for the 2 feeding strata were also similar and statistically significant (95.7% vs. 96.2%, respectively).

VE against severe RV GE using the Clark scale – Year 1 (Exploratory endpoint)
Compared to the Vesikari scale, the Clark scale classified less severe RV GE episodes in both treatment groups (Rotarix-2, placebo-15). However, VE_{Clark} was 93.3% (95% CI: 71.0-99.3%), similar to $VE_{Vesikari}$ (95.8%). VE against G1 (93.7%; 95% CI: 52.8-99.9%), G9 (91.6%; 95% CI: 30.5-99.8), and all non-G1 types pooled together (92.8; 95% CI: 43.7-99.8) reached statistical significance.

VE against any RV GE and severe RV GE, by country – Year 1 (Exploratory endpoint)
VE against any RV GE ranged from 78.9% to 100% in the Czech Republic, Finland, France, and Spain. However, only the VE estimate for Finland (88.6%; 81.0-93.4%) reached statistical significance due to a larger study population than in the other countries. VE could not be calculated for Germany and Italy due to one and zero RV GE episodes occurring, respectively.

Similarly, $VE_{Vesikari}$ and VE_{Clark} against severe RV GE reached statistical significance in Finland only (96.4%; 90.2-99.1% and 92.8; 68.6-99.2, respectively).

Year 1 Efficacy (Dose 1 to Visit 5) – TVC

Summary of RV GE episodes with vaccine strains
G1P8 vaccine strain was isolated from stools of 5 GE episodes occurring from Dose 1 up to 2 weeks post-Dose 2. One of the 5 episodes was reported as a mixed infection with G9P8 wild type RV; this wild-type RV was included in the efficacy analysis from Dose 1 up to 2 weeks post-Dose 2.
Summary of reported RV GE episodes
A total of 130 subjects in the TVC reported one episode of any RV GE from Dose 1 to Visit 5; 26 (1.0%) occurred in Rotarix recipients and 104 (7.7%) occurred in placebo recipients. No subject in either group had more than one RV GE episode. Stool results were not available for 10.0% of Rotarix and 11.2% of placebo recipients with GE episodes.

Severe RV GE was reported in 69 subjects (Rotarix-5, placebo-64) using the Vesikari scale and 17 subjects (Rotarix-2, placebo-15) using the Clark scale.

VE against any RV GE – Dose 1 to Visit 5 (Secondary endpoint)
The median duration of follow-up during this interval was approximately 8.4 months in the Rotarix group and 8.5 months in the placebo group. VE against any RV GE was 87.3% (95% CI: 80.3-92.0%), similar to the VE estimate for the primary endpoint in the ATP cohort (87.1%).

Similar to the ATP cohort, VE against wild-type G1, G3, G4, G9, and pooled non-G1 types reached statistical significance (95.8%, 85.4%, 89.1%, 77.7%, and 80.3%, respectively).

VE reached statistical significance in Finland (88.5%; 81.1-93.3%) and Spain (91.6%; 30.4-99.8%).

VE against severe RV GE – Dose 1 to Visit 5 (Secondary endpoint)
$VE_{Vesikari}$ against severe RV GE was 96.0% (95% CI: 90.2-98.8%), similar to the VE estimate for the primary endpoint in the ATP cohort (95.8%). Statistical significance was only reached in Finland (VE = 96.4%; 90.4-99.1%). VE against wild-type G1, G3, G4, G9, and pooled non-G1 types reached statistical significance (96.5%, 100%, 100%, 95.1%, and 95.8%, respectively). VE_{Clark} was 93.2% (70.8-99.2%).

VE against all cause GE episodes – Dose 1 to Visit 5 (Exploratory endpoint)
VE against GE episodes of any etiology was 14.6% (3.6-24.3%). VE against severe GE episodes of any etiology was 52.4% (39.0-62.8%).

VE against hospitalized RV GE episodes – Dose 1 to Visit 5 (Exploratory endpoint)
VE against hospitalized RV GE was 100% (81.7-100%).

VE against any RV GE episodes requiring medical attention – Dose 1 to Visit 5 (Exploratory)
VE was 92.0% (84.8-96.2%).
Year 1 Efficacy (Dose 1 to 2 weeks post-Dose 2) – TVC

Summary of reported RV GE episodes
Two Rotarix and 8 placebo recipients reported an episode of RV GE during this interval. No subject in either group had more than one RV GE episode. Severe RV GE was reported in 3 placebo subjects only using the Vesikari scale and 0 subjects using the Clark scale. Stool results were unavailable for 13.9% of Rotarix and 13.3% of placebo recipients with GE episodes.

VE against any RV GE – Dose 1 to 2 weeks post-Dose 2 (Exploratory endpoint)
The median duration of follow-up during this interval was 2.5 months in both groups.
VE was 87.3% (46.2-98.7%).

VE against severe RV GE – Dose 1 to 2 weeks post-Dose 2 (Exploratory endpoint)
$VE_{Vesikari}$ against severe RV GE was 100% (-23.3-100%).

Year 1 Efficacy (Dose 1 to pre-Dose 2) – TVC

Summary of reported RV GE episodes
One Rotarix and 5 placebo recipients reported an episode of RV GE during this interval. No subject had more than one RV GE episode. Severe RV GE was reported in 3 subjects (Rotarix-0, placebo-3) using the Vesikari scale and 0 subjects using the Clark scale. Stool results were not available for 14.7% of Rotarix and 14.9% of placebo recipients with GE episodes.

VE against any RV GE – Dose 1 to pre-Dose 2 (Exploratory endpoint not mentioned in protocol or as an additional analysis)
The median duration of follow-up was 2 months for both groups. VE was 89.8 (8.9-99.8%).

VE against severe RV GE – Dose 1 to pre-Dose 2 (Exploratory endpoint not mentioned in protocol or as an additional analysis)
$VE_{Vesikari}$ against severe RV GE was 100% (-23.3-100%).

Year 1 Immunogenicity – ATP immunogenicity cohort

Anti-RV IgA response
Anti-RV IgA seroconversion rates and GMCs at pre-Dose 1, Visit 3 (1-2 months post-Dose 2), and Visit 5 (3 months post-Dose 2, Spain only) are presented below. Visit 3 Post-Dose 2 seroconversion rates and GMCs were significantly greater in the Rotarix group compared to placebo. The difference in Visit 3 seroconversion rates between Rotarix and placebo groups was 79.86% (95% CI: 76.19-82.96%). Visit 3 rates ranged from 82.1% in Germany to 94.6% in Finland.

				≥ 20 U/ml				**GMC (U/ml)**		
						95% CI			**95% CI**	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
All	HRV	PRE	794	0	0.0	0.0	0.5	< 20	-	-
		PII(M3-M4)	787	681	**86.5**	83.9	88.8	197.2	175.2	222.0
		PII(M5)	184	152	82.6	76.3	87.8	113.3	90.8	141.5
	Placebo	PRE	422	0	0.0	0.0	0.9	< 20	-	-
		PII(M3-M4)	420	28	**6.7**	4.5	9.5	< 20		
		PII(M5)	90	14	15.6	8.8	24.7	< 20	--	--

Czech Republic	HRV	PRE	182	0	0.0	0.0	2.0	< 20	-	-
		PII(M3-M4)	182	154	84.6	78.5	89.5	152.5	118.9	195.4
	Placebo	PRE	90	0	0.0	0.0	4.0	< 20	-	-
		PII(M3-M4)	90	2	2.2	0.3	7.8	< 20	-	-
Finland	HRV	PRE	167	0	0.0	0.0	2.2	< 20	-	-
		PII(M3-M4)	167	158	94.6	90.0	97.5	412.2	325.9	521.2
	Placebo	PRE	105	0	0.0	0.0	3.5	< 20	-	-
		PII(M3-M4)	105	3	2.9	0.6	8.1	< 20	-	-
France	HRV	PRE	83	0	0.0	0.0	4.3	< 20	-	-
		PII(M3-M4)	83	70	84.3	74.7	91.4	181.8	126.4	261.6
	Placebo	PRE	43	0	0.0	0.0	8.2	< 20	-	-
		PII(M3-M4)	43	6	14.0	5.3	27.9	< 20	-	-
Germany	HRV	PRE	156	0	0.0	0.0	2.3	< 20	-126.0	-218.9
		PII(M3-M4)	156	128	82.1	75.1	87.7	166.0		
	Placebo	PRE	84	0	0.0	0.0	4.3	< 20	-	-
		PII(M3-M4)	84	5	6.0	2.0	13.3	< 20	-	-
Italy	HRV	PRE	13	0	0.0	0.0	24.7	< 20	-80.5	-522.7
		PII(M3-M4)	13	12	92.3	64.0	99.8	205.1		
	Placebo	PRE	9	0	0.0	0.0	33.6	< 20	-	-
		PII(M3-M4)	9	1	11.1	0.3	48.2	< 20	-	-
Spain	HRV	PRE	193	0	0.0	0.0	1.9	< 20	-	-
		PII(M3-M4)	186	159	85.5	79.6	90.2	156.3	123.4	198.0
		PII(M5)	184	152	82.6	76.3	87.8	113.3	90.8	141.5
	Placebo	PRE	91	0	0.0	0.0	4.0	< 20	-	-
		PII(M3-M4)	89	11 14	12.4	6.3	21.0	< 20		
		PII(M5)	90		15.6	8.8	24.7	< 20	--	--

HRV vaccine or placebo was administered at 3, 4 months of age in Czech Republic; 2, 3 months of age in France and Germany; 2, 4 months of age in Spain; 3, 5 months in Finland and Italy
N = number of subjects with available results; n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination; PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4, Spain only)
(Source: Study Report Body Rota-036Year 1, pg 133)

GMCs for seropositive subjects at 1-2 months post-Dose 2 and 3 months post-Dose 2 (Spain only) are summarized below.

				GMC (U/ml)		
					95% CI	
Country	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
All	**HRV**	**PII(M3-M4)**	681	**313.7**	**284.2**	**346.1**
		PII(M5)	152	**189.0**	**157.3**	**226.9**
	Placebo	**PII(M3-M4)**	28	290.9	159.3	531.2
		PII(M5)	14	172.9	82.7	361.5
CzechRepublic	**HRV**	**PII(M3-M4)**	154	250.2	202.0	309.9
	Placebo	**PII(M3-M4)**	2	840.9	78.9	8961.3
Finland	**HRV**	**PII(M3-M4)**	158	509.4	416.1	623.7
	Placebo	**PII(M3-M4)**	3	149.0	1.5	14845.5
France	**HRV**	**PII(M3-M4)**	70 6	311.6	234.5	414.0
	Placebo	**PII(M3-M4)**		259.1	28.9	2325.3
Germany	**HRV**	**PII(M3-M4)**	128	307.0	246.1	383.1
	Placebo	**PII(M3-M4)**	5	801.7	151.3	4247.8

Italy	**HRV** **Placebo**	**PII(M3-M4)** **PII(M3-M4)**	12 1	263.8 57.0	114.8 -	606.3 -
Spain	**HRV**	**PII(M3-M4)** **PII(M5)**	159 152	249.3 189.0	204.3 157.3	304.2 226.9
	Placebo	**PII(M3-M4)** **PII(M5)**	11 14	224.3 172.9	93.6 82.7	537.3 361.5

(Source: Study Report Body Rota-036Year 1, pg 134)

Visit 3 seroconversion rates and GMCs were similar by feeding category. Among subjects who were breastfed at one or more doses, seroconversion rates [GMCs] were 85.5% [185.8] for Rotarix recipients compared to 5.3% [<20] for placebo recipients. Among non-breastfed subjects, serconversion rates were 89.2% [231.5] and 11.1% [<20] in Rotarix and placebo recipients, respectively.

Post-Dose 3 (Visit 3; Visit 4 for Spain) immunogenicity of routine vaccinations – Czech Republic, France, Germany, Spain

Anti-meningococcal serum bactericidal activity (SBA)-MenC response (Spain) – Visit 4

One-hundred percent of subjects in both groups achieved an SBA-MenC titer ≥ 1:8 at 1 month post-Dose 3 of Meningitec. For a titer ≥ 1:128, the seropositivity rates in both groups remained similar (Rotarix-98.4%, placebo-100%); the difference in rates between groups at either titer was not statistically significant. The 95% CIs of GMTs for each group were overlapping. GMC ratios between groups were also not statistically significant.

				≥ 1:8 dilution				≥ 1:128 dilution				**GMT**		
						95% CI				**95% CI**			**95% CI**	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PIII(M3-M5)**	184	184	100	98.0	100	181	98.4	95.3	99.7	1455.4	1240.2	1707.9
	Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	90	100	96.0	100	1769.1	1374.3	2277.5

Meningitec was administered at 2, 4 and 6 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 4)
(Source: Study Report Body Rota-036Year 1, pg 135)

Anti-meningococcal anti-polysaccharide C (PSC) response (Spain) – Visit 4

One-hundred percent of subjects in both groups achieved an anti-PSC titer ≥ 0.3µg/ml at 1 month post-Dose 3 of Meningitec. For a titer ≥ 2.0µg/ml, seropositivity rates in both groups remained similar (Rotarix-97.9%, placebo-96.7%). The difference in rates between groups at either titer was not statistically significant. The 95% CIs of GMCs for each group overlapped. GMC ratios between groups were also not statistically significant.

				≥ 0.3 µg/ml				≥ 2.0 µg/ml				**GMC (µg/ml)**		
						95% CI				**95% CI**			**95% CI**	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PIII(M3-M5)**	187	187	100	98.0	100	183	97.9	94.6	99.4	7.63	6.81	8.55
	Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	88	96.7	90.7	99.3	8.76	7.56	10.15

(Source: Study Report Body Rota-036Year 1, pg 136)

Anti-pneumococcal antibody response to serotypes 4, 6B, 9V, 18C, 19F, 23F (France, Germany) – Visit 3

In France, 100% of subjects in both groups achieved anti-pneumococcal antibody titer ≥ 0.05µg/ml for serotypes 4, 9V, 14, and 19F. Seropositivity rates for 6B, 18C, and 23F were similar between groups with overlapping 95% CIs. For a titer ≥ 0.2µg/ml, seropositivity rates were 100% for serotypes 4, 9V, and 14, with rates for the other serotypes being similar between groups. GMCs were also comparable between groups for all serotypes.

In Germany, 100% of subjects in both groups achieved anti-pneumococcal antibody titer ≥ 0.05µg/ml for serotypes 4, 9V, 14, 18 and 19F. Seropositivity rates for 6B and 23F were similar between groups with overlapping 95% CIs. For a titer ≥ 0.2µg/ml, seropositivity rates were 100% in both groups for serotypes 4 and 19F, with rates for the other serotypes being similar between groups. GMCs were also comparable between groups for all serotypes.

For all serotypes, the difference in rates between groups at either titer, as well as the GMC ratio between the groups, were not statistically significant for any country.

					≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC (µg/ml)		
							95% CI				95% CI			95% CI	
Antibody	**Country**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Pneumonia serotype 4	**France**	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	83	100	95.7	100	2.40	2.02	2.85
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	43	100	91.8	100	2.39	2.02	2.83
	Germany	**HRV**	**PIII(M3-M5)**	155	155	100	97.6	100	155	100	97.6	100	3.17	2.80	3.59
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	84	100	95.7	100	3.11	2.56	3.78
Pneumonia serotype 6B	**France**	**HRV**	**PIII(M3-M5)**	83	80	96.4	89.8	99.2	69	83.1	73.3	90.5	0.79	0.59	1.07
		Placebo	**PIII(M3-M5)**	43	42	97.7	87.7	99.9	38	88.4	74.9	96.1	0.65	0.46	0.93
	Germany	**HRV**	**PIII(M3-M5)**	155	138	89.0	83.0	93.5	107	69.0	61.1	76.2	0.48	0.37	0.63
		Placebo	**PIII(M3-M5)**	84	77	91.7	83.6	96.6	59	70.2	59.3	79.7	0.49	0.35	0.70
Pneumonia serotype 9V	**France**	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	83	100	95.7	100	2.42	2.06	2.84
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	43	100	91.8	100	2.39	2.00	2.86
	Germany	**HRV**	**PIII(M3-M5)**	155	155	100	97.6	100	154	99.4	96.5	100	2.94	2.57	3.36
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	84	100	95.7	100	2.65	2.13	3.29
Pneumonia serotype 14	**France**	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	83	100	95.7	100	4.68	3.75	5.84
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	43	100	91.8	100	5.29	4.22	6.63
	Germany	**HRV**	**PIII(M3-M5)**	155	155	100	97.6	100	154	99.4	96.5	100	4.59	3.93	5.37
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	83	98.8	93.5	100	3.89	2.99	5.08
Pneumonia serotype 18C	**France**	**HRV**	**PIII(M3-M5)**	83	81	97.6	91.6	99.7	80	96.4	89.8	99.2	2.47	1.92	3.18
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	43	100	91.8	100	2.56	2.03	3.24
	Germany	**HRV**	**PIII(M3-M5)**	155	155	100	97.6	100	154	99.4	96.5	100	3.40	2.89	4.01
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	82	97.6	91.7	99.7	3.31	2.62	4.19
Pneumonia serotype 19F	**France**	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	81	97.6	91.6	99.7	2.85	2.30	3.52
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	42	97.7	87.7	99.9	2.75	2.05	3.69
	Germany	**HRV**	**PIII(M3-M5)**	155	155	100	97.6	100	154	99.4	96.5	100	3.62	3.06	4.27
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	84	100	95.7	100	3.51	2.87	4.29
Pneumonia serotype 23F	**France**	**HRV**	**PIII(M3-M5)**	83	82	98.8	93.5	100	76	91.6	83.4	96.5	1.25	0.95	1.65
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	41	95.3	84.2	99.4	1.35	1.01	1.80
	Germany	**HRV**	**PIII(M3-M5)**	155	147	94.8	90.1	97.7	137	88.4	82.3	93.0	1.31	1.03	1.68
		Placebo	**PIII(M3-M5)**	84	80	95.2	88.3	98.7	71	84.5	75.0	91.5	1.21	0.84	1.75

Prevnar was administered at 2, 3 and 4 months of age
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3)
(Source: Study Report Body Rota-036Year 1, pg 137)

Anti-diphtheria and anti-tetanus antibody responses – Visit 3, Visit 4 (Spain only)

Seroprotection rates against diphtheria were 100% for both groups in the Czech Republic, France, and Spain; rates were also similar in Germany. GMCs were also similar between groups in all countries. Seroprotection rates against tetanus were 100% for both groups in the Czech Republic and France, with rates also being similar in Germany and Spain; GMCs were also similar between groups in all countries. For both antigens, differences in rates between groups and GMC ratio between the groups were not statistically significant for any country.

					≥ 0.1 IU/ml				GMC (IU/ml)		
							95% CI			95% CI	
Antibody	**Country**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-diphtheria	**Czech Republic**	**HRV**	**PIII(M3-M5)**	182	182	100	98.0	100	2.321	2.097	2.569
		Placebo	**PIII(M3-M5)**	89	89	100	95.9	100	2.694	2.292	3.165
	France	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	1.168	0.963	1.417
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	1.118	0.838	1.490
	Germany	**HRV**	**PIII(M3-M5)**	155	148	95.5	90.9	98.2	1.389	1.140	1.694
		Placebo	**PIII(M3-M5)**	84	83	98.8	93.5	100	1.350	1.058	1.723
	Spain	**HRV**	**PIII(M3-M5)**	188	188	100	98.1	100	6.653	6.077	7.284
		Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	6.830	5.865	7.953
Anti-tetanus	**Czech Republic**	**HRV**	**PIII(M3-M5)**	182	182	100	98.0	100	1.918	1.690	2.177
		Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	1.789	1.499	2.136
	France	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	1.353	1.126	1.627
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	1.384	1.112	1.723
	Germany	**HRV**	**PIII(M3-M5)**	155	152	98.1	94.4	99.6	1.094	0.919	1.302
		Placebo	**PIII(M3-M5)**	84	84	100	95.7	100	1.150	0.924	1.430
	Spain	**HRV**	**PIII(M3-M5)**	188	187	99.5	97.1	100	1.665	1.469	1.888
		Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	1.669	1.408	1.978

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)
(Source: Study Report Body Rota-036Year 1, pg 138)

Anti-PT, anti-FHA, and anti-PRN antibody responses – Visit 3, Visit 4 (Spain only)

Seropositivity rates against PT were 100% for both groups in France, with rates being similar in the other countries; GMCs were also similar between groups in all countries. Seropositivity rates against FHA and against PRN were 100% for both groups in the Czech Republic, France, and Spain, with rates being similar in Germany. GMCs were also similar between groups in all countries. For all antigens, the differences in rates between groups, as well as the GMC ratio between the groups, were not statistically significant for any country.

					≥ 5 EL.U/ml				GMC (EL.U/ml)		
							95% CI			95% CI	
Antibody	**Country**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PT	**Czech Republic**	**HRV**	**PIII(M3-M5)**	181	180	99.4	97.0	100	55.6	50.6	61.0
		Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	53.4	46.5	61.3
	France	**HRV**	**PIII(M3-M5)**	83	83	100	95.7	100	42.1	37.2	47.8
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	46.3	39.3	54.5
	Germany	**HRV**	**PIII(M3-M5)**	153	140	91.5	85.9	95.4	30.2	25.7	35.5
		Placebo	**PIII(M3-M5)**	82	77	93.9	86.3	98.0	28.4	23.2	34.7
	Spain	**HRV**	**PIII(M3-M5)**	188	187	99.5	97.1	100	42.9	39.0	47.2
		Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	45.1	40.3	50.5
Anti-FHA	**Czech Republic**	**HRV**	**PIII(M3-M5)**	182	182	100	98.0	100	215.8	196.4	237.2
		Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	214.8	188.2	245.1
	France	**HRV**	**PIII(M3-M5)**	82	82	100	95.6	100	176.2	153.4	202.4
		Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	180.3	152.5	213.0
	Germany	**HRV**	**PIII(M3-M5)**	155	152	98.1	94.4	99.6	110.3	90.3	134.8
		Placebo	**PIII(M3-M5)**	84	82	97.6	91.7	99.7	97.5	74.7	127.3
	Spain	**HRV**	**PIII(M3-M5)**	188	188	100	98.1	100	159.2	144.6	175.3
		Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	161.1	141.8	183.1
Anti-PRN	**Czech Republic**	**HRV**	**PIII(M3-M5)**	182	182	100	98.0	100	112.8	100.5	126.7
		Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	113.8	97.0	133.5

France	**HRV**	**PIII(M3-M5)**	82	82	100	95.6	100	101.4	85.2	120.8
	Placebo	**PIII(M3-M5)**	43	43	100	91.8	100	110.7	82.5	148.7
Germany	**HRV**	**PIII(M3-M5)**	155	147	94.8	90.1	97.7	73.6	59.8	90.6
	Placebo	**PIII(M3-M5)**	84	82	97.6	91.7	99.7	75.6	57.2	100.0
Spain	**HRV**	**PIII(M3-M5)**	188	188	100	98.1	100	105.3	94.3	117.5
	Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	106.7	89.7	126.9

(Source: Study Report Body Rota-036Year 1, pg 139)

Anti-HBs antibody response - Visit 3, Visit 4 (Spain only)

Seroprotection rates and GMCs against HBs were the same or similar between groups in all countries. The differences in rates between groups, as well as the GMC ratios between groups, were not statistically significant for any country.

				≥ 10 mIU/ml				**GMC (mIU/ml)**		
						95% CI			**95% CI**	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Czech Republic	**HRV**	**PIII(M3-M5)**	181	177	97.8	94.4	99.4	408.6	330.2	505.6
	Placebo	**PIII(M3-M5)**	90	88	97.8	92.2	99.7	329.4	248.7	436.4
France	**HRV**	**PII(M3-M4)**	80	77	96.3	89.4	99.2	401.4	281.9	571.7
	Placebo	**PII(M3-M4)**	43	42	97.7	87.7	99.9	481.9	290.9	798.3
Germany	**HRV**	**PIII(M3-M5)**	152	119	78.3	70.9	84.6	143.2	102.1	200.8
	Placebo	**PIII(M3-M5)**	82	65	79.3	68.9	87.4	117.7	76.5	181.0
Spain	**HRV**	**PIII(M3-M5)**	187	184	98.4	95.4	99.7	832.5	676.2	1025.0
	Placebo	**PIII(M3-M5)**	90	85	94.4	87.5	98.2	861.3	589.6	1258.2

(Source: Study Report Body Rota-036Year 1, pg 140)

Anti-polio antibody responses to types 1, 2, 3 - Visit 3, Visit 4 (Spain only)

Seroprotection rates against all 3 poliovirus types were the same or similar between groups in all countries. GMTs were comparable between groups in all countries with overlapping 95% CIs. For each type, the difference in rates between groups was not statistically significant for any country, with the exception of the Czech Republic, where the rate difference (placebo-Rotarix) was -3.39% (95% CI: -11.54, -0.32), therefore favoring the Rotarix group. GMC ratios between the groups were not statistically significant for any country for any type.

					≥ 8 ED50				**GMT**		
							95% CI			**95% CI**	
Antibody	**Country**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-poliovirus type 1	**Czech Republic**	**HRV**	**PIII(M3-M5)**	122	122	100	97.0	100	445.5	343.4	578.0
		Placebo	**PIII(M3-M5)**	65	65	100	94.5	100	370.0	274.2	499.2
	France	**HRV**	**PIII(M3-M5)**	44	44	100	92.0	100	89.7	58.9	136.6
		Placebo	**PIII(M3-M5)**	30	29	96.7	82.8	99.9	142.3	75.5	268.3
	Germany	**HRV**	**PIII(M3-M5)**	108	99	91.7	84.8	96.1	119.1	82.0	173.0
		Placebo	**PIII(M3-M5)**	60	55	91.7	81.6	97.2	85.4	54.7	133.3
	Spain	**HRV**	**PIII(M3-M5)**	123	123	100	97.0	100	661.7	533.0	821.5
		Placebo	**PIII(M3-M5)**	58	58	100	93.8	100	590.9	438.6	796.2
Anti-poliovirus type 2	**Czech Republic**	**HRV**	**PIII(M3-M5)**	124	124	100	97.1	100	376.5	288.7	491.1
		Placebo	**PIII(M3-M5)**	59	57	96.6	88.3	99.6	269.8	173.1	420.6
	France	**HRV**	**PIII(M3-M5)**	44	41	93.2	81.3	98.6	52.5	33.2	82.8
		Placebo	**PIII(M3-M5)**	29	27	93.1	77.2	99.2	49.8	26.5	93.4
	Germany	**HRV**	**PIII(M3-M5)**	110	92	83.6	75.4	90.0	62.0	43.1	89.1
		Placebo	**PIII(M3-M5)**	62	51	82.3	70.5	90.8	51.7	32.6	82.2
	Spain	**HRV**	**PIII(M3-M5)**	118	117	99.2	95.4	100	402.6	310.7	521.8
		Placebo	**PIII(M3-M5)**	57	57	100	93.7	100	267.1	185.0	385.6
Anti-poliovirus	**Czech Republic**	**HRV**	**PIII(M3-M5)**	114	114	100	96.8	100	1153.0	884.4	1503.1
		Placebo	**PIII(M3-M5)**	65	65	100	94.5	100	970.6	696.6	1352.5

type 3	**France**	**HRV**	**PIII(M3-M5)**	44	44	100	92.0	100	217.3	128.9	366.1
		Placebo	**PIII(M3-M5)**	30	30	100	88.4	100	189.8	101.6	354.6
	Germany	**HRV**	**PIII(M3-M5)**	109	98	89.9	82.7	94.9	211.5	138.1	323.9
		Placebo	**PIII(M3-M5)**	59	52	88.1	77.1	95.1	107.2	60.8	189.1
	Spain	**HRV**	**PIII(M3-M5)**	120	117	97.5	92.9	99.5	1126.3	854.2	1485.2
		Placebo	**PIII(M3-M5)**	53	53	100	93.3	100	880.8	596.0	1301.8

(Source: Study Report Body Rota-036Year 1, pg 141)

Anti-PRP antibody response - Visit 3, Visit 4 (Spain only)

For both titer levels, seroprotection rates were similar between groups in all countries. GMCs were also similar between groups in all countries. The differences in rates between groups, as well as the GMC ratios between groups, were not statistically significant for any country.

				≥ 0.15 µg/ml				≥ 1.0 µg/ml				**GMC (µg/ml)**		
						95% CI				**95% CI**			**95% CI**	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Czech Republic	**HRV**	**PIII(M3-M5)**	182	179	98.4	95.3	99.7	139	76.4	69.5	82.3	2.862	2.349	3.486
	Placebo	**PIII(M3-M5)**	90	90	100	96.0	100	65	72.2	61.8	81.1	2.264	1.746	2.937
France	**HRV**	**PIII(M3-M5)**	80	76	95.0	87.7	98.6	46	57.5	45.9	68.5	1.388	1.006	1.916
	Placebo	**PIII(M3-M5)**	43	42	97.7	87.7	99.9	26	60.5	44.4	75.0	1.385	0.955	2.007
Germany	**HRV**	**PIII(M3-M5)**	154	133	86.4	79.9	91.4	93	60.4	52.2	68.2	1.344	1.028	1.757
	Placebo	**PIII(M3-M5)**	83	68	81.9	72.0	89.5	50	60.2	48.9	70.8	1.098	0.751	1.604
Spain	**HRV**	**PIII(M3-M5)**	187	182	97.3	93.9	99.1	148	79.1	72.6	84.7	2.796	2.268	3.447
	Placebo	**PIII(M3-M5)**	91	85	93.4	86.2	97.5	71	78.0	68.1	86.0	2.607	1.873	3.630

(Source: Study Report Body Rota-036Year 1, pg 142)

Post-Dose 3 (Visit 3) immunogenicity of routine vaccinations – Germany (Post-hoc analysis)

Post-hoc immunogenicity analysis was conducted in Germany to determine whether one study center, Center 7715, may have contributed to the overall lower immunogenicity response trends. A separate analysis was conducted on all German subjects excluding those from Center 7715. Only subjects who received 3 doses of childhood vaccinations up to 21 days before blood sampling were included in the analyses.

For subjects enrolled at Center 7715, immune responses to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2, and 3, and PRP was much lower in both groups than in the overall data presented above. In contrast, immune responses were much higher in both groups among subjects excluding those from Center 7715. Seroprotection rates for diphtheria and tetanus, as well as seropositivity rates for PT, FHA, and PRN, were 100% for both groups. Seroprotection rate for HBs (Rotarix-94.5%, placebo-100%), all polio types (Rotarix-100%, placebo-97.3 to 100%), and PRP (≥ 0.15µg/ml titer: Rotarix – 98.9%, placebo-92.3%; ≥ 1.0 µg/ml titer: Rotarix-76.3%, placebo-73.1%) were also high and comparable to estimates from other countries.

Post-Dose 2 (Visit 3) immunogenicity of routine vaccinations – Finland, Italy, Spain

In each country, seroprotection/seropositivity rates and GMCs/GMTs to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2, and 3, PRP, and SBA-MenC/PSC (Spain only) were similar between groups. Differences in rates and GMC or GMT ratios between groups for each vaccine antigen were not statistically significant, with the following exceptions: 1) difference in seroprotection rates against PRP (≥ 0.15µg/ml titer) in Finland favoring the Rotarix group 2) GMC ratios against polio type 3 in Finland and Spain, both favoring the Rotarix group

Year 1 Immunogenicity – TVC

Anti-RV IgA response
Anti-RV IgA seroconversion rates and GMCs at pre-Dose 1, Visit 3 (1-2 months post-Dose 2), and Visit 5 (3 months post-Dose 2, Spain only) are presented below. Results were similar to those from the ATP immunogenicity cohort. Seropositivity and GMC results by feeding criteria were also similar to those from the ATP analysis.

				≥ 20 U/ML				GMC		
						95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
All	**HRV**	**PRE**	902	19	2.1	1.3	3.3	< 20	-	-
		PII(M3-M4)	854	742	86.9	84.4	89.1	195.8	175.0	219.1
		PII(M5)	212	178	84.0	78.3	88.6	117.8	95.9	144.8
	Placebo	**PRE**	479	10	2.1	1.0	3.8	< 20	-	-
		PII(M3-M4)	473	45	9.5	7.0	12.5	< 20	-	-
		PII(M5)	110	26	23.6	16.1	32.7	21.9	16.3	29.4

(Source: Study Report Body Rota-036Year 1, pg 485)

Seroprotection/seropositivity rates and GMCs/GMTs to all childhood vaccine antigens for each group, by country, were similar to estimates obtained from the ATP analysis.

Immunogenicity – TVC of the immunogenicity-reactogenicity subset

Results of anti-RV IgA antibody immune responses, as well as post-Dose 2 or post-Dose 3 immune responses to childhood vaccinations, were generally consistent with those obtained from the ATP immunogenicity cohort.

Post-Dose 3 (Visit 6) immunogenicity of routine vaccinations - Finland
Anti-diphtheria seroprotection rates were high in both groups (Rotarix-99.4%, placebo-100%). Anti-tetanus seroprotection rates were 100% in both groups. GMCs to both antigens were similar between groups.

Anti-PT, anti-FHA, and anti-PRN seropositivity rates were 100% in both groups, with GMCs also being comparable between groups for each antigen.

Anti-HBs seroprotection rates were 100% in both groups, with GMCs comparable between groups.

Anti-poliovirus seroprotection rates against types 1 and 2 were 100% for both groups; seroprotection rates against type 3 were 100% for the Rotarix group and 98.8% for the placebo group. GMTs to all types were comparable between groups.

Anti-PRP seroprotection rates were 100% in both groups, with GMCs comparable between groups.

Post-Dose 3 (Visit 6) immunogenicity of routine vaccinations - Italy
Anti-diphtheria and anti-tetanus seroprotection rates were 100% in both groups, with similar GMCs to both antigens between groups.

Anti-PT, anti-FHA, and anti-PRN seropositivity rates were 100% in both groups, with GMCs also being comparable between groups for each antigen.

Anti-HBs seroprotection rates were 100% in the Rotarix group and 88.9% in the placebo group. GMCs were comparable between groups.

Anti-poliovirus seroprotection rates against types 1, 2 and 3 were 100% for both groups. GMTs to all types were comparable between groups.

Anti-PRP seroprotection rates were 100% in both groups, with GMCs comparable between groups.

Year 2 Efficacy (After Visit 5 to Visit 7) – ATP efficacy cohort

Summary of reported any RV GE and severe RV GE episodes – Year 2
The median duration of follow-up during the 2nd efficacy period was approximately 11.8 months in each group. Among Rotarix and placebo recipients, RV was detected in 61 and 110 GE episodes, respectively; no subject in either group had more than one RV GE episode during the 2nd efficacy follow-up period.

		HRV		Placebo	
	Total number of	N = 2554		N = 1294	
Event	episode reported	n	%	n	%
GE	1	573	22.4	315	24.3
	2	124	4.9	96	7.4
	3	25	1.0	13	1.0
	4	5	0.2	3	0.2
	5	1	0.0	2	0.2
	Any	728	28.5	429	33.2
RV GE	1	61	2.4	110	8.5
	Any	61	2.4	110	8.5

Source: Study Report Body Rota-036 Annex, pg 1340

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 19 Rotarix and 67 placebo recipients.

	Severity using Vesikari scale	HRV		Placebo	
Event		n	%	n	%
GE	Mild (1-6)	431	46.8	209	36.8
	Moderate (7-10)	324	35.2	195	34.3
	Severe (≥11)	158	17.2	159	28.0
	Unknown	8	0.9	5	0.9
	Any	921	100	568	100
RV GE	Mild (1-6)	12	19.7	13	11.8
	Moderate (7-10)	30	49.2	30	27.3
	Severe (≥11)	19	31.1	67	60.9
	Any	61	100	110	100

Source: Study Report Body Rota-036 Annex, pg 1341

Serotype G and P distribution is summarized below. G1 and G9 were the most prevalent serotypes.

		HRV N' = 61		Placebo N' = 110	
Country	**Serotype**	**n**	**%**	**N**	**%**
All countries	G1WT+G9+P8WT	0	0.0	1	0.9
	G1WT and unknown P type*	0	0.0	1	0.9
	G1WT+G2+P4	0	0.0	1	0.9
	G1WT+P8WT	14	23.0	40	36.4
	G2+G9+P4	0	0.0	1	0.9
	G2+P4	11	18.0	11	10.0
	G3+P8WT	2	3.3	5	4.5
	G4+P8WT	3	4.9	5	4.5
	G9+P8WT	25	41.0	42	38.2
	GX+P8WT	1	1.6	1	0.9

	P4 and unknown G type*	2	3.3	0	0.0
	Unknown G and P type*	3	4.9	2	1.8

GX = G12; * = not typable

Source: Study Report Body Rota-036 Annex, pg 1344

The percentages of unavailable stool sample results for each efficacy period are summarized below; percentages were comparable between groups.

	HRV N'= 921		Placebo N'= 568	
Category	**n**	**%**	**n**	**%**
No stools collected	100	10.9	68	12.0
Stools collected but no results available*	7	0.8	6	1.1
No stool results available	107	11.6	74	13.0

Source: Study Report Body Rota-036 Annex, pg 1341

Vaccine efficacy against severe RV GE – Year 2 (Secondary endpoint)
Nineteen (0.7%) Rotarix recipients reported severe RV GE compared to 67 (5.2%) placebo recipients. VE was 85.6% (95% CI: 75.8-91.9%).

VE against severe RV GE by main RV serotypes – Year 2 (Secondary endpoint)
VE against severe G1 RV GE was 96.5%. VE against G2, G9, and all non-G1 types pooled together reached statistical significance. However, the lower level of the 95% CI for VE against G2 was low (9.4%) compared to the other categories. Although the p-value was 0.047 for VE against G4, the lower level of the 95% CI was -28.0%. Although there were less G3 infections in Rotarix compared to placebo recipients, VE did not reach statistical significance.

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	**UL**	
G1						
Rotarix	2	0.1	96.5	86.2	99.6	<0.001
placebo	29	2.2				
G2						
Rotarix	1	0.0	89.9	9.4	99.8	0.018
placebo	5	0.4				
G3						
Rotarix	1	0.0	83.1	-110.3	99.7	0.114
placebo	3	0.2				
G4						
Rotarix	1	0.0	87.3	-28.0	99.7	0.047
placebo	4	0.3				
G9						
Rotarix	11	0.4	77.7	53.0	90.1	<0.001
placebo	25	1.9				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	14	0.5	80.8	63.7	90.4	<0.001
placebo	37	2.9				

GX=G12

Source: Study Report Body Rota-036 Annex, pg 1356

VE against hospitalized RV GE – Year 2 (Secondary endpoint)
Two Rotarix recipients (0.1%) were hospitalized for RV GE compared to 13 placebo (1.0%) recipients. VE was 92.2% (95% CI: 65.6-99.1%).

VE against RV GE requiring medical attention – Year 2 (Secondary endpoint)
Medical attention occurred significantly less in Rotarix than placebo recipients (31 vs 66, or 1.2% vs 5.1%, respectively). VE was 76.2% (95% CI: 63.0-85.0%).

VE against any RV GE – Year 2 (Exploratory endpoint)
Sixty-one (2.4%) Rotarix recipients reported any RV GE compared to 110 (8.5%) placebo recipients. VE was 71.9% (95% CI: 61.2-79.8%).

VE against any RV GE by main RV serotypes – Year 2 (Exploratory endpoint)
VE against any G1 RV GE was 83.5%. VE against G9 and all non-G1 types pooled together reached statistical significance. Although the p-values for VE against G2 and G3 were less than 0.05, the LL of the 95% CI for both serotypes were negative estimates. Also, although there were less G4 infections in Rotarix than placebo recipients, VE did not reach statistical significance.

Group (wild type)	n	% (n/N)	VE %	95%CI		P-value
				LL	UL	
G1						
Rotarix	14	0.5	83.5	69.3	91.7	<0.001
placebo	43	3.3				
G2						
Rotarix	11	0.4	57.1	-3.7	82.6	0.048
placebo	13	1.0				
G3						
Rotarix	2	0.1	79.7	-23.8	98.1	0.047
placebo	5	0.4				
G4						
Rotarix	3	0.1	69.6	-56.2	95.3	0.128
placebo	5	0.4				
G9						
Rotarix	25	1.0	71.2	51.9	83.1	<0.001
placebo	44	3.4				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	42	1.6	68.2	52.6	78.9	<0.001
placebo	67	5.2				

GX=G12
Source: Study Report Body Rota-036 Annex, pg 1354

VE against all cause any GE – Year 2 (Exploratory endpoint)
VE against GE of any etiology was 14.0% (95% CI: 2.9-23.8%).

VE against all cause severe GE – Year 2 (Exploratory endpoint)
VE against severe GE of any etiology was 50.7% (95% CI: 37.8-60.9%).

VE against all cause GE requiring hospitalization – Year 2 (Exploratory endpoint)
VE against GE of any etiology requiring hospitalization was 64.9% (95% CI: 33.5-81.9%).

VE against severe RV GE using the Clark scale – Year 2 (Exploratory endpoint)
Compared to the Vesikari scale, the Clark scale classified less severe RV GE episodes in both treatment groups (Rotarix-1, Placebo-15). VE_{Clark} was 96.6% (95% CI: 78.0-99.9%), compared to $VE_{Vesikari}$ of 85.6%.

VE against G1 (100.0%; 95% CI: 57.0-100%), G9 (92.8%; 95% CI: 43.7-99.8), and all non-G1 types pooled together (94.4%; 95% CI: 59.4-99.9%) reached statistical significance.

VE against any RV GE and severe RV GE, by country – Year 2 (Exploratory)
VE against any RV GE ranged from -5.7 to 75.1% in the Czech Republic, Finland, France, Germany and Spain. However, only the VE estimates for Finland (73.7%; 95% CI: 62.6-81.7%) and Spain (66.2; 95% CI: 1.8-89.1%) reached statistical significance due to a larger study population than in the other countries. VE could not be calculated for Italy due to 0 RV GE episodes occurring.

Similarly, $VE_{Vesikari}$ against severe RV GE reached statistical significance in Finland and Spain only. $VE_{Vesikari}$ was 85.7% (95% CI: 75.2-92.2%) for Finland and 83.9% (95% CI: 10.1-98.4%) for Spain. VE_{Clark} was 95.8% (95% CI: 71.6-99.9%) for Finland and 100.0% (95% CI: -16.7-100.0%) for Spain.

Combined Efficacy (2 weeks post-Dose 2 to Visit 7) – ATP efficacy cohort

Summary of reported any RV GE and severe RV GE episodes – Combined period

The median duration of follow-up during the combined efficacy period was approximately 17.5 months in each group. Among Rotarix and placebo recipients, RV was detected in 85 and 204 GE episodes, respectively; no subject in either group had more than one RV GE episode during the 1st efficacy follow-up period

		HRV		Placebo	
	Total number of	N = 2572		N = 1302	
Event	episode reported	n	%	n	%
GE	1	754	29.3	404	31.0
	2	239	9.3	179	13.7
	3	80	3.1	46	3.5
	4	20	0.8	10	0.8
	5	1	0.0	7	0.5
	6	2	0.1	1	0.1
	Any	1096	42.6	647	49.7
RV GE	1	85	3.3	204	15.7
	Any	85	3.3	204	15.7

Source: Study Report Body Rota-036 Annex, pg 86

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 24 Rotarix and 127 placebo recipients.

	Severity using	HRV		Placebo	
Event	Vesikari scale	n	%	n	%
GE	Mild (1-6)	733	46.7	366	37.3
	Moderate (7-10)	548	34.9	319	32.5
	Severe (≥11)	279	17.8	291	29.7
	Unknown	9	0.6	5	0.5
	Any	1569	100	981	100
RV GE	Mild (1-6)	20	23.5	24	11.8
	Moderate (7-10)	41	48.2	53	26.0
	Severe (≥11)	24	28.2	127	62.3
	Any	85	100	204	100

Source: Study Report Body Rota-036 Annex, pg 86

Serotype G and P distribution is summarized below. G1P8 was the most prevalent circulating type during the combined efficacy period, followed by G9P8.

	HRV		Placebo	
	N' = 85		N' = 204	
Serotype	n	%	n	%
G1WT+G4+P8WT	0	0.0	1	0.5
G1WT+G9+P8WT	0	0.0	1	0.5
G1WT and unknown P type*	0	0.0	1	0.5
G1WT+G2+P4	0	0.0	1	0.5
G1WT+P8WT	18	21.2	85	41.7
G2 and unknown P type*	0	0.0	1	0.5
G2+G9+P4	0	0.0	1	0.5
G2+P4	14	16.5	14	6.9
G3+P8WT	3	3.5	10	4.9
G4+P8WT	6	7.1	17	8.3
G9+P8WT	38	44.7	69	33.8
GX+P8WT	1	1.2	1	0.5
P4 and unknown G type*	2	2.4	0	0.0
Unknown G and P type*	3	3.5	2	1.0

N'= number of RV GE episodes reported
n (%)= number(percentage) of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type; GX = G12; * = not typable
Source: Study Report Body Rota-036 Annex, pg 87

The percentages of unavailable stool sample results for each efficacy period are summarized below; percentages were comparable between groups.

	HRV N'= 1569		Placebo N'= 981	
Category	**n**	**%**	**n**	**%**
No stools collected	142	9.1	102	10.4
Stools collected but no results available*	19	1.2	16	1.6
No stool results available	161	10.3	118	12.0

Source: Study Report Body Rota-036 Annex, pg 1311

Clinical characteristics of RV GE episodes – Combined period
The duration of looser than normal stools and vomiting were shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration, and hospitalization were also less in the Rotarix group compared to placebo.

Vaccine efficacy against severe RV GE – Combined period (Secondary endpoint)
VE of Rotarix against severe RV GE caused by circulating wild-type RV during the 1st efficacy follow-up period was 90.4%.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2572	24	0.9	0.6	1.4	90.4	85.1	94.1	<0.001
Placebo	1302	127	9.8	8.2	11.5				

Source: Study Report Body Rota-036 Annex, pg 88

VE reached 100% (95% CI: 93.1-100%) for a score of ≥ 17 points.

VE against severe RV GE by main RV serotypes – Combined period (Secondary endpoint)
VE against severe G1 RV GE was 96.4%. VE against G2, G3, G4, G9, and all non-G1 types pooled together reached statistical significance; the lower level of the 95% CI for VE against G2 was low (24.0%) compared to the other categories.

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	**UL**	
G1						
Rotarix	4	0.2	96.4	90.4	99.1	<0.001
placebo	57	4.4				
G2						
Rotarix	2	0.1	85.5	24.0	98.5	0.009
placebo	7	0.5				
G3						
Rotarix	1	0.0	93.7	52.8	99.9	0.001
placebo	8	0.6				
G4						
Rotarix	1	0.0	95.4	68.3	99.9	<0.001
placebo	11	0.8				
G9						
Rotarix	13	0.5	85.0	71.7	92.6	<0.001
placebo	44	3.4				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	17	0.7	87.7	78.9	93.2	<0.001

placebo	70	5.4				

GX=G12
Source: Study Report Body Rota-036 Annex, pg 90

VE against hospitalized RV GE – Combined period (Secondary endpoint)
Two (0.1%) Rotarix recipients were hospitalized for RV GE compared to 25 (1.9%) placebo recipients. VE was 96.0% (95% CI: 83.8-99.5%).

VE against RV GE requiring medical attention – Combined period (Secondary endpoint)
Medical attention occurred significantly less in Rotarix than placebo recipients (41 vs 128, or 1.6% vs 9.8%, respectively). VE was 83.8% (95% CI: 76.8-88.9%).

VE against any RV GE – Combined period (Exploratory endpoint)
VE of Rotarix against any RV GE caused by circulating wild-type RV was 78.9%.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2572	85	3.3	2.6	4.1	78.9	72.7	83.8	<0.001
Placebo	1302	204	15.7	13.7	17.8				

Source: Study Report Body Rota-036 Annex, pg 92

VE against any RV GE by main RV serotypes – Combined period (Exploratory)
VE against any G1 RV GE was 89.8%. VE against G2, G3, G4, G9, and all non-G1 types pooled together reached statistical significance. However, the lower level of the 95% CI for VE against G2 and G3 were low (10.1% and 41.0%, respectively) compared to the other categories.

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	**UL**	
G1						
Rotarix	18	0.7	89.8	82.9	94.2	<0.001
placebo	89	6.8				
G2						
Rotarix	14	0.5	58.3	10.1	81.0	0.020
placebo	17	1.3				
G3						
Rotarix	3	0.1	84.8	41.0	97.3	0.002
placebo	10	0.8				
G4						
Rotarix	6	0.2	83.1	55.6	94.5	<0.001
placebo	18	1.4				
G9						
Rotarix	38	1.5	72.9	59.3	82.2	<0.001
placebo	71	5.5				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	62	2.4	72.9	62.9	80.5	<0.001
placebo	116	8.9				

GX=G12
Source: Study Report Body Rota-036 Annex, pg 93

VE against all cause any GE – Combined period (Exploratory endpoint)
VE against GE of any etiology was 14.2% (95% CI: 5.4-22.3%).

VE against all cause severe GE – Combined period (Exploratory endpoint)
VE against severe GE of any etiology was 49.6% (95% CI: 39.8-57.8%).

VE against all cause GE requiring hospitalization – Combined (Exploratory endpoint)
VE against GE of any etiology requiring hospitalization was 71.5% (95% CI: 53.4-82.9%).

VE against any and severe RV GE by serum IgA status at Visit 3 – Combined period (Exploratory endpoint)
Among subjects who were negative for anti-RV IgA at Visit 3, 4 (3.6%) Rotarix recipients versus 43 (10.4%) placebo recipients reported any RV GE from 2 weeks post-Dose 2 to Visit 7; VE was 64.9% (95% CI: 3.4-90.9%). VE against severe RV GE was 100.0% (95% CI: 19.2-100.0%) among seronegative subjects. Among subjects who were seropositive at Visit 3, VE was 65.1% although not statistically significant; VE against severe RV GE could not be calculated. The applicant concluded that it was difficult to correlate seroconversion rate and VE because immunogenicity was evaluated in only a subset of subjects.

VE against severe RV GE by feeding criteria – Combined period (Exploratory endpoint)
VE against any RV GE among subjects that breastfed at the time of at least one dose was 76.2% (95% CI: 68.7-82.1%). VE among subjects not breastfed at any of the doses was 89.8% (95% CI: 77.6-95.9%). VE against severe RV GE among subjects that breastfed at the time of at least one dose was 88.4% (95% CI: 81.6-93.0%). VE among subjects not breastfed at any of the doses was 98.1% (95% CI: 88.2-100%).

VE against severe RV GE using the Clark scale – Combined period (Exploratory endpoint)
Compared to the Vesikari scale, the Clark scale classified less severe RV GE episodes in both treatment groups (Rotarix-3, Placebo-30). However, VE_{Clark} was 94.9% (95% CI: 83.7-99.0%), similar to $VE_{Vesikari}$ (90.4%).

VE against G1 (96.4%; 95% CI: 76.2-99.9%), G9 (92.2%; 95% CI: 65.6-99.1), and all non-G1 types pooled together (93.7%; 95% CI: 73.1-99.3%) reached statistical significance.

VE against any and severe RV GE, by country – Combined period (Exploratory endpoint)
VE against any RV GE ranged from -57.5 to 80.6% in the Czech Republic, Finland, France, Germany and Spain. However, only the VE estimates for Finland (80.6%; 95% CI: 74.3-85.6%) and Spain (69.3; 95% CI: 13.3-89.9%) reached statistical significance due to a larger study population than in the other countries. VE could not be calculated for Italy due to 0 RV GE episodes occurring.

Similarly, $VE_{Vesikari}$ against severe RV GE reached statistical significance in Finland and Spain only. $VE_{Vesikari}$ was 90.9% (95% CI: 85.4-94.5%) for Finland and 83.9% (95% CI: 10.1-98.4%) for Spain. VE_{Clark} was 94.2% (95% CI: 81.0-98.9%) for Finland and 100.0% (95% CI: -16.7-100.0%) for Spain.

Dose 1 to Visit 7 Efficacy – TVC

Summary of reported any RV GE and severe RV GE episodes – Dose 1 to Visit 7
The median duration of follow-up during this interval was approximately 20 months in each group. Among Rotarix and placebo recipients, wild-type RV was detected in 87 and 215 GE episodes, respectively; no subject in either group had more than one RV GE episode during the 1st efficacy follow-up period

		HRV		Placebo	
	Total number of	N= 2646		N= 1348	
Event	episode reported	n	%	n	%
GE	1	788	29.8	432	32.0
	2	292	11.0	196	14.5
	3	97	3.7	63	4.7
	4	31	1.2	16	1.2
	5	6	0.2	7	0.5
	6	5	0.2	1	0.1
	7	0	0.0	1	0.1
	Any	1219	46.1	716	53.1
RV GE	1	87	3.3	215	15.9
	Any	87	3.3	215	15.9

Source: Study Report Body Rota-036 Annex, pg 1362

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 24 Rotarix and 132 placebo recipients.

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-6)**	926	50.1	444	39.5
	Moderate (7-10)	607	32.9	363	32.3
	Severe (≥11)	303	16.4	308	27.4
	Unknown	11	0.6	10	0.9
	Any	1847	100	1125	100
RV GE	**Mild (1-6)**	21	24.1	25	11.6
	Moderate (7-10)	42	48.3	58	27.0
	Severe (≥11)	24	27.6	132	61.4
	Any	87	100	215	100

Source: Study Report Body Rota-036 Annex, pg 1362

Serotype G and P distribution is summarized below. G1 and G9 were the most prevalent wild-type circulating viruses. Of note, vaccine virus (G1P8) was detected in GE stool samples of 5 Rotarix recipients; G9P8 was also detected from 1 of the 5 subjects.

		HRV N' = 87		Placebo N' = 215	
Country	**Serotype**	**n**	**%**	**N**	**%**
All countries	G9+G1vac+P8WT+P8vac	1	1.1	0	0.0
	G1WT+G4+P8WT	0	0.0	1	0.5
	G1WT+G9+P8WT	0	0.0	1	0.5
	G1WT and unknown P type*	0	0.0	1	0.5
	G1WT+G2+P4	0	0.0	1	0.5
	G1WT+P8WT	18	20.7	87	40.5
	G2 and unknown P type*	0	0.0	1	0.5
	G2+G9+P4	0	0.0	1	0.5
	G2+P4	14	16.1	14	6.5
	G3+P8WT	4	4.6	12	5.6
	G4+P8WT	6	6.9	18	8.4
	G9+P8WT	38	43.7	75	34.9
	GX+P8WT	1	1.1	1	0.5
	P4 and unknown G type*	2	2.3	0	0.0
	Unknown G and P type*	3	3.4	2	0.9

vac=vaccine strain; GX = G12; * = not typable
Source: Study Report Body Rota-036 Annex, pg 1365

The percentages of unavailable stool sample results for each efficacy period are summarized below; percentages were comparable between groups.

	HRV N'= 1847		Placebo N'= 1125	
Category	**n**	**%**	**n**	**%**
No stools collected	174	9.4	117	10.4
Stools collected but no results available*	24	1.3	19	1.7
No stool results available	198	10.7	136	12.1

Source: Study Report Body Rota-036 Annex, pg 1362

Clinical characteristics of RV GE episodes – Dose 1 to Visit 7

The duration of looser than normal stools and vomiting were shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration, and hospitalization were also less in the Rotarix group compared to placebo.

Vaccine efficacy against severe RV GE – Dose 1 to Visit 7 (Exploratory endpoint)
VE of Rotarix against severe RV GE caused by circulating wild-type RV was 90.7%.

			n/N95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2646	24	0.9	0.6	1.3	90.7	85.6	94.3	<0.001
Placebo	1348	132	9.8	8.3	11.5				

Source: Study Report Body Rota-036 Annex, pg 1382

VE reached 100% (95% CI: 93.1-100%) for a score of ≥ 17 points.

VE against severe RV GE by main RV serotypes – Dose 1 to Visit 7 (Exploratory endpoint)
VE against severe G1 RV GE was 96.5%. VE against G2, G3, G4, G9, and all non-G1 types pooled together reached statistical significance. However, the lower level of the 95% CI for VE against G2 was low (23.6%) compared to the other categories.

Group (wild type)	**n**	**% (n/N)**	**VE %**	**95%CI**		**P-value**
				LL	**UL**	
G1						
Rotarix	4	0.2	96.5	90.5	99.1	<0.001
placebo	58	4.3				
G2						
Rotarix	2	0.1	85.4	23.6	98.5	0.009
placebo	7	0.5				
G3						
Rotarix	1	0.0	94.3	59.1	99.9	<0.001
placebo	9	0.7				
G4						
Rotarix	1	0.0	95.4	68.1	99.9	<0.001
placebo	11	0.8				
G9						
Rotarix	13	0.5	85.9	73.5	93.0	<0.001
placebo	47	3.5				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	17	0.6	88.3	80.0	93.5	<0.001
placebo	74	5.5				

GX=G12

Source: Study Report Body Rota-036 Annex, pg 1385

VE against hospitalized RV GE – Dose 1 to Visit 7 (Secondary endpoint)
Two (0.1%) Rotarix recipients were hospitalized for RV GE compared to 25 (1.9%) placebo recipients. VE was 95.9% (95% CI: 83.7-99.5%).

VE against RV GE requiring medical attention – Dose 1 to Visit 7 (Secondary endpoint)
Medical attention occurred significantly less in Rotarix than placebo recipients (42 vs 137, or 1.6% vs 10.2%, respectively). VE was 84.4% (95% CI: 77.8-89.2%).

VE against any RV GE – Dose 1 to Visit 7 (Exploratory endpoint)
VE of Rotarix against any RV GE caused by circulating wild-type RV was 79.4%.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2646	87	3.3	2.6	4.0	79.4	73.4	84.1	<0.001
Placebo	1348	215	15.9	14.0	18.0				

Source: Study Report Body Rota-036 Annex, pg 1380

VE against any RV GE by main RV serotypes – Dose 1 to Visit 7 (Exploratory endpoint)
VE against any G1 RV GE was 89.9%. VE against G2, G3, G4, G9, and all non-G1 types pooled together reached statistical significance. However, the lower level of the 95% CI for VE against G2 and G3 were low (9.6% and 44.0%, respectively) compared to the other categories.

Group (wild type)	n	% (n/N)	VE %	95%CI		P-value
				LL	UL	
G1						
Rotarix	18	0.7	89.9	83.2	94.3	<0.001
placebo	91	6.8				
G2						
Rotarix	14	0.5	58.0	9.6	80.9	0.020
placebo	17	1.3				
G3						
Rotarix	4	0.2	83.0	44.0	96.0	<0.001
placebo	12	0.9				
G4						
Rotarix	6	0.2	83.9	58.1	94.7	<0.001
placebo	19	1.4				
G9						
Rotarix	39	1.5	74.2	61.6	82.9	<0.001
placebo	77	5.7				
Pooled non-G1(G2, G3, G4, G9, GX)						
Rotarix	64	2.4	73.9	64.5	81.0	<0.001
placebo	125	9.3				

GX=G12
Source: Study Report Body Rota-036 Annex, pg 1382

VE against all cause any GE – Dose 1 to Visit 7 (Exploratory endpoint)
VE against GE of any etiology was 13.3% (95% CI: 4.7-21.0%).

VE against all cause severe GE – Dose 1 to Visit 7 (Exploratory endpoint)
VE against severe GE of any etiology was 47.9% (95% CI: 38.2-56.1%).

VE against all cause GE requiring hospitalization – Dose 1 to Visit 7 (Exploratory)
VE against GE of any etiology requiring hospitalization was 71.0% (95% CI: 53.4-82.3%).

VE against severe RV GE using the Clark scale – Dose 1 to Visit 7 (Exploratory endpoint)
Compared to the Vesikari scale, the Clark scale classified less severe RV GE episodes in both treatment groups (Rotarix-3, Placebo-30). VE_{Clark} was 94.9% (95% CI: 83.6-99.0%), compared to $VE_{Vesikari}$ (90.7%).

VE against G1 (96.4%; 95% CI: 76.1-99.9%), G9 (92.2%; 95% CI: 65.4-99.1), and all non-G1 types pooled together (93.7%; 95% CI: 72.9-99.3%) reached statistical significance.

VE against any RV GE and severe RV GE, by country – Dose 1 to Visit 7 (Exploratory)
VE against any RV GE ranged from 21.8 to 80.7% in the Czech Republic, Finland, France, Germany and Spain. However, only the VE estimates for Finland (80.7%; 95% CI: 74.5-85.6%) and Spain (76.2; 95% CI: 41.7-91.1%) reached statistical significance due to a larger study population than in the other countries. VE could not be calculated for Italy due to 0 RV GE episodes occurring.

Similarly, $VE_{Vesikari}$ against severe RV GE reached statistical significance in Finland and Spain only. $VE_{Vesikari}$ was 90.9% (95% CI: 85.4-94.6%) for Finland and 89.9% (95% CI: 52.5-98.9%) for Spain. VE_{Clark} was 94.2% (95% CI: 80.9-98.9%) for Finland and 100.0% (95% CI: -22.6-100.0%) for Spain.

Year 2 Immunogenicity – ATP immunogenicity cohort

Post-Dose 2 (Visit 4) and Post-Dose 3 (Visit 5/6) immunogenicity of routine vaccinations – Finland, Italy

Anti-diphtheria and anti-tetanus antibody responses – Visit 3, Visit 5/6

Seroprotection rates against diphtheria and tetanus were 100% for both groups at both visits in Italy. Seroprotection rates against tetanus were also 100% for both groups at both visits in Finland. Seroprotection rates against diphtheria in Finland were similar for both groups at both visits (>99% in both groups at Visit 5/6). GMCs were also similar between groups at both time points in both countries. For both antigens, the differences in rates between groups, as well as the GMC ratio between the groups, were not statistically significant at Visit 5/6 for either country.

Italy

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-Diphtheria	**HRV**	**PII (M3)**	13	13	100	75.3	100	2.223	1.358	3.640
		PIII (M9)	12	12	100	73.5	100	6.738	4.313	10.529
	Placebo	**PII (M3)**	9	9	100	66.4	100	2.876	1.950	4.240
		PIII (M9)	9	9	100	66.4	100	7.395	4.539	12.049
anti-Tetanus	**HRV**	**PII (M3)**	13	13	100	75.3	100	2.278	1.395	3.719
		PIII (M9)	12	12	100	73.5	100	5.766	3.656	9.095
	Placebo	**PII (M3)**	9	9	100	66.4	100	2.765	1.363	5.608
		PIII (M9)	9	9	100	66.4	100	6.453	3.392	12.273

PII (M3) = post dose 2 of routine childhood vaccination (Visit 3); PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Source: Study Report Body Rota-036 Annex, pg 102

Finland

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-Diphtheria	**HRV**	**PII (M3)**	167	153	91.6	86.3	95.3	0.569	0.470	0.689
		PIII (M10)	164	163	99.4	96.6	100	2.809	2.418	3.263
	Placebo	**PII (M3)**	105	99	94.3	88.0	97.9	0.550	0.441	0.687
		PIII (M10)	101	101	100	96.4	100	2.493	2.135	2.911
anti-Tetanus	**HRV**	**PII (M3)**	167	167	100	97.8	100	1.206	1.043	1.394
		PIII (M10)	164	164	100	97.8	100	5.583	5.043	6.181
	Placebo	**PII (M3)**	105	105	100	96.5	100	1.351	1.133	1.611
		PIII (M10)	101	101	100	96.4	100	4.976	4.378	5.656

PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

Source: Study Report Body Rota-036 Annex, pg 102

Anti-PT, anti-FHA, and anti-PRN antibody responses – Visit 3, Visit 5/6

Seropositivity rates against PT, FHA, and PRN were 100% for both groups at both time points in Italy. Seropositivity rates against PT and FHA were 100% for both groups at both time points in Finland; rates against PRN were 100% for both groups at Visit 5/6. GMCs were also similar between groups at both time points in both countries, except that Visit 5/6 anti-PT titers tended to be higher in the Rotarix group compared to placebo in Finland. For all 3 antigens, the differences in rates between groups, as well as the GMC ratio between the groups, were not statistically

significant at Visit 5/6 for either country, except that the anti-PT placebo/Rotarix GMC ratio in Finland was 0.85 (95% CI: 0.74-0.98), therefore favoring the Rotarix group.

Italy

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-PT	**HRV**	**PII (M3)**	13	13	100	75.3	100	47.3	25.2	89.0
		PIII (M9)	12	12	100	73.5	100	69.7	38.6	125.8
	Placebo	**PII (M3)**	8	8	100	63.1	100	44.0	27.4	70.6
		PIII (M9)	9	9	100	66.4	100	79.7	63.1	100.8
anti-FHA	**HRV**	**PII (M3)**	13	13	100	75.3	100	241.8	152.6	383.2
		PIII (M9)	12	12	100	73.5	100	504.4	323.1	787.5
	Placebo	**PII (M3)**	9	9	100	66.4	100	152.7	99.6	234.2
		PIII (M9)	9	9	100	66.4	100	531.3	392.9	718.3
anti-PRN	**HRV**	**PII (M3)**	13	13	100	75.3	100	124.0	59.8	257.3
		PIII (M9)	12	12	100	73.5	100	285.2	174.3	466.8
	Placebo	**PII (M3)**	9	9	100	66.4	100	168.9	117.7	242.4
		PIII (M9)	9	9	100	66.4	100	348.6	235.3	516.4

Source: Study Report Body Rota-036 Annex, pg 103

Finland

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-PT	**HRV**	**PII (M3)**	167	167	100	97.8	100	50.9	46.1	56.3
		PIII (M10)	164	164	100	97.8	100	96.1	88.3	104.5
	Placebo	**PII (M3)**	104	104	100	96.5	100	47.8	42.1	54.4
		PIII (M10)	101	101	100	96.4	100	81.7	72.6	91.8
anti-FHA	**HRV**	**PII (M3)**	167	167	100	97.8	100	179.0	160.1	200.1
		PIII (M10)	164	164	100	97.8	100	551.3	503.3	604.0
	Placebo	**PII (M3)**	105	105	100	96.5	100	173.8	152.7	197.9
		PIII (M10)	101	101	100	96.4	100	476.1	421.7	537.4
anti-PRN	**HRV**	**PII (M3)**	166	164	98.8	95.7	99.9	77.2	64.2	93.0
		PIII (M10)	164	164	100	97.8	100	307.7	275.2	343.9
	Placebo	**PII (M3)**	103	102	99.0	94.7	100	97.9	78.2	122.5
		PIII (M10)	101	101	100	96.4	100	303.3	262.4	350.6

Source: Study Report Body Rota-036 Annex, pg 104

<u>Anti-HBs antibody response - Visit 3, Visit 5/6</u>

Seroprotection rates and GMCs against HBs were higher in the Rotarix group than placebo at both time points in Italy, with rates being 100% at both visits for the Rotarix group. Seroprotection rates and GMCs were similar between groups at both time points in Finland; rates were 100% for both groups at Visit 5/6. The differences in rates between groups, as well as the GMC ratios between groups, were not statistically significant at Visit 5/6 for either country.

Italy

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-HBS	**HRV**	**PII (M3)**	11	11	100	71.5	100	711.9	272.9	1857.1
		PIII (M9)	12	12	100	73.5	100	4030.4	1759.8	9230.6
		PII (M3)	8	7	87.5	47.3	99.7	282.6	60.9	1312.8

	Placebo	**PIII (M9)**	8	7	87.5	47.3	99.7	2185.8	246.1	19413.3

Source: Study Report Body Rota-036 Annex, pg 104

Finland

				≥ 10 MIU/ML				**GMC**		
						95% CI			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-HBS	**HRV**	**PII (M3)**	166	162	97.6	93.9	99.3	431.6	345.3	539.4
		PIII (M10)	163	163	100	97.8	100	6638.9	5529.8	7970.5
	Placebo	**PII (M3)**	105	98	93.3	86.7	97.3	399.7	286.0	558.5
		PIII (M10)	101	101	100	96.4	100	5577.3	4270.6	7283.7

Source: Study Report Body Rota-036 Annex, pg 105

Anti-polio antibody responses to types 1, 2, 3 - Visit 3, Visit 5/6

Seroprotection rates against poliovirus types 1 and 2 were 100% for both groups at both time points in Italy, while rates were 100% for poliovirus type 3 for both groups at Visit 5/6. Seroprotection rates against all 3 types were similar between groups at both time points in Finland; rates were 100% against types 1 and 2 for both groups at Visit 5/6, while rates were 100% and 98% for the Rotarix and placebo groups, respectively, against type 3 at Visit 5/6. GMTs were also similar between groups at both time points in both countries, except that Visit 5/6 anti-Polio 2 titers tended to be higher in the Rotarix group compared to placebo in Finland. For each type, the differences in rates between groups, as well as the GMT ratio between the groups, were not statistically significant at Visit 5/6 for either country, except that the anti-Polio 2 placebo/Rotarix GMC ratio in Finland was 0.54 (95% CI: 0.34-0.86), therefore favoring the Rotarix group.

Italy

				≥ 8 ED50				**GMT**		
						95% CI			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-Polio 1	**HRV**	**PII (M3)**	5	5	100	47.8	100	415.8	190.3	908.7
		PIII (M9)	3	3	100	29.2	100	6502.0	2406.0	17570.7
	Placebo	**PII (M3)**	5	5	100	47.8	100	337.8	115.7	986.2
		PIII (M9)	4	4	100	39.8	100	3158.4	929.8	10728.8
anti-Polio 2	**HRV**	**PII (M3)**	4	4	100	39.8	100	107.6	9.3	1241.9
		PIII (M9)	4	4	100	39.8	100	5792.6	1922.5	17453.4
	Placebo	**PII (M3)**	6	6	100	54.1	100	256.0	153.1	428.2
		PIII (M9)	4	4	100	39.8	100	4466.8	1741.6	11456.0
anti-Polio 3	**HRV**	**PII (M3)**	4	3	75.0	19.4	99.4	234.8	1.9	28973.7
		PIII (M9)	4	4	100	39.8	100	4466.6	648.2	30780.4
	Placebo	**PII (M3)**	6	6	100	54.1	100	304.4	44.0	2107.4
		PIII (M9)	4	4	100	39.8	100	2655.9	197.0	35804.4

Source: Study Report Body Rota-036 Annex, pg 106

Finland

				≥ 8 ED50				**GMT**		
						95% CI			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-Polio 1	**HRV**	**PII (M3)**	151	132	87.4	81.0	92.3	47.3	36.2	61.9
		PIII (M10)	136	136	100	97.3	100	1072.1	865.3	1328.4
	Placebo	**PII (M3)**	98	85	86.7	78.4	92.7	37.2	26.9	51.3
		PIII (M10)	94	94	100	96.2	100	896.9	689.3	1167.0
anti-Polio 2	**HRV**	**PII (M3)**	154	97	63.0	54.8	70.6	11.9	9.7	14.7
		PIII (M10)	133	133	100	97.3	100	589.7	443.2	784.5

	Placebo	**PII (M3)**	98	60	61.2	50.8	70.9	11.4	9.0	14.6
		PIII (M10)	88	88	100	95.9	100	319.4	221.6	460.5
anti-Polio 3	**HRV**	**PII (M3)**	151	139	92.1	86.5	95.8	83.2	62.6	110.7
		PIII (M10)	129	129	100	97.2	100	1499.4	1153.4	1949.2
	Placebo	**PII (M3)**	94	82	87.2	78.8	93.2	49.5	34.3	71.6
		PIII (M10)	82	81	98.8	93.4	100	1028.4	714.8	1479.6

Source: Study Report Body Rota-036 Annex, pg 106

Anti-PRP antibody response - Visit 3, Visit 5/6

For both titer levels, seroprotection rates were 100% at Visit 5/6 for both groups in Italy. At the ≥ 0.15µg/ml titer, rates were 100% at Visit 5/6 for both groups in Finland; at ≥ 1 µg/ml titer, rates were >96.0% for both groups at Visit 5/6. GMCs were also similar between groups in all countries, except that Visit 5/6 titers in Finland tended to be higher in the Rotarix group. The difference in rates between groups for both titers was not statistically significant at Visit 5/6 for either country. The GMC ratio between the groups in Italy was also not statistically significant. In Finland, the anti-PRP placebo/Rotarix GMC ratio was 0.73 (95% CI: 0.55-0.98), therefore favoring the Rotarix group.

Italy

				≥ 0.15 UGR/ML				**≥ 1 UGR/ML**				**GMC**		
						95% CI				**95% CI**			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-PRP	**HRV**	**PII (M3)**	13	12	92.3	64.0	99.8	9	69.2	38.6	90.9	2.313	0.750	7.137
		PIII (M9)	12	12	100	73.5	100	12	100	73.5	100	13.191	6.450	26.980
	Placebo	**PII (M3)**	9	8	88.9	51.8	99.7	4	44.4	13.7	78.8	1.905	0.347	10.461
		PIII (M9)	9	9	100	66.4	100	9	100	66.4	100	14.265	4.464	45.580

Source: Study Report Body Rota-036 Annex, pg 107

Finland

				≥ 0.15 UGR/ML				**≥ 1 UGR/ML**				**GMC**		
						95% CI				**95% CI**			**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-PRP	**HRV**	**PII (M3)**	167	162	97.0	93.2	99.0	96	57.5	49.6	65.1	1.671	1.326	2.107
		PIII (M10)	163	163	100	97.8	100	158	96.9	93.0	99.0	16.051	13.429	19.186
	Placebo	**PII (M3)**	105	96	91.4	84.4	96.0	57	54.3	44.3	64.0	1.365	1.002	1.860
		PIII (M10)	101	101	100	96.4	100	100	99.0	94.6	100	11.752	9.372	14.736

Source: Study Report Body Rota-036 Annex, pg 107

Year 2 Immunogenicity – TVC for immunogenicity-reactogenicity

Post-Dose 2 (Visit 4) and Post-Dose 3 (Visit 5/6) immunogenicity of routine vaccinations – Finland, Italy

Immunogenicity results obtained in the TVC for immunogenicity-reactogenicity subset were generally consistent with those obtained from the ATP immunogenicity cohort.

Visit 5/6 anti-diphtheria and anti-tetanus seroprotection rates were >99.4% in both groups in either country, with similar GMCs to both antigens between groups.

Visit 5/6 anti-PT, anti-FHA, and anti-PRN seropositivity rates were 100% in both groups in either country, with GMCs also being comparable between groups for each antigen.

Anti-HBs seroprotection rates were 100% in the Rotarix group in either country. GMCs were comparable between groups.

Anti-poliovirus seroprotection rates against types 1, 2 and 3 were 100% in the Rotarix group in either country. GMTs to all types were comparable between groups.

Visit 5/6 anti-PRP seroprotection rates for both titers were >97.0% in both groups in either country, with GMCs being comparable between groups.

8.1.2.2.3 Safety outcomes

Year 1 Safety – TVC for immunogenicity-reactogenicity subset

Compliance in returning symptom sheets for general solicited AEs after each dose was high in both groups (>99%).

Overall incidence of AEs, solicited or unsolicited – Days 0-7 post-dose
The percentages of subjects who reported at least one solicited/unsolicited symptom after Dose 1 and after Dose 2, as well as the percentages who reported at least one symptom among those who received at least one study dose, were similar between groups. The incidence of AEs in either group did not increase with subsequent doses.

		Any symptom				
					95% CI	
	Group	**N**	**n**	**%**	**LL**	**UL**
Dose 1	HRV	914	620	67.8	64.7	70.9
	Placebo	490	330	67.3	63.0	71.5
Dose 2	HRV	905	589	65.1	61.9	68.2
	Placebo	486	327	67.3	62.9	71.4
Overall/dose	HRV	1819	1209	66.5	64.2	68.6
	Placebo	976	657	67.3	64.3	70.3
Overall/subject	HRV	914	736	80.5	77.8	83.0
	Placebo	490	410	83.7	80.1	86.8

For each dose: N = number of subjects having received the considered dose of HRV vaccine/placebo
n/% = number/percentage of subjects with at least one symptom for the considered dose, reported during the specified period
For overall/dose: N = total number of HRV vaccine/placebo doses administered
n/% = number/percentage of doses followed by at least one symptom, during the specified period
For overall/subject: N= number of subjects having received at least one dose of HRV vaccine/placebo
n%= number/percentage of subjects with at least one symptom, reported during the specified period
(Source: Study Report Body Rota-036Year 1, pg 159)

Overall incidence of Grade 3 AEs, solicited or unsolicited – Days 0-7 post-dose
The percentages of subjects who reported at least one Grade 3 solicited or unsolicited symptom after Dose 1 and after Dose 2, as well as the percentages who reported at least one Grade 3 symptom among those who received at least one study dose, were less in the Rotarix group compared to placebo. 95% CIs for the point estimates were overlapping between groups. The incidence of AEs in either group did not increase with subsequent doses.

		Any symptom				
					95% CI	
	Group	**N**	**n**	**%**	**LL**	**UL**
Dose 1	HRV	914	45	4.9	3.6	6.5
	Placebo	490	31	6.3	4.3	8.9
Dose 2	HRV	905	40	4.4	3.2	6.0
	Placebo	486	28	5.8	3.9	8.2
Overall/dose	HRV	1819	85	4.7	3.7	5.7
	Placebo	976	59	6.0	4.6	7.7
Overall/subject	HRV	914	79	8.6	6.9	10.7
	Placebo	490	53	10.8	8.2	13.9

(Source: Study Report Body Rota-036Year 1, pg 518)

Overall incidence of vaccine-related AEs, solicited or unsolicited – Days 0-7 post-dose
The percentages of subjects who reported at least one vaccine-related solicited/unsolicited symptom after Dose 1 and after Dose 2, as well as the percentages who reported at least one vaccine-related symptom among those who received at least one study dose, were less in the Rotarix group compared to placebo. 95% CIs for the point estimates were overlapping between groups. The incidence of AEs in either group did not increase with subsequent doses.

		Any symptom				
					95% CI	
	Group	**N**	**n**	**%**	**LL**	**UL**
Dose 1	HRV	914	402	44.0	40.7	47.3
	Placebo	490	226	46.1	41.6	50.7
Dose 2	HRV	905	361	39.9	36.7	43.2
	Placebo	486	202	41.6	37.1	46.1
Overall/dose	HRV	1819	763	41.9	39.7	44.3
	Placebo	976	428	43.9	40.7	47.0
Overall/subject	HRV	914	528	57.8	54.5	61.0
	Placebo	490	296	60.4	55.9	64.8

(Source: Study Report Body Rota-036Year 1, pg 519)

Solicited general AEs – Days 0-7 post-dose
The incidence of total AEs, Grade 3 AEs, and vaccine-related AEs for each symptom after each dose was similar between Rotarix and placebo group. Post-Dose 1 incidence for each symptom appeared similar to post-Dose 2 incidence, with the exception of total fever, which was 8.8% and 10.6% higher post-Dose 2 in Rotarix and placebo recipients, respectively. Smaller increases in Grade 3 and vaccine-related fever post-Dose 2 were also observed in both groups. Most of the post-vaccination fever AEs were Grade 1 and 2, and thought to be attributed by co-administered childhood vaccines.

Irritability/fussiness was the most common AE in both groups after each dose, followed by cough/runny nose. Diarrhea AEs were uncommon in both groups after each dose. Grade 3 AEs were uncommon for each symptom.

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Cough/Runny nose	**Total**	914	221	24.2	21.4	27.1	490	117	23.9	20.2	27.9
	Grade 3	914	7	0.8	0.3	1.6	490	2	0.4	0.0	1.5
	Related	914	58	6.3	4.9	8.1	490	29	5.9	4.0	8.4
Diarrhea	**Total**	914	24	2.6	1.7	3.9	490	11	2.2	1.1	4.0
	Grade 3	914	3	0.3	0.1	1.0	490	4	0.8	0.2	2.1
	Related	914	18	2.0	1.2	3.1	490	7	1.4	0.6	2.9
Fever	**Total**	914	166	18.2	15.7	20.8	490	91	18.6	15.2	22.3
	Grade 3	914	0	0.0	0.0	0.4	490	0	0.0	0.0	0.8
	Related	914	133	14.6	12.3	17.0	490	67	13.7	10.8	17.0
Irritability/Fussiness	**Total**	914	460	50.3	47.0	53.6	490	250	51.0	46.5	55.5
	Grade 3	914	23	2.5	1.6	3.8	490	19	3.9	2.4	6.0
	Related	914	299	32.7	29.7	35.9	490	171	34.9	30.7	39.3
Loss of appetite	**Total**	914	210	23.0	20.3	25.8	490	100	20.4	16.9	24.3
	Grade 3	914	4	0.4	0.1	1.1	490	1	0.2	0.0	1.1
	Related	914	126	13.8	11.6	16.2	490	71	14.5	11.5	17.9
Vomiting	**Total**	914	101	11.1	9.1	13.3	490	52	10.6	8.0	13.7
	Grade 3	914	10	1.1	0.5	2.0	490	6	1.2	0.5	2.6
	Related	914	44	4.8	3.5	6.4	490	24	4.9	3.2	7.2
Dose 2											
Cough/Runny nose	**Total**	905	234	25.9	23.0	28.8	486	149	30.7	26.6	35.0
	Grade 3	905	10	1.1	0.5	2.0	486	1	0.2	0.0	1.1

	Related	905	53	5.9	4.4	7.6	486	34	7.0	4.9	9.6
Diarrhea	**Total**	905	15	1.7	0.9	2.7	486	9	1.9	0.9	3.5
	Grade 3	905	6	0.7	0.2	1.4	486	6	1.2	0.5	2.7
	Related	905	6	0.7	0.2	1.4	486	8	1.6	0.7	3.2
Fever	**Total**	905	244	27.0	24.1	30.0	486	142	29.2	25.2	33.5
	Grade 3	905	2	0.2	0.0	0.8	486	4	0.8	0.2	2.1
	Related	905	164	18.1	15.7	20.8	486	95	19.5	16.1	23.4
Irritability/Fussiness	**Total**	905	390	43.1	39.8	46.4	486	215	44.2	39.8	48.8
	Grade 3	905	21	2.3	1.4	3.5	486	7	1.4	0.6	2.9
	Related	905	238	26.3	23.5	29.3	486	123	25.3	21.5	29.4
Loss of appetite	**Total**	905	195	21.5	18.9	24.4	486	102	21.0	17.5	24.9
	Grade 3	905	6	0.7	0.2	1.4	486	1	0.2	0.0	1.1
	Related	905	118	13.0	10.9	15.4	486	57	11.7	9.0	14.9
Vomiting	**Total**	905	53	5.9	4.4	7.6	486	46	9.5	7.0	12.4
	Grade 3	905	9	1.0	0.5	1.9	486	7	1.4	0.6	2.9
	Related	905	18	2.0	1.2	3.1	486	23	4.7	3.0	7.0

N = number of subjects having received the considered dose of HRV vaccine/placebo
n/% = number/percentage of subjects with the specified symptom reported for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
(Source: Study Report Body Rota-036Year 1, pg 161)

There appeared to be no significant and isolated peak in the percentage of subjects with diarrhea or vomiting during Day 0 to Day 7 after each dose. Fever occurred most frequently at Day 0 and Day 1 in both groups after each dose.

There were no significant differences in rates of total, Grade 3, or vaccine-related solicited AEs between groups for any of the symptoms after any dose (table below). Rates of AEs for each symptom after each dose were also similar between groups in each country. Distribution of AEs for each country appeared similar to the overall distribution for all countries pooled together.

In the Rotarix group, ≥ 10% of subjects reported any cough/runny nose, fever, irritability/fussiness, loss of appetite, and vomiting, while 4.2% reported any diarrhea.
Grade 3 symptoms reported in ≥ 1% and <10 % of Rotarix subjects were cougn/runny nose (1.8%), diarrhea (1.0%), irritability/fussiness (4.4%), loss of appetite (1.0%), and vomiting (2.0%).

		HRV					**Placebo**				
					95 % CI					**95 % CI**	
Symptom	**Type**	**N**	**N**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/dose											
Cough/Runny nose	**Total**	1819	455	25.0	23.0	27.1	976	266	27.3	24.5	30.2
	Grade 3	1819	17	0.9	0.5	1.5	976	3	0.3	0.1	0.9
	Related	1819	111	6.1	5.0	7.3	976	63	6.5	5.0	8.2
Diarrhea	**Total**	1819	39	2.1	1.5	2.9	976	20	2.0	1.3	3.1
	Grade 3	1819	9	0.5	0.2	0.9	976	10	1.0	0.5	1.9
	Related	1819	24	1.3	0.8	2.0	976	15	1.5	0.9	2.5
Fever	**Total**	1819	410	22.5	20.6	24.5	976	233	23.9	21.2	26.7
	Grade 3	1819	2	0.1	0.0	0.4	976	4	0.4	0.1	1.0
	Related	1819	297	16.3	14.7	18.1	976	162	16.6	14.3	19.1
Irritability/ Fussiness	**Total**	1819	850	46.7	44.4	49.1	976	465	47.6	44.5	50.8
	Grade 3	1819	44	2.4	1.8	3.2	976	26	2.7	1.7	3.9
	Related	1819	537	29.5	27.4	31.7	976	294	30.1	27.3	33.1
Loss of appetite	**Total**	1819	405	22.3	20.4	24.2	976	202	20.7	18.2	23.4
	Grade 3	1819	10	0.5	0.3	1.0	976	2	0.2	0.0	0.7
	Related	1819	244	13.4	11.9	15.1	976	128	13.1	11.1	15.4
Vomiting	**Total**	1819	154	8.5	7.2	9.8	976	98	10.0	8.2	12.1
	Grade 3	1819	19	1.0	0.6	1.6	976	13	1.3	0.7	2.3

	Related	1819	62	3.4	2.6	4.3	976	47	4.8	3.6	6.4
Overall/subject											
Cough/Runny nose	**Total**	914	366	40.0	36.8	43.3	490	205	41.8	37.4	46.3
	Grade 3	914	16	1.8	1.0	2.8	490	3	0.6	0.1	1.8
	Related	914	99	10.8	8.9	13.0	490	52	10.6	8.0	13.7
Diarrhea	**Total**	914	38	4.2	3.0	5.7	490	20	4.1	2.5	6.2
	Grade 3	914	9	1.0	0.5	1.9	490	10	2.0	1.0	3.7
	Related	914	24	2.6	1.7	3.9	490	15	3.1	1.7	5.0
Fever	**Total**	914	310	33.9	30.8	37.1	490	192	39.2	34.8	43.7
	Grade 3	914	2	0.2	0.0	0.8	490	4	0.8	0.2	2.1
	Related	914	234	25.6	22.8	28.6	490	137	28.0	24.0	32.2
Irritability/Fussiness	**Total**	914	567	62.0	58.8	65.2	490	308	62.9	58.4	67.1
	Grade 3	914	40	4.4	3.1	5.9	490	25	5.1	3.3	7.4
	Related	914	395	43.2	40.0	46.5	490	218	44.5	40.0	49.0
Loss of appetite	**Total**	914	310	33.9	30.8	37.1	490	161	32.9	28.7	37.2
	Grade 3	914	9	1.0	0.5	1.9	490	2	0.4	0.0	1.5
	Related	914	202	22.1	19.4	24.9	490	107	21.8	18.3	25.8
Vomiting	**Total**	914	131	14.3	12.1	16.8	490	80	16.3	13.2	19.9
	Grade 3	914	18	2.0	1.2	3.1	490	12	2.4	1.3	4.2
	Related	914	56	6.1	4.7	7.9	490	40	8.2	5.9	11.0

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
(Source: Study Report Body Rota-036Year 1, pg 162)

Year 1 Safety – TVC

Unsolicited AEs – Days 0-30 post-dose

The percentages of subjects who had at least one AE of any kind, one Grade 3 AE, and one vaccine-related AE were similar between groups (table below). Among unsolicited AEs of any kind, significant increase in Rotarix compared to placebo was observed for the PT *Flatulence* (risk difference= 1.33%) and PT *Irritability* (risk difference= 3.99%). These PTs were not statistically significant between groups among Grade 3 AEs, and only PT *Irritability* (3.19%) was statistically significant between groups among vaccine-related AEs. After further review of cases in these 2 PTs, the applicant concluded that there was no evidence of clinically relevant findings and that the imbalance was possibly a chance finding.

AE PTs of any intensity reported in ≥ 1% of Rotarix subjects were conjunctivitis (3.2%), upper abdominal pain (1.4%), constipation (1.9%), flatulence (3.8%), gastrointestinal disorder (2.9%), regurgitation of food (1.3%), teething (2.1%), vomiting (1.8%), fatigue (1.7%), injection site pain (4.0%), irritability (21%), pyrexia (23.1%), bronchiolitis (1.2%), bronchitis (1.5%), ear infection (1.0%), influenza (1.4%), nasopharyngitis (1.1%), otitis media (4.8%), respiratory tract infection (2.3%), rhinitis (11.6%), upper respiratory tract infection (7.3%), crying (8.3%), cough (5.1%), nasal congestion (1.2%), atopic dermatitis (1.2%), eczema (1.2%), rash (1.2%),

MedDRA PT	**HRV N = 2646**				**Placebo N = 1348**				**Risk Difference (HRV minus Placebo)**			**P-Value**
			95% CI				95% CI			95% CI		
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
Unsolicited AEs												
At least one symptom	1686	63.7	61.9	65.6	828	61.4	58.8	64.0	2.29	-0.87	5.49	0.156
SOC: Gastrointestinal disorders (10017947)	379	14.3	13.0	15.7	171	12.7	11.0	14.6	1.64	-0.64	3.82	0.155
PT: Diarrhea (10012735) 0	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047

PT: Flatulence (10016766)	100	3.8	3.1	4.6	33	2.4	1.7	3.4	1.33	0.17	2.40	0.027
SOC: General disorders and administration site conditions (10018065)	1009	38.1	36.3	40.0	477	35.4	32.8	38.0	2.75	-0.43	5.88	0.089
PT: Irritability (10022998)	555	21.0	19.4	22.6	229	17.0	15.0	19.1	3.99	1.41	6.48	0.003
SOC: Respiratory, thoracic and mediastinal disorders (10038738)	199	7.5	6.5	8.6	105	7.8	6.4	9.4	-0.27	-2.08	1.43	0.762
PT: Stridor (10042241)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
Grade 3 unsolicited AEs												
At least one symptom	233	8.8	7.8	10.0	118	8.8	7.3	10.4	0.05	-1.87	1.86	0.956
SOC: Infections and infestations (10021881)	150	5.7	4.8	6.6	73	5.4	4.3	6.8	0.25	-1.31	1.70	0.741
PT: Bronchiolitis (10006448)	4	0.2	0.0	0.4	8	0.6	0.3	1.2	-0.44	-1.03	-0.08	0.016
PT: Otitis externa (10033072)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
SOC: Respiratory, thoracic and mediastinal disorders (10038738)	27	1.0	0.7	1.5	20	1.5	0.9	2.3	-0.46	-1.32	0.23	0.199
PT: Rhinorrhoea (10039101)	0	0.0	0.0	0.1	6	0.4	0.2	1.0	-0.45	-0.97	-0.20	0.001
Unsolicited AEs assessed as related to vaccination												
At least one symptom	772	29.2	27.4	30.9	373	27.7	25.3	30.1	1.51	-1.48	4.42	0.320
SOC: General disorders and administration site conditions (10018065)	598	22.6	21.0	24.2	270	20.0	17.9	22.3	2.57	-0.14	5.20	0.063
PT: Irritability (10022998)	373	14.1	12.8	15.5	147	10.9	9.3	12.7	3.19	1.01	5.28	0.005

(Source: Study Report Body Rota-036Year 1, pg 164)

Reviewer Note: Reviewer obtained the following differences from the applicant, highlighted in bold italics. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

MedDRA PT	**HRV N = 2646**				**Placebo N = 1348**				**Risk Difference (HRV minus Placebo)**			**P-Value**
			95% CI				95% CI			95% CI		
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
Unsolicited AEs												
SOC: General disorders and administration site conditions (10018065)	***1008***	38.1			477	35.4						
Unsolicited AEs assessed as related to vaccination												
SOC: General disorders and administration site conditions (10018065)	***597***	22.6			270	20.0						

Grade 3 PTs reported in ≥ 1% of Rotarix subjects were irritability (1.0%), pyrexia (2.3%), otitis media (2.3%), upper respiratory tract infection (1.6%),

Vaccine-related PTs reported in ≥ 1% of Rotarix subjects were upper abdominal pain (1.2%), flatulence (1.9%), gastrointestinal disorder (2.2%), fatigue (1.4%), irritability (14.1%), pyrexia (13.4%), and crying (4.9%),

AEs reported after IM administration of study dose
One subject received Dose 1 of placebo IM by error. The subject experienced fever (T_{max}=38.5°C on Day 0), irritability (grade 1 on Day 0), and loss of appetite (grade 1 on Day 0). No injection site reactions were reported. The child was subsequently asymptomatic and event was considered resolved after 3 days; Dose 2 was administered Dose 2 orally. The treatment code for this subject was not broken.
Reviewer Note: Reviewer noted that Dose 1 was categorized as "administered according to protocol" and given orally ("OR") for this subject in the analysis database.

Reviewer Note: The reviewer also explored rates of bronchitis in each group. After PTs *Bronchitis* and *Bronchitis acute* were combined, no imbalances were observed within 31 days post-vaccination (Rotarix- 35 [1.3%], placebo - 18 [1.3%]) or within 43 days post-vaccination (Rotarix – 38 [1.4%], placebo – 20 [1.5%]).

Reviewer Note: The reviewer also explored rates of non-SAE pneumonia in each group. After PTs *Pneumonia* and *Bronchopneumonia* were combined, an imbalance not favoring the Rotarix group was not observed within 31 days post-vaccination (Rotarix- 3 [0.11%], placebo - 3 [0.22%]) or within 43 days post-vaccination (Rotarix – 3 [0.11%], placebo – 4 [0.30%]).

SAEs – Dose 1 to Visit 5
During this interval, there were significantly less Rotarix than placebo recipients who reported at least one SAE. None of the 268 SAEs were judged to be related to vaccination. The applicant did not provide distributions of SAEs by SOC or PT categories for this interval.

	Rotarix N = 2646				Placebo N = 1348				Risk Difference (Rotarix - Placebo)			
			95% CI				95% CI			95% CI		
	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one SAE	145	5.5	4.6	6.4	95	7.0	5.7	8.5	-1.57	-3.26	-0.01	0.049
At least one IS	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

IS=intussusception
(Source: Study Report Body Rota-036Year 1, pg 165)

Reviewer Note: The reviewer did not observe noticeable differences for each PT between groups. In addition, the reviewer calculated the number of subjects who reported at least one SAE from Day 0-30 post-dose as follows: Rotarix – 46 (17.4%), placebo – 28 (20.8%). Also, one Rotarix recipient reported a non-IS SAE that was categorized as causally related to vaccination (PT *Gastroenteritis*, 7 days post-Dose 1). No SAE PT was reported in ≥ 1% of Rotarix subjects.

One case of intussusception (IS) was reported. This subject, a 4 month-old male from the Czech Republic who developed abdominal pain and vomiting 8 days post-Dose 2 of Rotarix, was diagnosed by abdominal ultrasound, and underwent surgical correction without intestinal resection. Rectal swabs were negative for enteric pathogens. The event resolved after 7 days. The investigator considered this event to have possibly been related to vaccination. The treatment code for this subject was broken.

Deaths – Dose 1 to Visit 5
No deaths were reported during this interval.

SAEs and non-serious AEs leading to drop-out at Visit 5
Four subjects (all placebo recipients) dropped out of the study due to SAEs. Three of the 4 dropped out due to convulsion-related AEs (PTs *Convulsion*, *Epilepsy*, and *Infantile spasms*), while the fourth dropped out due to PT *Lissencephaly*. All SAEs were considered to be unrelated to vaccination.

Seven Rotarix recipients and 2 placebo recipients dropped out due to non-SAEs. Among the Rotarix recipients, 2 dropped out due to PT *Bronchospasm* (34 and 61 days post-dose), 1 due to

PT *Constipation* (14 days post-dose),1 due to PT *Gastroenteritis* (4 days post-dose), 1 due to PT *Hypersensitivity* (Day 0), 1 due to PT *Irritability* (2 days post-dose), and 1 due to PT *Hematochezia* (8 days post-Dose). The 2 placebo recipients dropped out due to PT *Motor dysfunction* (41 days post-dose) and PT *Gastrointestinal disorder* (4 days post-dose). Five of the 9 non-SAEs leading to drop-out were assessed as related to vaccination (Rotarix-4: *Bronchospasm, Gastroenteritis, Hypersensitivity, Hematochezia, Irritability*; placebo-1: *Gastrointestinal disorder*).

Follow-up safety (Dose 1 to Visit 7) – TVC, Year 2 efficacy period

SAEs – Dose 1 to Visit 7
During this interval, the percentage of Rotarix recipients who reported at least one SAE was less than that for placebo recipients. SAE PTs reported in ≥ 1% of Rotarix subjects were bronchiolitis (1.0%) and chronic bronchiolitis (1.6%),

	HRV N = 2646				**Placebo N = 1348**				**Risk Difference (HRV minus Placebo)**			
			95% CI				**95% CI**			**95% CI***		
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-Value**
At least one SAE	290	11.0	9.8	12.2	176	13.1	11.3	15.0	-2.10	-4.31	0.01	0.051
At least one IS	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988

Source: Study Report Body Rota-036 Annex, pg 109

Three cases of IS occurred during this interval. Of these, one was already described previously in the *Year 1 Safety – TVC* **SAEs- Dose 1 to Visit 5** section. The remaining two cases occurred after Visit 5 and were assessed as not causally related to vaccination. One case, a 10 month-old female, developed vomiting 7 months post-Dose 2 of Rotarix. An abdominal ultrasound was suggestive for intestinal invagination that was resolved by enema. A stool sample was RV positive. The subject was discharged from the hospital after one day.

The second case, a 12 month-old female, developed diarrhea 9 months post-Dose 2 of placebo, followed by abdominal pain, vomiting, irritability and lethargy. Abdominal ultrasound showed IS which spontaneously resolved during the ultrasound. Stool samples were negative for enteric pathogens. The subject was discharged from the hospital after two days.

SAEs in the MedDRA SOC *Infections and infestations,* were reported significantly less in the Rotarix group compared to the placebo group. The observed imbalance in this SOC was primarily driven by PTs *Gastroenteritis* and *Gastroenteritis rotavirus,* which were also reported significantly less in the Rotarix group than the placebo group, therefore reflecting the efficacy of Rotarix in preventing GE episodes.

PTs *Head injury* and *Testicular torsion* were also reported significantly less in the Rotarix group compared to placebo. These imbalances were judged to be likely a chance finding and not clinically relevant.

The PT *Pneumonia* was reported significantly more in the Rotarix group compared to the placebo group (24 vs 4, p=0.029). Of the 28 cases, 19 (Rotarix-17, placebo-2) were reported after Visit 5. Only one of the cases was reported within 30 days after vaccination (Rotarix group, 29 days post-Dose 2), and a significant imbalance between groups for PT *Pneumonia* as an unsolicited AE from Day 0 to Day 30 after any study dose was not observed. Upon further review of cases individually, the applicant determined that no clinically relevant finding were evident, therefore concluding that the potential imbalance was possibly due to chance.
Reviewer Note: Based on the data provided by the applicant, the reviewer noted that among the 28 cases of PT *Pneumonia*, 3 (Rotarix-3, placebo-0) occurred within 42 days post-vaccination. When the reviewer combined pneumonia-related PTs (*Pneumonia, Bronchopneumonia, Lobar pneumonia, Pneumonia viral*), an imbalance was still seen from Dose 1 to Visit 7 (Rotarix – 31, placebo – 7), within 31 days post-vaccination (Rotarix – 2, placebo – 0) and within 43 days post-vaccination (Rotarix – 5, placebo – 0).

Reviewer Note: The reviewer also explored rates of SAE bronchitis in each group. After PTs *Bronchitis* and *Bronchitis acute* were combined, an imbalance not favoring the Rotarix group was not observed within 31 days post-vaccination (Rotarix- 1 [0.04%], placebo - 2 [0.15%]) or within 43 days post-vaccination (Rotarix – 4 [0.15%], placebo – 3 [0.22%]).

Reviewer Note: The reviewer also explored rates of convulsion-related SAEs in each group. After PTs *Convulsion*, *Epilepsy*, *Infantile spasms*, *Myoclonus*, and *Partial seizures* were combined, an imbalance not favoring the Rotarix group was not observed within 31 or 43 days post-vaccination (Rotarix- 1 [0.04%], placebo - 1 [0.07%]).

Deaths – Dose 1 to Visit 7
No deaths were reported during this interval.

SAEs and non-serious AEs leading to drop-out at Visit 7
Five subjects (Rotarix-1, placebo-4) withdrew due to SAEs. The four placebo subjects were previously described in the *Year 1 Safety – TVC* **SAEs and non-serious AEs leading to drop-out at Visit 5** section. The remaining one Rotarix recipient withdrew due to PT *Primitive neuroectodermal tumour* which was assessed as not related to vaccination.

Ten subjects (Rotarix-7, placebo-3) dropped out due to non-SAEs. Nine of the subjects (Rotarix-7, placebo-2) were previously described in the *Year 1 Safety – TVC* **SAEs and non-serious AEs leading to drop-out at Visit 5** section. The remaining one placebo recipient withdrew due to PT *Varicella* which was assessed as not related to vaccination.

Individual report forms reviewed

Individual International Event Report (i.e. SAE) report forms were reviewed for all IS cases.

3. Comments & Conclusions

In Rota-036, two doses of Rotarix at a potency of $10^{6.5}$ $CCID_{50}$ per dose, administered to children 6 to 14 weeks of age at 1-month or 2-month intervals, were efficacious (87.1%) against any RV GE during the period from 2 weeks post-Dose 2 until the end of the 1st RV epidemic season (1st efficacy follow-up period). Rotarix was also efficacious against severe RV GE during this period high using either the Vesikari scale (95.8%) or Clark scale (93.3%). Furthermore, VE against RV GE leading to hospitalization or any medical attention during this interval was 100% and 91.8%, respectively. During the period from after Dose 1 to the end of the 1st RV epidemic season, efficacy was demonstrated against any RV GE and severe RV GE at 87.3% and 96.0%, respectively.

Statistically significant VE was observed against any wild-type G1 (95.6%), G3 (89.9%), G4 (88.3%), and G9 (75.6%) RV GE during the 1st efficacy follow-up period; however, the lower limit of the 95% CI for G3 was 9.5%. When all non-G1 types were pooled together, VE was over 79.3%. Statistically significant VE was also observed against severe wild-type G1 (96.4%), G3 (100%), G4 (100%), and G9 (94.7%) RV GE during the 1st efficacy follow-up period. However, the lower limit of the 95% CI for the G3 estimate was 44.8%. When all non-G1 types were pooled together, VE was 95.4%. Efficacy was >80% from Dose 1 to 1 year of age and was 79% during Year 2 of follow-up.

During the period from after Visit 5 (the end of the 1st RV epidemic season) until the end of the 2nd RV epidemic season (2nd efficacy follow-up period), Rotarix was efficacious against severe RV GE (85.6%), severe RV GE due to G1 (96.5%) and non-G1 (G2, G4, G9) strains (≥ 77% each, although the lower limits of the 95% CI for G2 and G4 were 9.4% and -28.0%, respectively), RV GE leading to hospitalization (92.2%), and RV GE requiring medical attention (76.2%). VE was also efficacious against any RV GE (71.9%), and any wild-type G1 (83.5%) and G9 (71.2%) RV GE.

During the period from 2 weeks post-Dose 2 until the end of the 2nd RV epidemic season (combined follow-up period), Rotarix was efficacious against severe RV GE (90.4%), severe RV GE due to G1 (96.4%) and non-G1 (G2, G3, G4, G9) strains (≥ 85% each, although the lower limit of the 95% CI for

G2 was 24.0%), RV GE leading to hospitalization (96%), and RV GE requiring medical attention (83.8%). VE was also demonstrated against any RV GE (78.9%) and any wild-type G1 (89.8%). VE was ≥ 58.3% each against RV GE due to G2, G3, G4, and G9 serotypes, although the 95% CIs for G2 and G3 were 10.1% and 41.0%, respectively.

Analyses of immune responses to routine childhood vaccinations demonstrated that there were no significant differences between treatment groups in seroprotection rates, seropositivity rates, or GMC/GMT to any of the vaccine antigens that did not favor the Rotarix group. Although there appeared to be no impact of Rotarix on the immune responses to routine co-administered vaccine antigens at different time points, clinical limits for non-inferiority of Rotarix compared to placebo were not pre-defined for this study.

An increased risk in IS was not seen within 31 days after any dose nor throughout the rest of the study; a total of only 3 cases (Rotarix-2, placebo-1) were reported. Overall rates of subjects who experienced a solicited or unsolicited AE from Day 0 to Day 7 post-dose were similar between treatment groups. Imbalances in rates of solicited AEs between groups were also not observed. Among the unsolicited AEs reported from Day 0 to 30 post-dose, flatulence and irritability were reported significantly more in the Rotarix group, most of which were below Grade 3 in intensity. After further review of cases reporting these AEs, here was no evidence of clinically relevant findings and that the imbalance was possibly a chance finding. Statistically significant differences in frequencies of SAEs not favoring the Rotarix group were only seen for MedDRA PT *Pneumonia*. However, only one of the cases of pneumonia, occurring in the Rotarix group, had onset within 31 days of vaccination.

The validity of the results was strengthened by the double-blinded, placebo-controlled, multi-center study design. Efficacy, safety, and immunogenicity endpoints, case definitions, and study cohorts were clearly defined and appropriate. Given the limited study population sizes in some of the countries, there were no significant efficacy or safety imbalances by country. Overall, the study was well-conducted without any noticeable sources of biases. Data quality was acceptable, and appropriate data analyses were conducted as stated in the protocol and amendments. Protocol deviations were minor, occurred infrequently, and did not lead to any SAEs. Subject dropouts and missing data were handled appropriately and according to protocol.

The applicant stated that the proposed indication for Rotarix is the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, G9). Results from Rota-036 support the use of Rotarix in the prevention of any and RV GE. Efficacy data supports the use of Rotarix in the prevention of any and severe RV GE caused by G1 wild-type strains; VE was statistically significant for Year 1, Year 2, and the combined efficacy periods. Efficacy data also supports the use of Rotarix in the prevention of any and severe RV GE caused by non-G1 types when pooled together. When VE was assessed for each non-G1 type individually, Rotarix demonstrated statistically significant efficacy against any and severe G9 RV GE during all three study periods. Statistically significant efficacy against any and severe G3 RV GE was demonstrated during Year 1 and the combined efficacy period. However, the lower limit of the 95% CIs against any and severe G3 RV GE during Year 1 were low. Efficacy against any and severe G4 RV GE was statistically significant during Year 1 and the combined efficacy period. Statistically significant VE was demonstrated against any and severe G2 RV GE during the Year 2 and combined period, although the lower limit of the 95% CI was low for each estimate.

8.1.3 Rota-004

8.1.3.1 Protocol 444563/004 (rota-004): A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SB Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with human rotavirus

8.1.3.1.1 Objective/Rationale

Primary Objectives
1. To determine if 2 doses of $10^{4.7}$ ffu ($10^{5.3}$ $CCID_{50}$) of Rotarix can prevent RV GE during the period from 2 weeks post-Dose 2 until the end of the 1st RV disease season post-vaccination

Secondary Efficacy Objectives
1. To assess VE of 2 doses of $10^{4.7}$ ffu of Rotarix against severe RV GE from the end of the 1st RV disease season until the end of the 2nd RV disease season post-vaccination
2. To assess VE of 2 doses of $10^{4.7}$ ffu of Rotarix against any and severe RV GE from 2 weeks post-Dose 2 until the end of the 2nd RV disease season post-vaccination
3. To assess VE of 2 doses of $10^{4.7}$ ffu of Rotarix against any and severe GE from 2 weeks post-Dose 2 until the end of the 2nd RV disease season post-vaccination
4. To assess VE of 2 doses of $10^{4.7}$ ffu of Rotarix against asymptomatic RV infection from 1 month post-Dose 2 until the end of each RV disease season post-vaccination
5. To assess if RV detection method (ELISA versus RT-PCR) modifies VE
6. To characterize the serotype of the wild RV strain by RT-PCR

Secondary Immunogenicity Objectives
1. To assess the immunogenicity (serum IgA antibody) of 2 doses of $10^{4.7}$ ffu of Rotarix

Secondary Safety Objectives
1. To assess safety and reactogenicity of 2 doses of $10^{4.7}$ ffu of Rotarix versus placebo
2. To assess the presence of RV antigen in any stool samples collected from the day of Dose 1 to 2 weeks post-Dose 2

8.1.3.1.2 Design Overview

Rota-004 was a double-blind, randomized, placebo-controlled study conducted at multiple sites in Finland. Healthy subjects 6 to 12 weeks of age at the time of Dose 1 were randomized to receive 2 doses of either Rotarix ($10^{4.7}$ ffu) or placebo on a 0, 2-month schedule. Subjects were randomized and administered Dose 1 of Rotarix or placebo on the same day (i.e. Day 0). Feeding 1 hour pre-vaccination was not allowed. Routine vaccinations were administered 14 days apart from study vaccination. A total enrollment of 360 evaluable subjects was targeted (Rotarix-240, placebo-120). The intended study duration was 2 years.

8.1.3.1.3 Population

Inclusion Criteria
1. Male or female 6-12 weeks of age at the time of Dose 1
2. Born after a normal gestation period (between 36 and 42 weeks)
3. Written informed consent obtained from parent/guardian prior to study procedures
4. Free of obvious health problems as established by medical history and clinical examination prior to entering the study

Reviewer Note: Inclusion Criteria #3 and #4 were the same as for Rota-023 and Rota-036. Inclusion Criteria #1 was the same as for Rota-023.

Exclusion Criteria
1. Use of any investigational or non-registered product other than the study vaccine within 30 days preceding the study vaccine or placebo, or planned use during the study
2. Use of antibiotics from 7 days before each dose of vaccine and ending 7 days after
3. Acute disease at the time of enrolment (defined as presence of moderate or severe illness with temperature ≥100.4°F [38.0°C] measured rectally)
4. Gastroenteritis within 7 days before study vaccine administration (warrants deferral)
5. Household contact with an immunosuppressed individual or pregnant woman

6. Abnormal stool pattern (typically ≥3/day or <3/week without laxatives or anti-diarrheal agents)
7. Previous confirmed occurrence of RV GE
8. Any clinically significant history of chronic gastrointestinal disease or other serious medical condition as determined by the investigator
9. Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine and ending 14 days after
10. Chronic administration (> 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed)
11. Any confirmed or suspected immunosuppressive/immunodeficient condition, including HIV
12. History of allergic disease or reaction likely to be exacerbated by any vaccine component
13. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period

Reviewer Note: Exclusion criteria #8 and #10-14 were also included in Rota-023 and Rota-036, while criterion #9 was also included in Rota-036.

Participating Countries
Finland

8.1.3.1.4 Products mandated by the protocol

Rotarix
Each dose of Rotarix consisted of a lyophilized preparation of $10^{4.7}$ ffu of 89-12 HRV strain (RIX4414). The amount of sucrose, dextran, sorbitol, and amino acids used as excipients were the same as in Rota-023 and Rota-036. GSK's calcium carbonate buffer consisting of -- mg $CaCO_3$ and --- ml xanthane ---------- was used as the diluent. Lot DRVC005A46 was used for Rotarix. Lot 00C16/1000 was used for the diluent.

Placebo
The formulation was the same as for Rotarix but without RIX4414 virus. Lot DRVC006A46PL was used for the placebo. Lot 00C16/1000 was used for the diluent.

8.1.3.1.5 Endpoints

Primary Endpoints
1. Occurrence of RV GE from 2 weeks post-Dose 2 until the end of the 1st RV disease season post-vaccination as detected by ELISA in stool samples

Secondary Efficacy Endpoints
1. Occurrence of RV GE from 2 weeks post-Dose 2 until the end of the 1st RV disease season post-vaccination as detected by RT-PCR in stool samples
2. Occurrence of severe RV GE from the end of the 1st RV disease season until the end of the 2nd RV disease season post-vaccination as detected by ELISA and RT-PCR in stool samples
3. Occurrence of any and severe RV GE from 2 weeks post-Dose 2 until the end of the 2nd RV disease season post-vaccination as detected by ELISA and RT-PCR in stool samples
4. Occurrence of any and severe GE from 2 weeks post-Dose 2 until the end of the 2nd RV disease season post-vaccination
5. Occurrence of asymptomatic RV infections from 1 month post-Dose 2 until the end of each RV disease season post-vaccination
6. G type of the wild RV strain by RT-PCR

Secondary Immunogenicity Endpoints – subset of subjects
1. RV IgA titers at pre-Dose 1, 1 month post-Dose 2, and end of each RV disease season

Secondary Safety and Reactogenicity Endpoints

1. For each type of solicited symptom, occurrence of the symptom within the 15-day solicited follow-up period post-dose
2. Presence of RV antigen in any stool samples collected from Dose 1 until 2 weeks post-Dose 2
3. Occurrence of unsolicited symptoms within 42 days post-dose, according to WHO classification
4. Occurrence of SAEs throughout the entire study period

Definitions

***GE*:** same as in Rota-023 and Rota-036
Diarrhea: same as in Rota-023 and Rota-036
Vomiting: same as in Rota-023 and Rota-036
RV GE: same as in Rota-036
Severe RV GE: same as in Rota-023 and Rota-036
Asymptomatic RV infection: ≥ 4-fold increase in IgA antibody titers from 1 month post-Dose 2 to each end of season sampling time points
RV disease seasons: 1st season – December 1, 2000 to June 1, 2001; 2nd season – December 1, 2001 to June 1, 2002
Seroconversion: same as in Rota-023 and Rota-036
Seropositive: same as in Rota-023 and Rota-036
Seronegative: same as in Rota-023 and Rota-036

Summary of Significant Protocol Amendments

1. Amendment 1 – March 25, 2002
   a. Presentation of the results obtained until Visit 4 (end of the 1st RV season) in a summary form at medical congresses
   b. Additional testing of GE stool samples that were negative for RV by RT-PCR to detect the presence of other gastrointestinal viruses in order to establish the etiology of the gastrointestinal symptoms for the research interest of the PI. This additional testing of the stool samples was the responsibility of the PI and the results of the analyses were not described in the annex study report written after study end.

8.1.3.1.6 Surveillance

Follow-up visits

The table below summarizes the follow-up visits for safety/efficacy/immunogenicity.
A total of 405 subjects were targeted for enrollment to obtain 360 evaluable subjects.

	Visit 1 Day 0	**Visit 2 Month 2**	**Visit 3 Month 3**	**Visit 4 June 2001**	**Visit 5 June 2002**
Rotarix (N=270)	X	X	X	X	X
Placebo (N=135)	X	X	X	X	X

Vaccination with Rotarix or placebo took place at Visits 1 and 2. Subjects received a physical examination at all visits.

Safety diary cards for solicited and unsolicited symptoms were collected at Visits 2 and 3. On day 14 post-dose, a study nurse contacted the parents/guardians by telephone or other methods to remind them to bring the completed diary card at the next visit. GE diary cards for individual GE episodes were collected at Visits 3, 4, and 5.

Pre-vaccination blood samples were obtained from all subjects at Visit 1, while post-vaccination blood samples were drawn at Visit 3, Visit 4, and Visit 5.

GE Case Ascertainment
Follow-up of GE symptoms for VE assessment was conducted from 2 weeks post-Dose 2 until Visit 5. During each RV disease season post-vaccination, a study nurse contacted the parents/guardians by telephone every 2 weeks to check for the occurrence of any GE symptoms. Parents/guardians were also asked to contact the study nurse or investigator for any symptoms suggestive of GE from 2 weeks post-Dose 2 until Visit 5.

GE Case Follow-Up
For each GE episode that occurred from 2 weeks post-Dose 2 until Visit 5, a diary card was completed daily by parents/guardians until symptoms resolved, and returned to the investigator at the following study visit. The GE diary card allowed assessment recording of rectal temperature, number of vomiting episodes, and number of looser than normal stools. During each GE episode, the study nurse contacted the parents/guardians by telephone every day until symptoms resolve.

The 20-point (Vesikari) scale was used to assess the intensity of each GE episode.

For each GE episode, stool samples were collected no later than 7 days after illness onset. At least 2 samples were collected on different days for GE episodes lasting more than one day. Samples were also collected from the day of Dose 1 until 2 weeks post-Dose 2. Samples were frozen until returned to the investigation site; refrigerated samples were returned within 24 hours after collection.

Stool samples were analyzed by ELISA at the laboratory of Dr. R. Ward in Cincinnati, US, and by RT-PCR at the laboratory of ---------- in Finland. Specimens in which RV was detected were further analyzed by RT-PCR to determine G type. A subset of stool samples was used for ELISA and RT-PCR validation at GSK's laboratory in Belgium.

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AE/SAE Monitoring, including IS
Solicited symptoms (fever, fussiness/irritability, loss of appetite, vomiting, diarrhea) occurring from Day 0 to Day 14 after each dose were monitored using diary cards.

Unsolicited symptoms occurring within 42 days after each dose were recorded for all subjects. SAEs occurring throughout the study period were recorded for all subjects.

SAE monitoring, including IS, was conducted using similar procedures in Rota-023 and Rota-036. Procedures for grading intensity of unsolicited AEs/SAEs, assessing causality of AEs/SAEs to vaccination, follow-up of AEs/SAEs, and SAE reporting were also similar to Rota-023 and Rota-036.

Unsolicited symptoms were coded using WHO's Dictionary for Adverse Reaction Terminology. Every verbatim term from safety reports was matched to an appropriate WHO Preferred Term.

IS Case Ascertainment and Follow-up
Follow-up diagnostic procedures for IS cases were similar to that in Rota-023 and Rota-036. Each IS case was reviewed by external advisers.

Serology Analysis
Sera were collected from all subjects at Visit 1 (pre-Dose 1), Visit 3 (1 month post-Dose 2), Visit 4, and Visit 5. Anti-RV IgA antibody concentrations were measured by ELISA at Dr. Ward's laboratory, with a subset used for ELISA validation at GSK in Belgium.

Forms
1. GE diary card
2. Safety diary card for solicited and unsolicited symptoms

3. Paper Case Report Form (CRF)

8.1.3.1.7 Statistical Considerations

Power Considerations - Primary Efficacy Objective
Assuming a true VE of 70%, a frequency of RV GE of 20% in the placebo group from 2 weeks post-Dose 2 until the end of the 1st RV disease season, 240 subjects in the Rotarix and 120 in the placebo groups, the study had 95% power to observe a LL of the VE 95% CI of 46%.

Study Cohorts
Total vaccinated cohorts (TVCs) consisted of all subjects for whom data (safety, efficacy, immunogenicity) were available, and underwent the following analyses:

- Secondary safety analysis (TVC for safety)
- Secondary immunogenicity analysis if needed (TVC for immunogenicity)
- Secondary efficacy analysis (TVC for efficacy)

The ATP safety (reactogenicity) cohort consisted of vaccinated subjects who 1) received at least 1 dose of vaccine/placebo according to their random assignment, 2) had sufficient data to perform safety analysis (i.e. had at least one documented dose), 3) did not receive a vaccine forbidden by or not specified in the protocol, 4) did not have their randomization codes broken and did not receive a replacement vial, and 5) were negative for serum anti-RV IgA antibodies on the day of Dose 1. The ATP safety cohort was to have been used for the primary safety analysis.

The ATP efficacy cohort consisted of all subjects from the ATP safety cohort who 1) received 2 doses of vaccine/placebo according to their random assignment, 2) had entered into the surveillance period (had follow-up beyond 2 weeks post-Dose 2), and 3) had no RV other than vaccine strain in stool samples collected between the day of Dose 1 and 2 weeks post-Dose 2. The ATP efficacy cohort was used for primary efficacy analysis.

The ATP immunogenicity cohort consisted of all subjects from the ATP safety cohort who 1) complied with blood sample and vaccination schedules per protocol, 2) had not received medication forbidden by the protocol, 3) did not have an underlying medical condition forbidden by the protocol, 4) had no protocol violation of demographics, 5) had immunogenicity data for IgA antibodies at pre-Dose 2 and 1 month post-Dose 2, 6) had no RV other than vaccine strain in stool samples collected from Dose 1 until Visit 3, and 7) had no concomitant infection unrelated to the vaccine which may have influenced the immune response. The ATP immunogenicity cohort was used for the primary immunogenicity analysis.

Subjects excluded from the ATP cohorts were identified before data analysis after a review of individual subject data blinded to group allocation.

Final Analyses
The following analyses were performed:

1. Demographics: age and height/weight (mean, range, and SD per group), race, gender

2. Efficacy:
   a. VE against RV GE from 2 weeks post-Dose 2 until end of 1st RV season
   b. VE against severe RV GE from end of 1st RV season until end of 2nd RV season
   c. VE against any and severe RV GE from 2 weeks post-Dose 2 until end of 2nd RV season
   d. VE against any and severe GE from 2 weeks post-Dose 2 until end of 2nd RV season
   e. VE against asymptomatic RV GE from 1 month post-Dose 2 until end of each RV season

If a subject reported multiple episodes of GE, only the most severe episode was included in the efficacy analysis.

An episode of GE was classified as RV positive if stool samples were positive by ELISA/RT-PCR.

Samples collected at Visits 4 and 5 were used to detect asymptomatic RV infections.

The 95% CIs for VE were derived using a conditional to cases approach. In addition, the Cox proportional-hazard model including the group effect as the only regressor was used to estimate VE (and 95% CI) against the primary endpoint for exploratory analysis.

3. Immunogenicity:
   a. Seroconversion rates 1 month post-Dose 2, Visit 4, and Visit 5, by group (for ATP cohort, seroconversion rate= seropositivity rate)
   b. GMTs of IgA antibody, by group, by time point; antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off
   c. % of subjects reporting at least one RV GE episode during the 1st efficacy follow-up period, by serological status for IgA antibody concentration one month post-Dose 2

4. Safety
   a. Overall incidence of any AEs (solicited and unsolicited), by group, by dose, for overall doses, per subject; same calculations for Grade 3 and vaccine-related symptoms
   b. Incidence of each solicited general symptom, by group, over the follow-up period, after each dose, for all doses, per subject; same calculations for Grade 3 and vaccine-related AEs
   c. Number of subjects with presence of RV in stool samples collected in case of diarrhea and/or vomiting from day of Dose 1 until 2 weeks post-Dose 2
   d. % of subjects with unsolicited symptoms within Days 0-42, by WHO body system/WHO preferred terms; similar tabulations for vaccine-related unsolicited symptoms
   e. Number of subjects reporting at least one SAE, per group
   f. % of subjects who took ≥1 concomitant medication during the solicited follow-up period, per group
   g. SAEs described in detail

As an exploratory analysis, the following was compared between groups using Fisher Exact test:
- % of subjects with at least one symptom (solicited/unsolicited) from Days 0-14 post-dose
- % of subjects reporting specific solicited symptoms from Days 0-14 post-dose
- % of subjects reporting unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 post-dose

Final statistical analysis

A final statistical analysis was performed at the end of the 1st RV disease season and presented results of objectives related to the period from Visit 1 until Visit 4. Data analyses from Visit 4 until Visit 5, as well as efficacy analyses over both efficacy follow-up periods, were presented as an annex. Access to individual treatment decode was strictly controlled and restricted to some GSK Biologicals' personnel.

Interim analysis

An unplanned interim analysis of uncleaned efficacy data was performed after completion of Visit 4. VE against any RV GE was calculated, with results being kept in-house and no report being written. Individual decoding during this analysis was restricted to the statistician and the database administrator. Results of this analysis were consistent with the results in the Final Study Report.

Additional analyses/changes

Changes were made to the planned analyses included the following:
- The TVC was used for the primary safety analysis instead of the ATP cohort
- One stool sample per GE episode occurring after December 1, 2000 was tested by RT-PCR at ---------- laboratory, irrespective of positive or negative ELISA results
- A few samples collected before December 1, 2000 that tested negative by ELISA were mistakenly tested by RT-PCR and found positive; one subject, who tested negative by ELISA but positive by RT-PCR before December 1, 2000, was considered as having a RV GE in the efficacy calculation using RT-PCR method
- An unplanned interim analysis was performed (see above)

- Intensity of GE episodes from Day of Dose 1 until 2 weeks post-Dose 2 was calculated
- 95% CIs for VE were derived according to the method described in the Report Analysis Plan (RAP, detailed in Appendix B) rather than using the Mantel-Haenszel approach specified in the protocol
- Seroconversion rate, VE against severe RV GE, and VE against hospitalization due to any GE during the 1st efficacy period were calculated in accordance with the RAP
- VE against hospitalization due to any GE during 2nd and combined efficacy periods
- GMCs to anti-RV IgA antibody on seropositive subjects were calculated
- Access to the treatment code for some subjects was made available to the GSK Biologicals' Clinical Team prior to study end; this was done because efficacy analysis of the 1st RV season revealed that subjects who had seroconverted were better protected against natural infection than those who had not. In order to completely analyze the possible correlation between immunological markers and efficacy, access to the treatment code for subjects with RV GE (ELISA/RT-PCR positive) during the 1st RV season was given to the Clinical Development Manager and Director prior to study end.
- ELISA or RT-PCR tests were repeated for 4 subjects (Year 1 – 1, Year 2 – 3) due to inconsistencies in test results; RT-PCR test was performed for 2 subjects (Year 1 – 1, Year 2 – 2) with previous missing results; calculations pertaining to the main study objectives (i.e. VE) were redone with corrected ELISA and RT-PCR results
- Quantitative PCR and sequencing were conducted post-hoc to help distinguish RV G1 wild type versus vaccine strain for 5 Rotarix recipients who reported G1 RV GE detected by RT-PCR but not by ELISA
- Sequencing of G1 strains from GE episodes reported from Dose 1 to 2 weeks post-Dose 2 was conducted post-hoc to distinguish between RV G1 wild type versus vaccine strain

8.1.3.2 Results, by Trial (Objective information)

Study initiation date: August 21, 2000
Data lock point (for Final Study Report, Year 1): July 11, 2001
Date of Last Visit: June 26, 2002
Final Report date (Year 1): April 30, 2003
Annex Report date (Year 2: November 14, 2003

8.1.3.2.1 Populations enrolled/analyzed

Efficacy - 1st Efficacy Follow-up Period (Year 1)

Study population by site
A total of 405 subjects were in the TVC. Distribution by treatment group among the 6 sites in Finland is summarized below.

Site	HRV	Placebo	Total	
	n	n	n	%
1	34	17	51	12.6
2	54	27	81	20.0
3	82	41	123	30.4
4	38	19	57	14.1
5	34	17	51	12.6
6	28	14	42	10.4
All	270	135	405	100

Source: Study Report Body Rota-004, pg 67

Drop-outs at Visit 5
As noted below, 372 out of 405 (91.9%) subjects in the TVC completed Visit 4.

	Group		Total
	HRV	placebo	
Number of subjects enrolled	270	135	405

Number of subjects completed	249	123	372
Number of subjects dropped-out	21	12	33
Reasons for drop-out:			
Serious adverse event	0	0	0
Non-serious adverse event	6	2	8
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	13	8	21
Migrated/moved from study area	1	1	2
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	1	1	2
Others	0	0	0

Enrolled = number of subjects who where entered in the study; Completed = number of subjects who completed study Visit 4
Dropped-out = number of subjects who did not return for study Visit 4
Source: Study Report Body Rota-004, pg 68

Protocol deviations – ATP efficacy cohort for 1st follow-up period
Protocol deviations leading to subject exclusion from the ATP cohort were as follows:

- 4 (Rotarix-4) received DTP vaccination in time window forbidden in the protocol
- 3 (Rotarix-2, placebo-1) had randomization failure
- 1 (Rotarix-1) received study dose not administered per protocol (subject vomited 10 minutes after vaccine administration)
- 6 (Rotarix-4, placebo-2) had unknown RV serological status on the day of Dose 1
- 22 (Rotarix-13, placebo-9) did not receive Dose 2 of Rotarix or placebo
- 1 (Rotarix-1) did not enter into the surveillance period of the 1st efficacy follow-up

A total of 368 subjects were included in the ATP efficacy cohort.

Protocol deviations – ATP immunogenicity cohort
Protocol deviations leading to subject exclusion from the ATP cohort were as follows:

- 3 (Rotarix-1, placebo-2) were administered medication forbidden in the protocol
- 11 (Rotarix-8, placebo-3) were non-compliant with vaccination schedule
- 9 (Rotarix-7, placebo-2) were non-compliant with blood sampling schedule
- 47 (Rotarix-34, placebo-13) did not have a one month post-Dose 2 blood sample

A total of 321 subjects were included in the ATP immunogenicity cohort.

Study demographics – ATP efficacy cohort (N=368)
Demographic characteristics are included in the table below. The median age at Dose 1 (8 weeks) was the same between groups. Nearly 100% of the subjects in either group were White/Caucasian. The female-to-male ratios were comparable between groups. Median height and weight measurements were also the same or similar between groups.

Characteristics	**Parameters or Categories**	**HRV N = 245**		**Placebo N = 123**		**Total N = 368**	
		Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at the first dose (weeks)	Mean SD Median Minimum Maximum	8.3 1.70 8 6 12	 -----	8.2 1.64 8 6 12	 -----	8.2 1.70 8 6 12	 -----
Gender	Male Female	131 114	53.5 46.5	62 61	50.4 49.6	193 175	52.4 47.6
Race	White Black Oriental Other	243 0 0 2	99.2 0.0 0.0 0.8	123 0 0 0	100.0 0.0 0.0 0.0	366 0 0 2	99.5 0.0 0.0 0.5
Height (cm)	Mean SD Median	58.6 2.46 58	---	58.6 2.09 58	---	58.6 2.30 58	---

Weight (kg)	Mean SD Median	5.6 0.74 5.6	---	5.5 0.72 5.5	---	5.5 0.70 5.5	---

Source: Study Report Body Rota-004, pg 72

Study demographics – TVC (N=405)
Demographic characteristics were the same or similar as in the ATP efficacy cohort.

Dose distribution – TVC

Total number of doses received	HRV (N = 270)		Placebo (N= 135)		Total (N = 405)	
	n	%	n	%	n	%
1	14	5.2	9	6.7	23	5.7
2	256	94.8	126	93.3	382	94.3
Any	270	100	135	100	405	100

Source: Study Report Body Rota-004, pg 80

Study demographics – ATP immunogenicity cohort (N=321)
Demographic characteristics were the same or similar as the ATP efficacy cohort and TVC.

Efficacy – 2nd Efficacy Follow-up Period (Year 2)

Drop-outs at Visit 5
As depicted in the table below, 363 out of 405 (89.6%) subjects in the TVC completed Visit 5. Between Visit 4 and Visit 5, 9 subjects (Rotarix-5, placebo-4) dropped out due to reasons other than SAEs or non-SAEs.

	Group		Total
	HRV	placebo	
Number of subjects enrolled	270	135	405
Number of subjects completed	244	119	363
Number of subjects dropped-out	26	16	42
Reasons for drop-out:			
Serious adverse event	0	0	0
Non-serious adverse event	6	2	8
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	14	7	21
Migrated/moved from study area	1	3	4
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	5	2	7
Others	0	2	2

Source: Study Report Body Rota-004 Annex 1, pg 50

Reviewer Note: Based on the analysis data provided by the applicant, the reviewer obtained a total of 10 subjects (Rotarix-6, placebo-4) who withdrew consent not due to an AE.

Protocol deviations – ATP efficacy cohort for 2nd follow-up period
The following is a summary of protocol deviations that led to subject exclusion in the ATP cohort:

- 7 (Rotarix-4, placebo-3) did not enter into the 2nd efficacy surveillance period

Therefore, 361 subjects were included in the ATP efficacy cohort for the 2nd follow-up period.

8.1.3.2.2 Efficacy endpoints/outcomes

Year 1 Efficacy (2 weeks post-Dose 2 to Visit 4) – ATP efficacy cohort

Summary of reported any RV GE and severe RV GE episodes – Year 1
The median duration of follow-up during the Year 1 efficacy period was approximately 5.6 months in each group. Numbers of GE and RV GE episodes, as well as numbers of subjects, are depicted for each group in the table below. RV was detected by ELISA in 8 GE episodes of Rotarix recipients

and 13 episodes in placebo recipients. RV was detected by RT-PCR in 12 GE episodes from each group. No subject in either group had more than one RV GE episode during the 1st efficacy follow-up period

Event	Total number of episodes reported	HRV N = 245		Placebo N = 123	
		n	%	n	%
GE	1	62	25.3	35	28.5
	2	19	7.8	6	4.9
	3	4	1.6	4	3.3
	Any	85	34.7	45	36.6
Rotavirus GE					
ELISA	1	8	3.3	13	10.6
	Any	8	3.3	13	10.6
RT-PCR	1	12	4.9	12	9.8
	Any	12	4.9	12	9.8

Any=number and % of subjects reporting at least one specified symptom=sum of the "Total number of episodes reported"
Source: Study Report Body Rota-004, pg 106

Applicant Erratum Note: As mentioned previously, inconsistencies in laboratory results of stool samples for 2 subjects resulted in the following:

- One Rotarix recipient who initially tested positive for RV by ELISA and negative by RT-PCR was found to be negative by ELISA upon repeat testing; thus, this subject was reclassified as RV negative (by ELISA and RT-PCR)
- One placebo recipient who had not been initially tested by RT-PCR was RT-PCR positive for G1 type after testing; thus this subject was reclassified as RV positive (by RT-PCR)

Due to these errors, the following changes were made to the table above as highlighted in bold and italicized font:

Event	Total number of episodes reported	HRV N = 245		Placebo N = 123	
		n	%	n	%
Rotavirus GE					
ELISA	1	***7***	***2.9***	13	10.6
	Any	***7***	***2.9***	13	10.6
RT-PCR	1	12	4.9	***13***	***10.6***
	Any	12	4.9	***13***	***10.6***

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) as determined by either ELISA or RT-PCR was reported in 1 Rotarix and 5 placebo recipients. Severe GE was not reported among episodes in which RV was detected only by RT-PCR. The Rotarix subject who developed severe RV GE had an interval of 21 days between vaccinations (outside adapted interval of 49-83 days).

Event	Severity	HRV n	HRV %	Placebo n	Placebo %
Any GE	Unknown	2	1.8	0	0.0
	Mild (1 . 6)	78	69.6	39	66.1
	Moderate (7 . 10)	27	24.1	12	20.3
	Severe (≥ 11)	5	4.5	8	13.6
	Any	112	100	59	100
RV GE by ELISA	Mild (1 . 6)	2	25.0	3	23.1
	Moderate (7 . 10)	5	62.5	5	38.5
	Severe (≥ 11)	1	12.5	5	38.5
	Any	8	100	13	100
RV GE by RT-PCR	Mild (1 . 6)	6	50.0	3	25.0
	Moderate (7 . 10)	5	41.7	4	33.3
	Severe (≥ 11)	1	8.3	5	41.7
	Any	12	100	12	100

n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the first efficacy follow-up period
Any = any specified symptom reported, regardless of severity
Source: Study Report Body Rota-004, pg 74

Serotype G distribution is summarized below. G1 was the most prevalent circulating type. RV G type could not be identified in 2 subjects; one subject (Rotarix recipient) had a positive ELISA result but negative RT-PCR result, while the other subject (placebo recipient) had a positive ELISA result but RT-PCR was not performed.

	HRV N = 245		Placebo N = 123	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	8	3.3	13	10.6
Unknown	1	0.4	1	0.8
G1	7	2.9	10	8.1
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8
RT-PCR				
Any	12	4.9	12	9.8
G1	12	4.9	10	8.1
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8

n/% = number/percentage of subjects reporting at least once the specified type in each group
Source: Study Report Body Rota-004, pg 75

Reviewer Note: Due to the reclassification of the 2 subjects mentioned previously, the reviewer obtained the following differences (highlighted in bold italics):

	HRV N = 245		Placebo N = 123	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	***7***	***2.9***	13	10.6
Unknown	***0***	***0.0***	***0***	0.8
G1	7	2.9	***11***	8.1
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8
RT-PCR				
Any	12	4.9	***13***	***10.6***
G1	12	4.9	***11***	***8.9***
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8

Applicant Post-hoc Laboratory Analyses: Of the 5 Rotarix recipients who tested positive by RT-PCR and negative by ELISA, 4 had negative or very low RV load in their retested stool samples. Sequencing data showed that the RV strains in 4 of the 5 subjects were the vaccine strain, while the fifth subject was infected with a wild type G1 RV; however, this subject had a negative stool viral load, leading to the possibility of false positive results. All 5 subjects had mild GE and could have possibly been infected by other pathogens.

ELISA results for GE stool samples were not available for 7.1% of episodes in the Rotarix group and 5.1% of episodes in the placebo group. RT-PCR results were not available for 9.8% of episodes in the Rotarix group and 6.8% of episodes in the placebo group. Results were unavailable due to non-collection of stool samples, invalid test results or non-testing of samples.
Reviewer Note: Due to the reclassification of the Rotarix recipient mentioned previously who was tested by RT-PCR after not being previously tested by this method, the percentage of RT-PCR results not available for GE episodes in the Rotarix group should have been recalculated. However, the applicant did not provide the corrected estimate.

Clinical characteristics of RV GE episodes – Year 1
The duration of looser than normal stools and vomiting were shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration, and rehydration treatment

were also less in the Rotarix group compared to placebo. No episodes in either group required hospitalization.
Reviewer Note: Due to the reclassification of the 2 subjects mentioned previously, clinical characteristics of RV GE episodes for each group should have been recalculated. However, the applicant did not provide corrected figures.

Vaccine efficacy against any RV GE detected by ELISA – Year 1 (Primary endpoint)
VE against any RV GE as detected by ELISA during the 1st efficacy follow-up period was 69.1% (95% CI: 19.6-88.9%). A similar estimate was obtained using the Cox proportional-hazard mode (results not included in the study report).

			T	n / T			n / N			Vaccine efficacy			p-
Group	N	n	(year)	value	95%CI		rate	95%CI		% 95%CI			value
Any RV GE													
HRV	245	8	112.1	0.071	0.036	0.143	3.3	1.4	6.3	69.1	19.6	88.9	0.007
Placebo	123	13	55.2	0.236	0.137	0.406	10.6	5.7	17.4				

N = number of subjects included in each group; n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N= percentage of subjects reporting at least one RV GE episode in each group; n/T= person-year rate of RV GE in each group
p-value = two-sided Fisher.s exact test (significant level of α=0.05)
Source: Study Report Body Rota-004, pg 76

Applicant Erratum Note: Due to the reclassification of the 2 subjects mentioned previously, VE against any RV GE detected by ELISA during the 1st efficacy follow-up period was recalculated as 73.0% (95% CI: 27.1-90.9%).

VE against any RV GE detected by RT-PCR – Year 1 (Secondary endpoint)
VE against any RV GE as detected by RT-PCR during the 1st efficacy follow-up period was 49.8%, an estimate that did not reach statistical significance.

			T	n / T			n / N			Vaccine efficacy			p-
Group	N	n	(year)	value	95%CI		rate	95%CI		% 95%CI			value
Any RV GE													
HRV	245	12	110.5	0.109	0.062	0.191	4.9	2.6	8.4	49.8	-22.2	79.4	0.115
Placebo	123	12	55.3	0.217	0.123	0.382	9.8	5.1	16.4				

Source: Study Report Body Rota-004, pg 77

Applicant Erratum Note: Due to the reclassification of the 2 subjects mentioned previously, VE against any RV GE detected by RT-PCR during the 1st efficacy follow-up period was recalculated as 53.7% (95% CI: -10.2-80.7%).

VE against severe RV GE detected by ELISA – Year 1 (Primary endpoint)
VE gainst severe RV GE detected by ELISA during the 1st efficacy follow-up period was 90.0% (95% CI: 10.3-99.8%). A similar estimate was obtained using the Cox proportional-hazard mode (results not included in the study report).

			T	n / T			n / N			Vaccine efficacy			p-
Group	N	n	(year)	value	95%CI		rate	95%CI		% 95%CI			value
Severe RV GE													
HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	56.0	0.089	0.037	0.214	4.1	1.3	9.2				

Source: Study Report Body Rota-004, pg 76

VE against severe RV GE detected by RT-PCR – Year 1 (Secondary endpoint)
VE against severe RV GE detected by RT-PCR during the 1st efficacy follow-up period was 90.0% (95% CI: 10.3-99.8%), the same as for VE against severe RV GE detected by ELISA.

			T	n / T			n / N			Vaccine efficacy			p-
Group	N	n	(year)	value	95%CI		rate	95%CI		% 95%CI			value

Severe RV GE													
HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	56.0	0.089	0.037	0.214	4.1	1.3	9.2				

Source: Study Report Body Rota-004, pg 77

VE against any RV GE by main RV serotypes – Year 1 (Secondary endpoint)
VE against any G1 RV GE detected by ELISA and RT-PCR was 64.9% and 39.8%, respectively; both estimates had LL of the 95% CIs that included 0. VE against G2 and G9 was 100% with 95% CI that included 0 due to limited number of severe RV GE episodes caused by these serotypes.

Type	Group	N	n	T (year)	n / T	95%CI		n / N	95%CI		Vaccine efficacy 95%CI %		
				ELISA									
G1	HRV	245	7*	112.4	0.062	0.030	0.131	2.9	1.2	5.8	64.9	-2.3	88.6
	Placebo	123	10*	55.6	0.180	0.097	0.334	8.1	4.0	14.4			
				RT-PCR									
G1	HRV	245	12	110.5	0.109	0.062	0.191	4.9	2.6	8.4	39.8	-55.7	76.1
	Placebo	123	10	55.6	0.180	0.097	0.334	8.1	4.0	14.4			
				ELISA or RT-PCR									
G2	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			
				ELISA or RT-PCR									
G9	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			

N = number of subjects included in each group; n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N = percentage of subjects reporting at least one RV GE episode in each group;
n/T = person-year rate of RV GE symptom in each group
NE = can not be estimated; *Type is not known for one subject
Source: Study Report Body Rota-004, pg 109

Reviewer Note: Due to the reclassification of the 2 subjects mentioned previously, VE against any G1 RV GE detected by RT-PCR during the 1st efficacy follow-up period should have been recalculated. However, the applicant did not provide the corrected VE estimate.

VE against severe RV GE by main RV serotypes – Year 1 (Secondary endpoint)
VE against severe G1 RV GE was 87.4% although the lower level of the 95% CI crossed 0. VE against G2 was 100% with wide 95% CI that crossed 0 due to the limited number of severe RV GE episodes due to this serotype.

Type	Group	N	n	T (year)	n / T	95%CI		n / N	95%CI		Vaccine efficacy % 95%CI		
ELISA or RT-PCR													
G1	HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	87.4	-26.8	99.7
	Placebo	123	4	56.2	0.071	0.027	0.190	3.3	0.9	8.1			
ELISA or RT-PCR													
G2	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			

Source: Study Report Body Rota-004, pg 110

VE against any GE requiring hospitalization – Year 1 (Exploratory endpoint)
VE against any GE leading to hospitalization could not be calculated due to limited numbers of hospitalized GE cases (only 1 hospitalized case in the Rotarix group).

Anti-RV IgA status at Visit 3 versus RV GE occurrence during Year 1, Rotarix group
The percentages of subjects in the Rotarix group that reported at least one RV GE during the 1st efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3 and detection method for RV, are included in the table below. For either detection method, there were less subjects who had an RV GE episode in the seropositive group.

Anti-rotavirus IgA status at Visit 3	N	n	%	95%CI	
ELISA					
Negative	45	4	8.9	2.5	21.2
Positive	180	3	1.7	0.3	4.8
Unknown	20	1	5.0	0.1	24.9
RT-PCR					
Negative	45	5	11.1	3.7	24.1
Positive	180	6	3.3	1.2	7.1
Unknown	20	1	5.0	0.1	24.9

Source: Study Report Body Rota-004, pg 164

None of the RV GE episodes in seropositive Rotarix recipients were severe in nature. A single subject who developed severe RV GE had not seroconverted one month post-Dose 2.

Year 1 Efficacy (Visit 3 to Visit 4) – ATP efficacy cohort

VE against asymptomatic infection – Year 1 (Secondary endpoint)
A total of 299 subjects (Rotarix-197, placebo-102) and 298 subjects (Rotarix-195, placebo-103) were used to calculate VE against asymptomatic RV infection detected by ELISA and RT-PCR, respectively. VE against asymptomatic RV infection during the 1st efficacy follow-up period was similarly high between RV detection methods (94.2% by ELISA and 94.7% by RT-PCR).

Group	N	n	%	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA									
HRV	197	1	0.5	0.0	2.8	94.2	58.5	99.9	< 0.001
Placebo	102	9	8.8	4.1	16.1				
RT-PCR									
HRV	195	1	0.5	0.0	2.8	94.7	62.9	99.9	< 0.001
Placebo	103	10	9.7	4.8	17.1				

N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 4 and who did not report a RV GE between Visits 3 and 4
Source: Study Report Body Rota-004, pg 78

Year 1 Efficacy (2 weeks post-Dose 2 to Visit 4) – TVC for efficacy 1st efficacy period

A total of 381 subjects (Rotarix-255, placebo-126) were included in Year 1 efficacy analyses. The median duration of follow-up during this interval was 5.6 months for both groups.

Summary of reported RV GE episodes
The numbers of any and severe RV GE episodes for each group and for each RV detection method, as well as the numbers of RV GE episodes by serotype, were the same as in the ATP efficacy cohort.

VE against any RV GE – Year 1
VE against any RV GE detected by ELISA was 69.6% (95% CI: 20.9-89.1%), similar to the VE estimate for the primary endpoint in the ATP cohort. VE against any RV GE detected by RT-PCR was 50.6% but did not reach statistical significance.
Reviewer Note: Due to the reclassification of the 2 subjects mentioned previously, VE against any RV GE detected by ELISA and by RT-PCR during the 1st efficacy follow-up period should have been recalculated. However, the applicant did not provide the corrected VE estimates.

VE against any RV GE by main RV serotypes – Year 1
VE against any G1 RV GE detected by ELISA and RT-PCR was 65.4% and 40.7%, respectively; both estimates had lower levels of the 95% CIs that crossed 0. VE against G2 and G9 was 100% with wide 95% CI that crossed 0 due to the limited number of severe RV GE episodes due to these serotypes.
Reviewer Note: Due to the reclassification of the 2 subjects mentioned previously, VE against any G1 RV GE detected by RT-PCR during the 1st efficacy follow-up period should have been recalculated. However, the applicant did not provide the corrected VE estimate.

VE against severe RV GE – Year 1
VE against severe RV GE detected by ELISA or by was 90.1% (95% CI: 11.7-99.8%), similar to the VE estimate for the primary endpoint in the ATP cohort.

VE against severe RV GE by main RV serotypes – Year 1
VE against severe G1 RV GE detected by ELISA or by RT-PCR was 87.6% although the lower level of the 95% CI crossed 0. VE against G2 was 100% with wide 95% CI that crossed 0 due to the limited number of severe RV GE episodes due to this serotype.

VE against any GE requiring hospitalization – Year 1
VE against any GE leading to hospitalization could not be calculated due to limited numbers of hospitalized GE cases.

Year 1 Efficacy (1 month post-Dose 2 to Visit 4) – TVC

VE against asymptomatic infection – Year 1 (Secondary endpoint)
A total of 308 subjects (Rotarix-203, placebo-105) and 307 subjects (Rotarix-201, placebo-106) were used to calculate VE against asymptomatic RV infection detected by ELISA and RT-PCR, respectively. VE against asymptomatic RV infection detected by ELISA and RT-PCR during the 1st efficacy follow-up period was similarly high at 88.5% and 89.5%, respectively.

Year 1 Immunogenicity – ATP immunogenicity cohort

Anti-RV IgA response
Anti-RV IgA seroconversion rates at 1 month post-Dose 2 were 80.4% in the Rotarix group and 0% in the placebo group; the 95% CI of the difference in seroconversion rates between groups was 73.5-86.3%. GMCs increased at this time point compared to pre-Dose 1 level in the Rotarix group. At the end of the 1st RV season, 75.7% of Rotarix recipients remained seropositive.

			≥ 20 U/ml	≥ 20 U/ml	95% CI	95% CI	GMC (U/ml)	95% CI	95% CI	GMC (U/ml)	GMC (U/ml)
Group	**Timing**	**N**	**n**	**%**	**L.L.**	**U.L.**	**Value**	**L.L.**	**U.L.**	**Min**	**Max**
HRV	Pre	209	0	0.0	0.0	1.7	<20	-	-	<20	<20
	PII(M3)	209	168	80.4	74.3	85.5	164.0	129.7	207.3	<20	4161
	ES1	189	143	75.7	68.9	81.6	83.2	67.2	103.0	<20	3211
Placebo	Pre	112	0	0.0	0.0	3.2	<20	-	-	<20	<20
	PII(M3)	112	0	0.0	0.0	3.2	<20	-	-	<20	<20
	ES1	106	16	15.1	8.9	23.4	<20	-	-	<20	1101

N= number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off; 95% CI = 95% confidence interval
Min = Minimum concentration ; Max = Maximum concentration; L.L. = lower limit, U.L. = upper limit
Pre = Pre-vaccination; PII(M3) = one month after the second vaccination; ES1 = end of the first RV season
Source: Study Report Body Rota-004, pg 91

Anti-RV IgA antibody GMCs for seropositive subjects are summarized below.

			GMC (U/ml)				
				95% CI		Range	
Group	**Timing**	**N**	**Value**	**L.L.**	**U.L.**	**Min**	**Max**
HRV	PII(M3)	168	324.6	273.0	385.9	30	4161
	ES1	143	164.5	139.4	194.1	27	3211

Placebo	ES1	16	573.9	407.6	808.0	116	1101

Source: Study Report Body Rota-004, pg 91

Year 1 Immunogenicity – TVC

Anti-RV IgA response

Seroconversion rates and GMC results were similar to those in the ATP immunogenicity cohort.

Group	Timing	N	≥ 20 U/ml				GMC (IU/ml)		
					95% CI			95% CI	
			n	%	L.L.	U.L.	Value	L.L.	U.L.
HRV	Pre	265	0	0.0	0.0	1.4	<20	-	-
	PII(M3)	233	186	79.8	74.1	84.8	157.0	125.7	196.1
	ES1	224	170	75.9	69.7	81.3	81.8	67.4	99.1
Placebo	Pre	133	0	0.0	0.0	2.7	<20	-	-
	PII(M3)	122	1	0.8	0.0	4.5	<20	-	-
	ES1	119	21	17.6	11.3	25.7	20.9	15.6	28.1

Source: Study Report Body Rota-004, pg 165

Anti-RV IgA GMCs for seropositive subjects were also similar to the ATP immunogenicity cohort.

			GMC (U/ml)				
				95% CI		Range	
Group	Timing	N	Value	L.L.	U.L.	Min	Max
HRV	PII(M3)	186	314.8	266.8	371.5	28	4161
	ES1	170	159.4	137.4	184.9	24	3211
Placebo	PII(M3)	1	668.0	-	-	668	668
	ES1	21	659.4	489.3	888.6	116	1824

Source: Study Report Body Rota-004, pg 167

Year 2 Efficacy (After Visit 4 to Visit 5) – ATP efficacy cohort

Summary of reported any RV GE and severe RV GE episodes – Year 2

The median duration of follow-up during the 2nd efficacy period was 1 year in each group. RV was detected by ELISA in 7 GE episodes of Rotarix recipients and 12 episodes in placebo recipients. RV was detected by RT-PCR in 6 GE episodes of Rotarix and 10 episodes of placebo recipients.

One subject (Rotarix group) had 2 RV GE episodes during the 2nd efficacy follow-up period (detected by ELISA). This subject had 2 episodes separated by 9 days. Both were graded as very mild and tested positive for RV by ELISA; one episode tested positive for G1 by RT-PCR.

Event	Total number of episodes reported	HRV N = 241		Placebo N = 120	
		n	%	n	%
GE					
	1	77	32.0	35	29.2
	2	29	12.0	13	10.8
	3	8	3.3	10	8.3
	4	3	1.2	0	0.0
	5	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	119	49.4	58	48.3
RV GE					
ELISA	1	6	2.5	12	10.0
	2	1	0.4	0	0.0
	Any	7	2.9	12	10.0

RT-PCR	1	6	2.5	10	8.3
	Any	6	2.5	10	8.3

N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom
Source: Study Report Body Rota-004 Annex 1, pg 77

Applicant Erratum note: As mentioned previously, inconsistencies in laboratory results of stool samples for 4 subjects resulted in the following:

- One Rotarix recipient and one placebo recipient initially RV positive by ELISA and negative by RT-PCR were negative by ELISA upon repeat testing; thus, these subjects were reclassified as RV negative (by ELISA and RT-PCR)
- One placebo recipient not been initially tested by RT-PCR was RT-PCR positive for G1 type after testing; this subject was reclassified as RV positive (by RT-PCR)
- One Rotarix recipient previously negative by RT-PCR was RT-PCR positive for G1 type after retesting; this patient also a separate episode of G1 RV GE during Year 1

Due to these errors, the following changes were made to the table above as highlighted in bold and italicized font:

Event	**Total number of episodes reported**	**HRV N = 241**		**Placebo N = 120**	
		n	**%**	**n**	**%**
RV GE					
ELISA	1	***5***	2.5	***11***	10.0
	2	1	0.4	0	0.0
	Any	***6***	2.9	***11***	10.0
RT-PCR	1	6	2.5	***11***	8.3
	Any	6	2.5	***11***	8.3

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) as determined by either ELISA or RT-PCR was classified for 2 episodes in the Rotarix group and 6 episodes in the placebo group. Of note, one of the 2 subjects in the Rotarix group did not serocovert one month post-Dose 2; this subject was infected with G9 type.

		HRV		**Placebo**	
Event	**Severity**	**n**	**%**	**n**	**%**
Any GE	Mild (1 – 6)	129	70.1	56	61.5
	Moderate (7 – 10)	46	25.0	29	31.9
	Severe (≥ 11)	9	4.9	6	6.6
	Any	184	100	91	100
RV GE	Mild (1 – 6)	3	37.5	2	16.7
by ELISA	Moderate (7 – 10)	3	37.5	4	33.3
	Severe (≥ 11)	2	25.0	6	50.0
	Any	8	100	12	100
RV GE	Mild (1 – 6)	1	16.7	1	10.0
by RT-PCR	Moderate (7 – 10)	3	50.0	3	30.0
	Severe (≥ 11)	2	33.3	6	60.0
	Any	6	100	10	100

n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the second efficacy follow-up period
Any = any specified symptom reported, regardless of severity
Source: Study Report Body Rota-004 Annex 1, pg 55

Serotype G distribution is summarized below. G1 was the most prevalent circulating type. RV G type could not be identified in 4 subjects (Rotarix-2, placebo-2).

	HRV N = 241		**Placebo N = 120**	
Type	**n**	**%**	**n**	**%**

ELISA					
	Any	7	2.9	12	10.0
	Unknown	2	0.8	2	1.7
	G1	5	2.1	10	8.3
	G9	1	0.4	0	0.0
RT-PCR					
	Any	6	2.5	10	8.3
	G1	5	2.1	10	8.3
	G9	1	0.4	0	0.0

n/% = number/percentage of subjects reporting at least once the specified type in each group
Source: Study Report Body Rota-004 Annex 1, pg 55

Reviewer Note: Due to the reclassification of the 4 subjects mentioned previously, the table above should be corrected as follows:

	HRV N = 241		**Placebo N = 120**	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	***6***	***2.5***	***11***	***9.2***
Unknown	***0***	***0.0***	***0***	***0.0***
G1	5	2.1	***11***	***9.2***
G9	1	0.4	0	0.0
RT-PCR				
Any	6	2.5	***11***	***9.2***
G1	5	2.1	***11***	***9.2***
G9	1	0.4	0	0.0

ELISA results for GE stool samples during the 2nd efficacy period were not available for 7.1% of episodes in the Rotarix group and 9.9% of episodes in the placebo group. RT-PCR results were not available for 4.3% of episodes in the Rotarix and 6.6% of episodes in the placebo groups. Results were unavailable due to non-collection of stools, invalid test results or non-testing of samples.
Reviewer Note: Due to the reclassification of the 1 placebo recipient mentioned previously who was tested by RT-PCR after not being previously tested by this method, the percentage of RT-PCR results not available for GE episodes in the placebo group should have been recalculated. However, the applicant did not provide the corrected figure.

Clinical characteristics of RV GE episodes – Year 2
The duration of vomiting was shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C was also less in the Rotarix group compared to placebo. One episode in the Rotarix group required hospitalization.
Reviewer Note: Due to the reclassification of the 4 subjects mentioned previously, clinical characteristics of RV GE episodes for each group should have been recalculated. However, the applicant did not provide corrected figures.

VE against severe RV GE detected by ELISA – Year 2 (Secondary endpoint)
VE against severe RV GE as detected by ELISA during the 2nd efficacy follow-up period was 83.4% (95% CI: 7.2-98.4%).

			T	**n / T**				**n / N**		**Vaccine efficacy**			**p-**
Group	**N**	**n**	**(year)**	**rate**	**95% CI**		**%**	**95% CI**		**% 95% CI**			**value**
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Study Report Body Rota-004 Annex 1, pg 57

VE against severe RV GE detected by RT-PCR – Year 2 (Secondary endpoint)

VE against severe RV GE as detected by RT-PCR during the 2nd efficacy period was 83.4% (95% CI: 7.2-98.4%), the same as for VE against severe RV GE detected by ELISA.

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Study Report Body Rota-004 Annex 1, pg 58

VE against severe RV GE by main RV serotypes – Year 2 (Secondary endpoint)

VE against severe G1 RV GE detected by ELISA or RT-PCR was 91.7% (95% CI: 31.6-99.8%). VE against G9 could not be calculated due to limited numbers.

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
	ELISA or RT-PCR												
G1	HRV	241	1	238.7	0.004	0.001	0.030	0.4	0.0	2.3	91.7	31.6	99.8
	Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6			
	ELISA or RT-PCR												
G9	HRV	241	1	237.8	0.004	0.001	0.030	0.4	0.0	2.3	infinity	infinity	98.7
	Placebo	120	0	119.4	0.0	NE		0.0	0.0	3.0			

NE= cannot be estimated

Source: Study Report Body Rota-004 Annex 1, pg 81

VE against any RV GE detected by ELISA – Year 2

VE against any RV GE as detected by ELISA during the 2nd efficacy follow-up period was 71.0% (95% CI: 20.0-90.3%).

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	241	7	236.5	0.030	0.014	0.062	2.9	1.2	5.9	71.0	20.0	90.3	0.010
Placebo	120	12	114.8	0.105	0.059	0.184	10.0	5.3	16.8				

Source: Study Report Body Rota-004 Annex 1, pg 57

Applicant Erratum note: Due to the reclassification of the 4 subjects mentioned previously, VE against any RV GE detected by ELISA during the 2nd efficacy follow-up period was recalculated as 72.8% (95% CI: 19.9-91.8%).

Vaccine efficacy against any RV GE detected by RT-PCR – Year 2

VE against any RV GE as detected by ELISA during the 2nd efficacy follow-up period was 70.1% (95% CI: 9.3-91.1%).

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	241	6	237.0	0.025	0.011	0.056	2.5	0.9	5.3	70.1	9.3	91.1	0.015
Placebo	120	10	116.1	0.086	0.046	0.160	8.3	4.1	14.8				

Source: Study Report Body Rota-004 Annex 1, pg 58

Applicant Erratum note: Due to the reclassification of the 4 subjects mentioned previously, VE against any RV GE detected by RT-PCR during the 2nd efficacy follow-up period was recalculated as 72.8% (95% CI: 19.9-91.8%).

VE against any RV GE by main RV serotypes – Year 2 (Secondary endpoint)

VE against any G1 RV GE detected by ELISA or RT-PCR was 75.1% (95% CI: 20.1-93.3%). VE against G9 could not be calculated due to limited numbers.

Type	Group	N	n	T (year)	n / T rate	95% CI	%	n / N 95% CI		Vaccine efficacy %	95% CI	
	ELISA or RT-PCR											
G1	HRV	241	5	238.0	0.021	0.009 0.050	2.1	0.7	4.8	75.1	20.1	93.3
	Placebo	120	10	116.1	0.086	0.046 0.160	8.3	4.1	14.8			
	ELISA or RT-PCR											
G9	HRV	241	1	237.8	0.004	0.001 0.030	0.4	0.0	2.3	infinity	infinity	98.7
	Placebo	120	0	119.4	0.000	NE	0.0	0.0	3.0			

Source: Study Report Body Rota-004 Annex 1, pg 80

Applicant Erratum Note: Due to the reclassification of the 4 subjects mentioned previously, VE against any G1 RV GE detected by ELISA or RT-PCR during the 2nd efficacy follow-up period was recalculated as 77.4% (95% CI: 29.3-93.8%).

VE against any GE requiring hospitalization – Year 2 (Exploratory endpoint)
VE against any GE leading to hospitalization could not be calculated due to limited numbers of hospitalized GE cases (only 1 hospitalized RV GE case in the Rotarix group).

Anti-RV IgA status at Visit 3 versus RV GE occurrence, Rotarix group – Year 2
The percentages of subjects in the Rotarix group that reported at least one RV GE during the 2nd efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3 and detection method for RV, are included in the table below.

Anti-RV IgA status at Visit 3	N	n	%	95% CI	
	ELISA				
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	1	6.3	0.2	30.2
	RT-PCR				
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	0	0.0	0.0	20.6

N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
Source: Study Report Body Rota-004 Annex 1, pg 83

Applicant Erratum note: Due to the reclassification of Rotarix subjects mentioned previously, the table above was corrected as follows:

Anti-RV IgA status at Visit 3	N	n	%	95% CI	
	ELISA				
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	***0***	***0***	***0***	***20.6***

Year 2 Efficacy (After Visit 4 to Visit 5) – TVC for efficacy during the 2nd efficacy period

A total of 374 subjects (Rotarix-251, placebo-123) were included in Year 2 efficacy analyses. The median duration of follow-up during this interval was 1 year for both groups.

Summary of reported RV GE episodes
The numbers of any and severe RV GE episodes for each group and for each RV detection method, as well as the numbers of RV GE episodes by G serotype, were the same as in the ATP efficacy cohort.

VE against severe RV GE – Year 2
VE against severe RV GE as detected by ELISA or by RT-PCR during the 2nd efficacy follow-up period was 83.7% (95% CI: 8.6-98.4%), similar to the VE estimate for the ATP cohort.

VE against any RV GE – Year 2
VE against any RV GE detected by ELISA was 71.4% (95% CI: 21.2-90.5%), similar to the VE estimate for the ATP cohort. VE against any RV GE detected by RT-PCR was 70.6% (95% CI: 10.7-91.2%).
Reviewer Note: Due to the reclassification of the 4 subjects mentioned previously, VE against any RV GE detected by ELISA and by RT-PCR during the 2nd efficacy follow-up period should have been recalculated. However, the applicant did not provide the corrected VE estimates.

VE against any RV GE by main RV serotypes – Year 2
VE against any G1 RV GE detected by ELISA or by RT-PCR was 75.5% (95% CI: 21.3-93.4%). VE against G9 could not be calculated due to limited numbers (1 subject in the Rotarix group).
Reviewer Note: Due to the reclassification of the 4 subjects mentioned previously, VE against any G1 RV GE detected by ELISA or by RT-PCR during the 2nd efficacy follow-up period should have been recalculated. However, the applicant did not provide the corrected VE estimates.

VE against severe RV GE by main RV serotypes – Year 2
VE against severe G1 RV GE detected by ELISA or by RT-PCR was 91.8% (95% CI: 32.7-99.8%). VE against G9 could not be calculated due to limited numbers (Rotarix -1 subject).

VE against any GE requiring hospitalization – Year 2
VE against any GE leading to hospitalization could not be calculated due to limited numbers of cases (1 subject in the Rotarix group).

Anti-RV IgA status at Visit 3 versus RV GE occurrence during Year 2, Rotarix group
The percentages of subjects in the Rotarix group that reported at least one RV GE during the 2nd efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3 and detection method for RV, are included in the table below.

Anti-RV IgA status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	47	2	4.3	0.5	14.5
Positive	186	4	2.2	0.6	5.4
Unknown	18	1	5.6	0.1	27.3
RT-PCR					
Negative	47	2	4.3	0.5	14.5
Positive	186	4	2.2	0.6	5.4
Unknown	18	0	0.0	0.0	18.5

Source: Study Report Body Rota-004 Annex 1, pg 95

Applicant Erratum Note: Due to the reclassification of Rotarix subjects mentioned previously, figures in the Unknown subcategory under the ELISA category should have been corrected. However, corrected figures were not provided.

Combined Efficacy (2 weeks post-Dose 2 to Visit 5) – ATP efficacy cohort

The ATP efficacy cohort used for Year 1 was also used for the combined efficacy period. The median duration of follow-up during this period was approximately 17.6 months in each group.

Summary of reported any RV GE and severe RV GE episodes – Combined period
RV was detected by ELISA in 16 GE episodes of Rotarix recipients and 25 episodes in placebo recipients. RV was detected by RT-PCR in 18 GE episodes of Rotarix recipients and 23 episodes of placebo recipients.

Two subject (Rotarix-1, placebo-1) had 2 RV GE episode during the 2nd efficacy period. The Rotarix recipient has been previously discussed under the *Year 1 Efficacy* section. The placebo recipient had one G2 RV GE episode during Year 1 and one G1 RV GE during Year 2; both episodes were classified as severe. This subject had anti-RV IgA antibodies at the end of Year 1.

Event	Total number of episodes reported	HRV N = 245		Placebo N = 123	
		n	%	n	%
GE	1	85	34.7	37	30.1
	2	44	18.0	24	19.5
	3	21	8.6	15	12.2
	4	6	2.4	2	1.6
	5	3	1.2	0	0.0
	6	1	0.4	2	1.6
	7	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	162	66.1	80	65.0
RV GE by ELISA	1	14	5.7	23	18.7
	2	1	0.4	1	0.8
	Any	15	6.1	24	19.5
RV GE by RT-PCR	1	16	6.5	21	17.1
	2	1	0.4	1	0.8
	Any	17	6.9	22	17.9

Source: Study Report Body Rota-004 Annex, pg 97

Reviewer Note: Due to the reclassification of the 6 subjects mentioned previously, the table above should be corrected as follows:

Event	Total number of episodes reported	HRV N = 245		Placebo N = 123	
		n	%	n	%
RV GE by ELISA	1	***12***	***4.9***	***22***	***17.9***
	2	1	0.4	1	0.8
	Any	***13***	***5.3***	***23***	***18.7***
RV GE by RT-PCR	1	16	6.5	***22***	***17.9***
	2	1	0.4	1	0.8
	Any	17	6.9	***23***	***18.7***

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) as determined by either ELISA or RT-PCR was classified for 3 episodes in the Rotarix group and 11 episodes in the placebo group. Of the 3 Rotarix recipients who had severe disease, 2 did not serocovert one month post-Dose 2.

Event	Severity	HRV n	HRV %	Placebo n	Placebo %
Any GE	Unknown	2	0.7	0	0.0
	Mild (1-6)	207	69.9	95	63.3
	Moderate (7-10)	73	24.7	41	27.3
	Severe (≥11)	14	4.7	14	9.3
	Any	296	100	150	100
RV GE by ELISA	Mild (1-6)	5	31.3	5	20.0
	Moderate (7-10)	8	50.0	9	36.0
	Severe (≥11)	3	18.8	11	44.0
	Any	16	100	25	100
RV GE by RT-PCR	Mild (1-6)	7	38.9	4	17.4
	Moderate (7-10)	8	44.4	8	34.8
	Severe (≥11)	3	16.7	11	47.8

	Any	18	100	23	100

Source: Study Report Body Rota-004 Annex 1, pg 61

Serotype G distribution is summarized below. G1 was the most prevalent circulating type. RV G type could not be identified in 5 subjects (Rotarix-3, placebo-2).

	HRV N = 245		Placebo N = 123	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	15	6.1	24	19.5
Unknown	3	1.2	2	1.6
G1	12	4.9	21	17.1
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8
RT-PCR				
Any	17	6.9	22	17.9
G1	16	6.5	21	17.1
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8

Any = number of subjects reporting at least one RV GE episode, whatever the type
Source: Study Report Body Rota-004 Annex 1, pg 62

Reviewer Note: Due to the reclassification of the 6 subjects mentioned previously, the table above should be corrected as follows:

	HRV N = 245		Placebo N = 123	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	***13***	***5.3***	***23***	***18.7***
Unknown	***0***	***0.0***	***0***	***0.0***
G1	12	4.9	***22***	***17.9***
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8
RT-PCR				
Any	17	6.9	***23***	***18.7***
G1	16	6.5	***22***	***17.9***
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8

Clinical characteristics of RV GE episodes – Combined period

The duration of looser than normal stools and vomiting were shorter in the Rotarix group compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration, and rehydration treatment were also less in the Rotarix group compared to placebo.

VE against any RV GE detected by ELISA – Combined period (Secondary endpoint)

VE against any RV GE as detected by ELISA during the combined follow-up period was 68.6% (95% CI: 37.7-84.7%).

			T	n / T			n / N			Vaccine efficacy			p-
Group	**N**	**n**	**(year)**	**rate**	**95% CI**		**%**	**95% CI**		**% 95% CI**			**value**
Any RV GE													
HRV	245	15	340.4	0.044	0.027	0.073	6.1	3.5	9.9	68.6	37.7	84.7	<0.001
Placebo	123	24	157.2	0.153	0.102	0.228	19.5	12.9	27.6				

Source: Study Report Body Rota-004 Annex 1, pg 63

Applicant Erratum Note: Due to the reclassification of the 6 subjects mentioned previously, VE against any RV GE detected by ELISA during the combined period was 71.6% (95% CI: 41.6-86.8%).

VE against any RV GE detected by RT-PCR – Combined period (Secondary endpoint)
VE against any RV GE as detected by RT-PCR during the combined follow-up period was 61.2% (95% CI: 23.5-80.7%).

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	245	17	335.5	0.051	0.031	0.082	6.9	4.1	10.9	61.2	23.5	80.7	0.002
Placebo	123	22	158.6	0.139	0.091	0.211	17.9	11.6	25.8				

Source: Study Report Body Rota-004 Annex 1, pg 63

Applicant Erratum Note: Due to the reclassification of the 6 subjects mentioned previously, VE against any RV GE detected by ELISA during the combined period was 62.9% (95% CI: 27.4-81.4%).

VE against severe RV GE detected by ELISA – Combined period (Secondary endpoint)
VE against severe RV GE as detected by ELISA during the combined follow-up period was 84.9% (95% CI: 41.5-97.3%).

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Study Report Body Rota-004 Annex 1, pg 63

VE against severe RV GE detected by PCR – Combined period (Secondary endpoint)
VE against severe RV GE as detected by RT-PCR during the combined follow-up period was 84.9% (95% CI: 41.5-97.3%), the same as for VE against severe RV GE detected by ELISA.

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Study Report Body Rota-004 Annex 1, pg 63

VE against any RV GE by main RV serotypes – Combined period (Secondary endpoint)
VE against any G1 RV GE detected by ELISA was 71.3% (95% CI: 38.9-87.1%). VE detected by RT-PCR was 61.7% (95% CI: 23.1-81.3). VE against G2 and G9 RV GE was 100% and 49.8%, respectively, although 95% CIs for both estimates were wide and crossed 0 due to limited case numbers of these two serotypes.
Applicant Erratum Note: Due to the reclassification of the 6 subjects mentioned previously, VE against any G1 RV GE detected by ELISA was recalculated as 72.6% (95% CI: 42.2-87.6%). VE against any G1 RV GE detected by RT-PCR was recalculated as 63.5% (95% CI: 27.2-82.1%).

VE against severe RV GE by main RV serotypes – Combined period (Secondary endpoint)
VE against severe G1 RV GE detected by ELISA or by RT-PCR was 90.0% (95% CI: 52.9-98.9%). VE against severe G2 RV GE was 100%, although the 95% CI for was very wide and crossed 0 due to limited case numbers of this serotype. VE against severe G9 RV GE could not be calculated due to limited case numbers.

VE against any GE – Combined period (Secondary endpoint)
VE against GE of any etiology was -1.7% (95% CI: -34.6-22.7%).

VE against severe GE – Combined period (Secondary endpoint)
VE against severe GE of any etiology was 45.2% (95% CI: -37.0-77.9%).

VE against any GE requiring hospitalization – Combined period (Exploratory endpoint)
VE against hospitalized GE of any etiology or intensity could not be calculated due to limited case numbers (2 cases in the Rotarix group – 1 due to non-RV GE and one due to G9 RV GE).

Anti-RV IgA status at Visit 3 versus RV GE occurrence, Combined period, Rotarix group
The percentages of subjects in the Rotarix group that reported at least one RV GE during the combined efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3 and detection method for RV, are included in the table below. For either detection method, there were less subjects who had an RV GE episode in the seropositive group.

Anti-RV status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	45	6	13.3	5.1	26.8
Positive	181	7	3.9	1.6	7.8
Unknown	19	2	10.5	1.3	33.1
RT-PCR					
Negative	45	7	15.6	6.5	29.5
Positive	181	9	5.0	2.3	9.2
Unknown	19	1	5.3	0.1	26.0

Source: Study Report Body Rota-004 Annex 1, pg 103

Applicant Erratum Note: Due to the reclassification of 2 Rotarix subjects mentioned previously, the table above was corrected as follows:

Anti-RV status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	45	6	13.3	5.1	26.8
Positive	181	***6***	***3.3***	***1.2***	***7.1***
Unknown	19	***1***	***5.3***	***0.1***	***26.0***

Combined Efficacy (Visit 3 to Visit 5) – ATP efficacy cohort

VE against asymptomatic infection – Combined period (Secondary endpoint)
A total of 281 subjects (Rotarix-194, placebo-87) were included for the analysis of VE against asymptomatic RV infection detected by ELISA. VE against asymptomatic RV infection detected by ELISA from Visit 3 to Visit 5 was 82.1% (95% CI: 37.8-95.9%).

282 subjects (Rotarix-193, placebo-89) were included for the analysis of VE against asymptomatic RV infection detected by RT-PCR from Visits 3 to 5. VE was 83.2% (95% CI: 43.4-96.1%).

Group	N	n	%	95% CI		Vaccine efficacy %	95% CI		p-value
ELISA									
HRV	194	4	2.1	0.6	5.2	82.1	37.8	95.9	0.002
Placebo	87	10	11.5	5.7	20.1				
RT-PCR									
HRV	193	4	2.1	0.6	5.2	83.2	43.4	96.1	0.001
Placebo	89	11	12.4	6.3	21.0				

N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 5 and who did not reported a RV GE episode between Visits 3 and 5
n = number of subjects reporting asymptomatic RV infection in each group
Source: Study Report Body Rota-004 Annex 1, pg 66

Applicant Erratum Note: Due to the reclassification of 6 subjects mentioned previously, the table above was corrected as follows:

Group	N	n	%	95%CI		Vaccine efficacy % 95%CI			p-value
ELISA									
HRV	***195***	4	2.1	0.6	5.2	***81.9***	***37.4***	***95.9***	0.002
Placebo	***88***	10	***11.4***	***5.6***	***19.9***				
RT-PCR									
HRV	193	4	2.1	0.6	5.2	***81.8***	***36.8***	***95.8***	***0.002***
Placebo	***88***	***10***	***11.4***	***5.6***	***19.9***				

Source: Study Report Body Rota-004 Annex 1, pg 10

Combined Efficacy (2 weeks post-Dose 2 to Visit 5) – TVC for efficacy

The TVC for efficacy used for Year 1 was also used for the combined efficacy period. The median duration of follow-up during the combined efficacy period was 17.6 months in each group.

Summary of reported RV GE episodes
The numbers of any and severe RV GE episodes for each group and for each RV detection method, as well as the numbers of RV GE episodes by G serotype, were the same as in the ATP efficacy cohort.

VE against any RV GE – Combined period
VE against any RV GE detected by ELISA during the combined period was 69.1% (95% CI: 38.7-84.9%), similar to the VE estimate for the ATP cohort. VE against any RV GE detected by RT-PCR was 61.8% (95% CI: 24.7-81.0%).
Reviewer Note: Due to the reclassification of the 6 subjects mentioned previously, VE against any RV GE detected by ELISA and by RT-PCR during the combined period should have been recalculated. However, the applicant did not provide the corrected VE estimates.

VE against severe RV GE – Combined period
VE of Rotarix against severe RV GE as detected by ELISA or by RT-PCR during the combined period was 85.2% (95% CI: 42.4-97.4%), similar to the VE estimate for the ATP cohort.

VE against any RV GE by main RV serotypes – Combined period
VE against any G1 RV GE detected by ELISA was 71.8% (95% CI: 39.9-87.3%). VE against any G1 RV GE detected by RT-PCR was 62.4% (95% CI: 24.3-81.6%). VE against G2 and G9 RV GE detected either by ELISA or RT-PCR was 100% and 50.6%, respectively, although 95% CIs for both estimates were wide and crossed 0 due to limited case numbers of these two serotypes.
Reviewer Note: Due to the reclassification of the 6 subjects mentioned previously, VE against any G1 RV GE detected by ELISA and by RT-PCR during the combined period should have been recalculated. However, the applicant did not provide the corrected VE estimates.

VE against severe RV GE by main RV serotypes – Combined period
VE against severe G1 RV GE detected by ELISA or by RT-PCR was 90.1% (95% CI: 53.6-98.9%). VE against severe G2 RV GE was 100%, although the 95% CI for was very wide and crossed 0 due to limited case numbers of this serotype. VE against severe G9 RV GE could not be calculated due to limited case numbers.

VE against any GE – Combined period (Secondary endpoint)
VE against GE of any etiology was 0.6% (95% CI: -31.2-24.2%).

VE against severe GE – Combined period (Secondary endpoint)
VE against severe GE of any etiology was 46.1% (95% CI: -34.8-78.2%).

VE against any GE requiring hospitalization – Combined period
VE against any GE leading to hospitalization could not be calculated due to limited numbers of cases (2 subjects in the Rotarix group).

Anti-RV IgA status at Visit 3 versus RV GE occurrence, Combined period, Rotarix group
The percentages of subjects in the Rotarix group that reported at least one RV GE during the combined efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3 and detection method for RV, are included in the table below. For either detection method, there were less subjects who had an RV GE episode in the seropositive group.

Anti-RV IgA status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	47	6	12.8	4.8	25.7
Positive	187	7	3.7	1.5	7.6
Unknown	21	2	9.5	1.2	30.4
RT-PCR					
Negative	47	7	14.9	6.2	28.3
Positive	187	9	4.8	2.2	8.9
Unknown	21	1	4.8	0.1	23.8

Source: Study Report Body Rota-004 Annex 1, pg 118

Reviewer Note: Due to the reclassification of Rotarix subjects mentioned previously, figures in the Unknown and Positive subcategories under the ELISA category should have been corrected. However, corrected figures were not provided.

Combined Efficacy (Visit 3 to Visit 5) – TVC for efficacy

VE against asymptomatic infection – Combined period (Secondary endpoint)
291 subjects (Rotarix-201, placebo-90) were included for the analysis of VE against asymptomatic RV infection detected by ELISA from Visit 3 to Visit 5. VE was 77.6% (95% CI: 28.1-94.0%).

292 subjects (Rotarix-200, placebo-92) were included for the analysis of VE against asymptomatic RV infection detected by RT-PCR from Visit 3 to Visit 5. VE was 79.1% (95% CI: 34.7-94.3%).
Reviewer Note: Due to the reclassification of 6 subjects mentioned previously, VE estimate figures for both detection methods should have been corrected. However, corrected figures were not provided.

Year 2 – TVC for immunogenicity

A total of 404 subjects (Rotarix-269, placebo-135) were included in this immunogenicity analysis.

Applicant Erratum Note: GMC results for 4 subjects (Rotarix-2, placebo-2) were modified after Year 1 immunogenicity analyses; 1 subject (Rotarix group) had a modified result for Visit 3 GMC, while 3 subjects (Rotarix-1, placebo-2) had modified results for Visit 4 GMC. These modified results were included in the immunogenicity analyses below.
Reviewer Note: The applicant did not state why immunogenicity analyses for Year 2 were not also performed on the ATP immunogenicity cohort.

Anti-RV IgA response
Seropositivity rates and GMCs at pre-vaccination, 1 month post-Dose 2, end of 1st RV season, and end of 2nd RV season, are summarized below. These results demonstrate a decrease in both seropositivity rates and GMCs from Visit 3 to Visit 5 in the Rotarix group. However, these decreases did not parallel a decrease in VE from Years 1 to 2, as VE of both periods were similar.

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)				
					95% CI		Value	95% CI		Range	
			n	%	L.L.	U.L.		L.L.	U.L.	Min	Max

HRV	Pre	265	0	0.0	0.0	1.4	<20	NA	NA	<20	<20
	PII(M3)	234	187	79.9	74.2	84.9	159.0	127.2	198.7	<20	4161
	ES1	224	170	75.9	69.7	81.3	81.8	67.4	99.1	<20	3211
	ES2	229	154	67.2	60.8	73.3	53.1	43.9	64.4	<20	11749
Placebo	Pre	133	0	0.0	0.0	2.7	<20	NA	NA	<20	<20
	PII(M3)	122	1	0.8	0.0	4.5	<20	NA	NA	<20	668
	ES1	120	22	18.3	11.9	26.4	21.8	16.1	29.5	<20	3014
	ES2	115	33	28.7	20.6	37.9	29.3	21.1	40.7	<20	3422

N = number of subjects with available data; n/% = number/percentage of subjects with concentration above the cut-off
Pre = Pre-vaccination; PII(M3) = one month after the second vaccination
ES1 = end of the first RV season; ES2 = end of the second RV season
Comment: NA = not applicable

Anti-RV IgA GMCs for seropositive subjects are presented below. Assuming that immune responses in the placebo group were due to wild type RV, immunogenicity was higher after wild type RV than after Rotarix at all 3 time points.

Group	Timing	N	GMC (U/ml)				
			Value	95% CI L.L.	U.L.	Min	Range Max
HRV	PII(M3)	187	318.7	269.8	376.4	28	4161
	ES1	170	159.3	137.4	184.8	24	3211
	ES2	154	119.8	100.6	142.7	27	11749
Placebo	PII(M3)	1	668.0	NA	NA	668	668
	ES1	22	697.3	510.9	951.5	116	3014
	ES2	33	422.2	296.3	601.6	62	3422

N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
PII(M3) = one month after the second vaccination; ES1 = end of the first RV season; ES2 = end of the second RV season
Comment: NA = not applicable
Source: Study Report Body Rota-004 Annex 1, pg 72

8.1.3.2.3 Safety outcomes

Year 1 Safety – TVC

Symptom sheets (i.e. diary cards) for general solicited AEs were completed for 98.9% (520/526) of all Rotarix doses and 98.5% (257/261) of all placebo doses. Compliance in completing diary cards was at least 98.1% after either dose in either treatment group. Data concerning solicited and unsolicited AEs was reported following 99.2% (522/526) of Rotarix and 98.5% of placebo doses.

Dose	Group	Number of Doses	Doses NOT according to protocol	Number of general SS	Compliance % general
1	HRV	270	0	265	98.1
	Placebo	135	0	133	98.5
2	HRV	256	1	255	99.6
	Placebo	126	0	124	98.4
Total	HRV	526	1	520	98.9
	Placebo	261	0	257	98.5

SS= symptom sheet
Source: Study Report Body Rota-004, pg 102

Overall incidence of AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects who reported at least one solicited/unsolicited symptom after Dose 1 and after Dose 2, and the percentages who reported at least one symptom among those who received at least one study dose, were similar between groups (Rotarix-87.6%, placebo-83.5%).

		Symptoms					
		N	n	%	95% CI		
					L.L.	U.L.	
Dose 1	HRV	267	197	73.8	68.1	79.0	
	Placebo	133	94	70.7	62.2	78.2	
Dose 2	HRV	255	190	74.5	68.7	79.7	
	Placebo	124	90	72.6	63.8	80.2	
Overall doses	HRV	522	387	74.1	70.2	77.8	
	Placebo	257	184	71.6	65.7	77.0	
Overall subjects	HRV	267	234	87.6	83.1	91.3	p-value = 0.281
	Placebo	133	111	83.5	76.0	89.3	

Each dose:
N = number of documented doses, for the considered dose
(a documented dose is defined as a dose for which a symptom sheet was completed and/or an unsolicited symptom was reported)
n/% = number/percentage of documented doses leading to reporting of at least one symptom, for the considered dose
Overall/dose:
N = total number of documented doses;
n/% = total number/percentage of documented doses leading to reporting of at least one symptom
Overall/subject:
N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting at least one symptom
Source: Study Report Body Rota-004, pg 81

Overall incidence of Grade 3 AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects who reported at least one Grade 3 solicited or unsolicited symptom after Dose 1 were higher in the Rotarix group compared to the placebo group, although 95% CIs overlapped. Percentages were less in the Rotarix group than placebo group after Dose 2, although 95% CIs also overlapped. The percentage who reported at least one Grade 3 symptom among those who received at least one study dose was slightly higher in the Rotarix group compared to placebo (15% versus 13.5%), although 95% CIs overlapped.

		Symptoms				
		N	n	%	95% CI	
					L.L.	U.L.
Dose 1	HRV	267	24	9.0	5.8	13.1
	Placebo	133	6	4.5	1.7	9.6
Dose 2	HRV	255	18	7.1	4.2	10.9
	Placebo	124	12	9.7	5.1	16.3
Overall doses	HRV	522	42	8.0	5.9	10.7
	Placebo	257	18	7.0	4.2	10.8
Overall subjects	HRV	267	40	15.0	10.9	19.8
	Placebo	133	18	13.5	8.2	20.5

Source: Study Report Body Rota-004, pg 124

Overall incidence of vaccine-related AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects who reported at least one vaccine-related solicited or unsolicited symptom after Dose 1 and after Dose 2 were higher in the Rotarix group compared to the placebo group, although 95% CIs overlapped. The percentage who reported at least one vaccine-related symptom among those who received at least one study dose was higher in the Rotarix group compared to placebo (72.3% versus 64.7%), although 95% CIs overlapped.

		Symptoms				
		N	n	%	95% CI	
					L.L.	U.L.
Dose 1	HRV	267	150	56.2	50.0	62.2
	Placebo	133	62	46.6	37.9	55.5
Dose 2	HRV	255	139	54.5	48.2	60.7

	Placebo	124	65	52.4	43.3	61.5
Overall doses	HRV	522	289	55.4	51.0	59.7
	Placebo	257	127	49.4	43.1	55.7
Overall subjects	HRV	267	193	72.3	66.5	77.6
	Placebo	133	86	64.7	55.9	72.7

Source: Study Report Body Rota-004, pg 125

Solicited general AEs – Days 0-14 post-dose

The differences in incidence of total AEs for each symptom after any dose were not statistically significant between Rotarix and placebo groups except for loss of appetite, which occurred in 38.9% in the Rotarix group compared to 28.6% in the placebo group.

Irritability/fussiness was the most common AE in both groups (Rotarix-77.0%, placebo-71.4%) after each dose, followed by loss of appetite and fever. Diarrhea AEs were the least common in both groups. Grade 3 AEs were less common for each symptom, and were reported at a similar incidence both groups. Grade 3 AEs that were reported at a rate ≥ 1% and <10% in the Rotarix group were diarrhea (1.9%), fussiness/irritability (8.3%), and vomiting (4.5%). The majority of solicited symptoms were assessed as related to vaccination; for each symptom, the 95% CIs for both groups overlapped.

For any dose

		HRV N = 265				Placebo N = 133				p-value
Symptoms		**n**	**%**	**95% CI L.L.**	**95% CI U.L**	**n**	%	**95% CI L.L.**	**95% CI U.L.**	
Diarrhea	Total	30	11.3	7.8	15.8	8	6.0	2.6	11.5	0.105
	Grade 3	5	1.9	0.6	4.3	0	0.0	0.0	2.7	
	Related	25	9.4	6.2	13.6	5	3.8	1.2	8.6	
Fever	Total	85	32.1	26.5	38.1	33	24.8	17.7	33.0	0.163
	Grade 3	1	0.4	0.0	2.1	0	0.0	0.0	2.7	
	Related	52	19.6	15.0	24.9	17	12.8	7.6	19.7	
Fussiness/ Irritability	Total	204	77.0	71.4	81.9	95	71.4	63.0	78.9	0.269
	Grade 3	22	8.3	5.3	12.3	12	9.0	4.7	15.2	
	Related	163	61.5	55.4	67.4	74	55.6	46.8	64.2	
Loss of appetite	Total	103	38.9	33.0	45.0	38	28.6	21.1	37.0	0.046
	Grade 3	1	0.4	0.0	2.1	0	0.0	0.0	2.7	
	Related	74	27.9	22.6	33.7	25	18.8	12.5	26.5	
Vomiting	Total	34	12.8	9.1	17.5	14	10.5	5.9	17.0	0.625
	Grade 3	12	4.5	2.4	7.8	2	1.5	0.2	5.3	
	Related	27	10.2	6.8	14.5	11	8.3	4.2	14.3	

N = number of subjects with at least one solicited symptom sheet completed
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Fever = rectal temperature ≥38.0°C or oral temperature ≥37.5°C
Source: Study Report Body Rota-004, pg 82

There were no major differences between groups in incidence of total AEs for each symptom after all doses. Irritability/fussiness and diarrhea were the most common and least common AE, respectively. Grade 3 AEs were less common for each symptom, and were reported at a similar incidence both groups.

For all doses

Symptom		All doses					
		HRV N = 520			Placebo N = 257		
		n	**%**	**95% CI**	**n**	**%**	**95% CI**

				L.L.	U.L.			L.L.	U.L.
Diarrhea	Total	31	6.0	4.1	8.4	9	3.5	1.6	6.5
	Grade 3	5	1.0	0.3	2.2	0	0.0	0.0	1.4
	Related	26	5.0	3.3	7.2	6	2.3	0.9	5.0
Fever	Total	101	19.4	16.1	23.1	45	17.5	13.1	22.7
	Grade 3	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Related	61	11.7	9.1	14.8	21	8.2	5.1	12.2
Irritability	Total	313	60.2	55.8	64.4	146	56.8	50.5	63.0
	Grade 3	23	4.4	2.8	6.6	12	4.7	2.4	8.0
	Related	243	46.7	42.4	51.1	103	40.1	34.0	46.3
Loss of appetite	Total	124	23.8	20.2	27.7	47	18.3	13.8	23.6
	Grade 3	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Related	89	17.1	14.0	20.6	31	12.1	8.3	16.7
Vomiting	Total	39	7.5	5.4	10.1	17	6.6	3.9	10.4
	Grade 3	12	2.3	1.2	4.0	2	0.8	0.1	2.8
	Related	30	5.8	3.9	8.1	13	5.1	2.7	8.5

Source: Study Report Body Rota-004, pg 83

Incidences for each symptom were comparable between groups after each dose. Only fever demonstrated a noticeable increase in incidence from Dose 1 to Dose 2 in both groups. This may have been due to Dose 2 being administered between mid-October and end-January during which time the incidences of common cold or other winter-related conditions are higher. Grade 3 fever rarely occurred in either group.

Dose		1								2							
		HRV (N = 265)				Placebo (N= 133)				HRV (N = 255)				Placebo (N= 124)			
		n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				L.L.	UL			L.L.	U.L.			L.L.	U.L.			L.L.	U.L.
Diarrhea	Total	20	7.5	4.7	11.4	7	5.3	2.1	10.5	11	4.3	2.2	7.6	2	1.6	0.2	5.7
	Grade 3	4	1.5	0.4	3.8	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	16	6.0	3.5	9.6	5	3.8	1.2	8.6	10	3.9	1.9	7.1	1	0.8	0.0	4.4
Irritability	Total	163	61.5	55.4	67.4	80	60.2	51.3	68.5	150	58.8	52.5	64.9	66	53.2	44.1	62.2
	Grade 3	14	5.3	2.9	8.7	5	3.8	1.2	8.6	9	3.5	1.6	6.6	7	5.6	2.3	11.3
	Related	129	48.7	42.5	54.9	55	41.4	32.9	50.2	114	44.7	38.5	51.0	48	38.7	30.1	47.9
Loss of appetite	Total	64	24.2	19.1	29.8	22	16.5	10.7	24.0	60	23.5	18.5	29.2	25	20.2	13.5	28.3
	Grade 3	0	0.0	0.0	1.4	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	47	17.7	13.3	22.9	14	10.5	5.9	17.0	42	16.5	12.1	21.6	17	13.7	8.2	21.0
Fever	Total	32	12.1	8.4	16.6	14	10.5	5.9	17.0	69	27.1	21.7	33.0	31	25.0	17.7	33.6
	Grade 3	0	0.0	0.0	1.4	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	22	8.3	5.3	12.3	7	5.3	2.1	10.5	39	15.3	11.1	20.3	14	11.3	6.3	18.2
Vomiting	Total	23	8.7	5.6	12.7	6	4.5	1.7	9.6	16	6.3	3.6	10.0	11	8.9	4.5	15.3
	Grade 3	6	2.3	0.8	4.9	0	0.0	0.0	2.7	6	2.4	0.9	5.1	2	1.6	0.2	5.7
	Related	18	6.8	4.1	10.5	5	3.8	1.2	8.6	12	4.7	2.5	8.1	8	6.5	2.8	12.3

Source: Study Report Body Rota-004, pg 126

There was no noticeable peak day in the prevalence of diarrhea, vomiting, or fever from Day 0 to Day 14 after either dose for either group. Mean duration of diarrhea, vomiting, and fever during the 15-day period after each dose were similar between groups, ranging from 1.5 to 3 days. In the Rotarix group, all three symptoms lasted slightly longer after Dose 2 compared to Dose 1.

Seven subjects (Rotarix-6, placebo-1) experienced diarrhea and vomiting simultaneously during the 15-day solicited follow-up period. One of these subject reported Grade 3 symptoms after Dose 1; G1 RV was detected by RT-PCR in stool samples, while ELISA results were negative for RV. Another subject, who reported grade 1 diarrhea and vomiting, tested positive for RV by ELISA and G1 type by RT-PCR.

RV GE – Day of Dose 1 to 2 weeks post-Dose 2
Among Rotarix recipients, RV was detected by ELISA in 9 GE episodes from 9 (3.4%) subjects and by RT-PCR in 19 episodes from 17 (6.4%) subjects. G1 type was detected in all RT-PCR-positive cases, and all ELISA-positive cases were also RT-PCR-positive. Sequencing was not performed to distinguish wild-type versus vaccine G1 virus. Of all the ELISA and/or RT-PCR positive subjects with GE data needed to determine disease severity, none were graded as severe RV GE (although severity grading was unknown for 2 of the 9 episodes detected by ELISA and 4 of the 19 episodes detected by RT-PCR). No placebo subject tested positive for RV by either test method.
Applicant Post-hoc Analyses: Sequencing analyses of RV identified from the 19 GE episodes showed that 17 were vaccine strains, one was a wild type strain, and one was negative. Of the 17 episodes with vaccine G1 RV strains, onset of GE from previous Rotarix dose ranged from 0 to 40 days (median – 2 days).
Reviewer Note: In Study Rota-004, inclusion in the ATP efficacy cohort required that a subject had no RV other than vaccine strain in stool samples collected between the day of Dose 1 and 2 weeks post-Dose 2. Similarly, inclusion in the ATP immunogenicity cohort required that a subject had no RV other than vaccine strain in stool samples collected from Dose 1 until Visit 3. In the applicant's post-hoc analysis, one subject with G1 wild type strain based on sequencing analysis was identified. However, based on information provided in the study reports and analyses databases, this subject was not excluded from either the ATP efficacy or immunogenicity cohorts.

Unsolicited AEs – Days 0- 42 post-dose
The percentages of subjects with at least one unsolicited AE of any kind were similar between groups (Rotarix-190, 71.2%; placebo-93, 69.9%). There were no statistically significant differences between groups for any WHO Preferred Term. In Rotarix recipients, PTs that were reported at a rate ≥ 10% (in subjects reporting the specified AE at least once) were rhinitis (26.2%), nervousness (24%) and fever (13.9%). PTs that were reported at a rate ≥ 1% and <10% in the Rotarix group were abnormal crying (2.6%), pain (4.1%), abdominal pain (4.1%), anorexia (1.1%), constipation (3.4%), diarrhea (2.6%), flatulence (6.4%), gastroesophageal reflux (6.7%), tooth ache (2.2%), vomiting (1.5%), insomnia (1.9%), viral infection (2.6%), moniliasis (2.2%), otitis media (8.2%), upper respiratory tract infection (9.4%), coughing (9.7%), eczema (3.4%), rash (2.2%), and conjunctivitis (7.5%).

The percentages of subjects with at least one Grade 3 unsolicited AE was less in the Rotarix compared to the placebo group (17, 6.4% versus 13, 9.8%). There were no noticeable differences between groups for any WHO Preferred Term. In Rotarix recipients, there were no Grade 3 PTs reported at a rate ≥ 10%. Grade 3 PTs that were reported at a rate ≥ 1% and <10% in the Rotarix group were fever (1.1%), flatulence (1.5%), upper respiratory tract infection (1.1%), rhinitis (1.5%).

The percentages of subjects with at least one vaccine-related unsolicited AE was more in the Rotarix group compared to the placebo group (40, 15% versus 14, 10.5%), although 95% CIs for both groups overlapped. Among the WHO Preferred Terms, Abdominal Pain (3.0% versus 0.8%) and Flatulence (3.7% versus 0.8%) were reported slightly more in the Rotarix group than in the placebo group, although 95% CIs for both groups overlapped for each of the PTs. Other vaccine-related PTs that were reported at a rate ≥ 1% and <10% in the Rotarix group were fatigue (1.9%) and gastroesophageal reflux (5.6%). There were no vaccine-related AEs reported at a rate ≥ 10%.

Unsolicited AEs that were both Grade 3 and vaccine-related are summarized below.

WHO Preferred term (CODE)	Onset	Duration	Group
Abdominal pain (0268)	Day 2 post Dose 1	16 days	Rotarix
Abdominal pain (0268) and crying abnormal (1162)	Day 6 post Dose 1	11 days	Placebo

Flatulence (0285)	Day 5 post Dose 1	6 days	Rotarix
Flatulence (0285)	Day 5 post Dose 1	1 day	Rotarix
Flatulence (0285)	Day 0 post Dose 1	9 days	Rotarix
Fatigue (0724)	Day 0 post Dose 2	2 days	Placebo
Gastroesophageal reflux (1149)	Day 4 post Dose 2	1 day	Rotarix

Source: Study Report Body Rota-004, pg 88

The percentage of subjects with at least 1 unsolicited gastrointestinal AE, 1 vaccine-related GI AE, and 1 Grade 3 GI AE, were higher in the Rotarix group compared to the placebo group, although 95% CIs for both groups overlapped.

WHO Body System (CODE)		**HRV N = 267**				**Placebo N = 133**			
				95% CI				**95% CI**	
	Symptom	**s**	**%**	**L.L.**	**U.L.**	**s**	**%**	**L.L.**	**U.L.**
Gastrointestinal system (600)	Any	64	24.0	19.0	29.6	20	15.0	9.4	22.3
	Related	30	11.2	7.7	15.7	5	3.8	1.2	8.6
	Grade 3	6	2.2	0.8	4.8	2	1.5	0.2	5.3

Source: Study Report Body Rota-004, pg158

Reviewer Note: The reviewer obtained a total of 63 Rotarix subjects who had at least 1 unsolicited gastrointestinal AE, based on the analysis data provided by the applicant. Because this number did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the figure submitted by the applicant.

Concomitant medications/vaccinations – Days 0-14 post-dose
The percentages of subjects who started taking any medication and any antipyretics after each dose were comparable between groups. Overall, 63.3% of Rotarix recipients and 63.0% of placebo recipients started taking a medication between Visit 1 and Visit 4.

SAEs – Dose 1 to Visit 4
Nineteen subjects (Rotarix-15 [5.6%], placebo-4 [3.0%]) reported at least one SAE during this interval. None of the SAEs were judged to be related to study vaccination. No cases of IS were reported. The distributions of SAEs by WHO Body System or WHO Preferred Term were not provided in the report.
Reviewer Note: Based on analysis data provided by the applicant, the reviewer found a total of 26 SAEs during this period; one (PT *Growth retarded*) had onset before this interval. Of the remaining 25 SAEs, only 5 had onset between Day 0 and Day 19 post-dose (PTs *Appetite increased, Crying abnormal, Seborrhea, Pneumonia,* and *Infection viral*). *Pneumonia* (1.5%) was the only SAE PT reported at a rate ≥ 1% in the Rotarix group.

Deaths – Dose 1 to Visit 4
No deaths were reported during this interval.

SAEs and non-serious AEs leading to drop-out at Visit 4
No subjects dropped out of the study due to SAEs.

Eight subjects (Rotarix-6, placebo-2) dropped out at Visit 4 due to non-SAEs. Of these, 5 subjects had vaccine-related AEs consisting mostly of Grade 1/Grade 2 diarrhea, vomiting, irritability, and vomiting. Vaccine-related Grade 3 AEs occurred as follows: vomiting 4 days post-Dose 2 in a Rotarix recipient, colicky stomach ache 2 days post-Dose 2 in a Rotarix recipient, and irritability 2 days post-Dose 1 in a Rotarix recipient. Of the non-vaccine-related AEs, one placebo subject had Grade 2 melena 1 day post-Dose 2, one Rotarix subject had 2 RV negative GE episodes 16 days (Grade 2) and 57 days (Grade 1) post-Dose 1, and one Rotarix subject had Grade 2 cough 5 days post-Dose 1 along with Grade 2 shortness of breath 9 days post-Dose.

Year 2 safety (after Visit 4 to Visit 5) – TVC

SAEs – after Visit 4 to Visit 5
During this interval, 20 subjects (Rotarix-13, placebo-7) reported at least one SAE during this interval. None of the SAEs were judged to be related to study vaccination. No cases of IS were reported. The distributions of SAEs by WHO Body System or WHO Preferred Term were not provided in the report.
Reviewer Note: Based on analysis data provided by the applicant, the reviewer found a total of 28 SAEs during this period. Onsets of the SAEs ranged from 57 to 558 days after the last study dose. There were no noticeable imbalances in specific SAEs between groups. SAE PTs that were reported at a rate ≥ 1% in the Rotarix group were *Bronchitis* (1.9%) and *Pneumonia* (1.5%).

Deaths – after Visit 4 to Visit 5
No deaths were reported during this interval.

SAEs and non-serious AEs leading to drop-out at Visit 5 - after Visit 4 to Visit 5
There were no SAEs or non-SAES that lead to drop out at Visit 5 during this interval.

Individual report forms reviewed
Individual case narratives were reviewed for all SAEs reported up to Visit 4.

8.1.3.3 Comments & Conclusions

In Rota-004, two doses of Rotarix at a lower concentration of vaccine virus ($10^{4.7}$ ffu of RIX4414) than that used in the 2 pivotal trials (Rota-023 and Rota-036), administered to children 6 to 12 weeks 2 months apart, demonstrated efficacy of 73.0% against any RV GE detected by ELISA during the 1st efficacy period. VE against severe RV GE detected either by ELISA during this period was 90.3%. VE against any RV GE and severe RV GE detected by ELISA during the 2nd efficacy period was 72.8% and 83.4%, respectively. VE against any RV GE (71.6%) and severe RV GE (84.9%) during the combined follow-up period were similar to estimates for the 1st efficacy period. The LLs of the 95% CI for all these estimates were below 50%.

Statistically significant VE was not observed against any wild-type G1 RV GE (64.9%) and severe G1 RV GE (87.4%) detected by ELISA during the 1st efficacy follow-up period due to limited numbers of cases. However, statistically significant VE was observed against any wild-type G1 RV GE (77.4%; LL 95% CI: 20.1%) and severe wild-type G1 RV GE (91.7%; LL 95% CI: 31.6%) detected by ELISA during the 2nd efficacy follow-up period. VE estimates against any wild-type G1 RV GE (72.6%; LL 95% CI: 42.4%) and severe G1 RV GE (90%) were also statistically significant. VE estimates against G2 and/or G9 RV GE during any of the follow-up periods were either not statistically significant or not calculated due to limited case numbers.

Overall, VE estimates against RV GE endpoints detected by RT-PCR were comparable to estimates using the ELISA method, except for VE against any RV GE during the 1st efficacy period in which 5 subjects who tested RV positive by RT-PCR were negative by ELISA. Post-hoc analyses later identified RV vaccine strains in 4 of the 5 subjects.

No cases of IS nor deaths were seen throughout the study. SAEs were relatively infrequent, and distributions by WHO Preferred Term were not noticeably different between groups. Overall rates of subjects who experienced a solicited or unsolicited AE from Day 0 to Day 14 post-dose were similar between treatment groups. Imbalances in rates of solicited AEs between groups were also not observed, except for loss of appetite which occurred at a higher rate in the Rotarix group. However, only one grade 3 AE for loss of appetite occurred in either group combined. The percentages of subjects with at least one unsolicited AE from Day 0 to Day 42 post-dose were similar between groups. The percentages of subjects with at least one Grade 3 unsolicited AE was less in the Rotarix group compared to the placebo group. Overall, there were no noticeable differences between groups for any unsolicited AE by WHO Preferred Term.

The validity of the results was strengthened by the double-blinded, placebo-controlled, study design. Efficacy, safety, and immunogenicity endpoints, case definitions, and study cohorts were clearly defined and appropriate. Overall, the study was well-conducted without any noticeable sources of biases. Data quality was acceptable, and appropriate data analyses were conducted as stated in the protocol and amendments. Protocol deviations were minor and occurred infrequently. Subject dropouts and missing data were handled appropriately and according to protocol. Retesting of stool samples due to initial laboratory inconsistencies was conducted appropriately, with reanalyses performed for main efficacy endpoints as appropriate. Post-hoc laboratory analyses were clearly explained and conducted in an acceptable manner.

Results from Rota-004 support the use of Rotarix in the prevention of any and RV GE, although LLs of the 95% CI were low. Efficacy data supports the use of Rotarix in the prevention of any and severe RV GE caused by G1 wild-type strains, although VE estimates did not reach statistical significance during the 1st efficacy follow-up period. VE against other serotypes could not be adequately assessed due to limited GE cases caused by each non-G1 serotype.

8.1.4 Rota-006 (2-dose subset)

8.1.4.1 Protocol 444563/006 (rota-006): A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$, and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine (Amended Feb 12, 2001)

8.1.4.1.1 Objective/Rationale (2-dose subset)

Primary Objectives – 2-dose subset (amended May 3, 2002)

1. For a range of viral concentrations ($10^{4.7}$, $10^{5.2}$, and $10^{5.8}$ ffu; equivalent to $10^{5.3}$, $10^{5.6}$, and $10^{6.6}$ $CCID_{50}$, respectively) of Rotarix, to demonstrate efficacy of 2 doses of Rotarix given concomitantly with routine vaccinations in preventing any RV GE from 2 weeks post-Dose 2 until the end of 1st efficacy follow-up period (amended Feb 12, 2001 & Sep 20, 2002)

Secondary Efficacy Objectives – 2-dose subset (amended May 3 & Sep 20, 2002)

1. For the same 3 vaccine concentrations, to assess if 2 doses of Rotarix given concomitantly with routine vaccinations can (amended Feb 12, 2001):
   a. Prevent severe RV GE from 2 weeks post-Dose 2 until end of 1st efficacy period
   b. Prevent RV GE due to virus types heterologous to vaccine strain from 2 weeks post-Dose 2 until the end of 1st efficacy period (amended Feb 12, 2001)
   c. Prevent any and severe pure RV GE 2 weeks post-Dose 2 until end of 1st efficacy period
   d. Prevent mixed RV GE (GE associated with RV and at least one other pathogen) from 2 weeks post-Dose 2 until the end of 1st efficacy period
   e. Prevent any hospitalization for RV GE 2 weeks post-Dose 2 until end of 1st efficacy period

Secondary Efficacy Objectives – subset for 2nd efficacy period (amended Aug 21, 2003)

1. To evaluate efficacy of Rotarix from the end of the 1st efficacy follow-up period to the end of the 2nd efficacy follow-up period (endpoints similar as for 1st year follow-up)
2. To evaluate efficacy of Rotarix from 2 weeks after the last study dose to the end of the 2nd efficacy follow-up period (end points similar as for 1st year follow-up)

Secondary Immunogenicity Objectives – 2-dose subset

1. In a subset of 800 subjects uninfected with RV pre-vaccination, to assess vaccine take 2 months after each study dose (amended Feb 12, 2001)
2. To assess persistence of serum RV IgA at the end of the 1st efficacy follow-up period

3. In a subset of 800 subjects, to explore the effect of Rotarix on the immune response to concurrently administered routine vaccinations (amended Feb 12, 2001)
4. To explore the effect of unrestricted feeding on vaccine immunogenicity
5. In a subset of Rotarix subjects, to assess viral shedding (amended Feb 12, 2001)

Secondary Safety/Reactogenicity Objectives

1. To assess the safety and reactogenicity of 2 doses of Rotarix at each viral concentrations ($10^{4.7}$, $10^{5.2}$, and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo (amended Feb 12, 2001)

8.1.4.1.2 Design Overview

Rota-006 was a double-blind, randomized, placebo-controlled, multi-country and multi-center study. Healthy and previously RV-uninfected subjects 6 to 12 weeks of age at the time of Dose 1 were randomized to receive 2 doses of either Rotarix at one of 3 virus concentrations ($10^{4.7}$, $10^{5.2}$, or $10^{5.8}$ ffu) or placebo on a 0, 2-month schedule. Subjects were randomized and administered Dose 1 of Rotarix or placebo on the same day (i.e. Day 0). DTPw, Hib, and Hepatitis B vaccines were co-administered with study doses, while OPV was administered either at least 2 weeks before or 2 weeks after study vaccination (amended Feb 12, 2001). A total enrollment of 2360 evaluable subjects was targeted (590 for each Rotarix concentration, 590 for placebo). All subjects were followed for efficacy until 1 year of age, and a subset were followed for efficacy until a maximum of 2 years of age (amended Sep 20, 2002, Aug 21, 2003). The duration of the study per subject was 10 months for subjects followed for 1 efficacy period and 22 months at most for subjects followed for 2 efficacy periods.

8.1.4.1.3 Population

Inclusion Criteria

1. Male or female 6-12 weeks of age at the time of Dose 1
2. Born after a normal gestation period (36-42 weeks) or a birth weight> 2000 g
3. Written informed consent obtained from parent/guardian prior to study procedures
4. Free of obvious health problems as established by medical history and clinical examination prior to entering the study

Reviewer Note: Inclusion Criteria #3 and #4 were the same for Rota-004, Rota-023 and Rota-036. Inclusion Criteria #1 was the same for Rota-004 and Rota-023. Part of Inclusion Criteria #2 (born 36-42 weeks gestation) was the same for Rota-004, while the other part of Inclusion Criteria #2 (birth weight> 2000 g) was the same for Rota-036.

Exclusion Criteria

1. Use of antibiotics with 7 days preceding dose 1 (warrants deferral of vaccination)
2. Acute disease at the time of enrolment (defined as presence of moderate or severe illness with or without fever , i.e. temperature ≥100.4°F [38.0°C] measured rectally
3. History of diphtheria, tetanus, pertussis, Hib disease and/or hepatitis B
4. Previous vaccination against diphtheria, tetanus, pertussis, and/or *H. influenzae* type b)
5. Household contact with an immunosuppressed individual or pregnant woman
6. Previous confirmed occurrence of RV GE
7. Any clinically significant history of chronic gastrointestinal disease, including any uncorrected congenital malformation of the GI tract, or other serious medical condition
8. Gastroenteritis within 7 days before study vaccine administration (warrants deferral)
9. Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine and ending 14 days after
10. Use of any investigational or non-registered product other than the study vaccine within 30 days preceding the study vaccine/placebo, or planned use during the study
11. Chronic administration (> 14 days) of immunosuppressants or other immune-modifying drugs since birth (topical steroids allowed)

12. Any confirmed or suspected immunosuppressive/immunodeficient condition, including HIV
13. History of allergic disease or reaction likely to be exacerbated by any vaccine component
14. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period
15. Planned administration of OPV with 2 weeks before or after each study dose

Reviewer Note: Exclusion criteria #7 and #10-14 were also included in Rota-004, Rota-023 and Rota-036. Exclusion criteria #8 and #9 were also included in Rota-004 and Rota-036. Exclusion criteria #2-4 were also included in Rota-036. Exclusion criteria #5-7 were included in Rota-004. Exclusion criterion #1 was similar for Rota-004, except that use of antibiotics within 7 days after each vaccine dose was not included.

Procedures Allowed
1. Co-administration of routine vaccinations (DTPw-Hepatitis B + Hib vaccine) at 2, 4, and 6 months of age, except for OPV which was given at least 2 weeks apart from Rotarix vaccination
2. Hepatitis B, BCG and OPV vaccination at birth according to local Expanded Program of Immunization (EPI)
3. Unrestricted feeding pre- and post-vaccination

Participating Countries
Brazil, Mexico, Venezuela

8.1.4.1.4 Products mandated by the protocol

Rotarix
Each dose of Rotarix consisted of a lyophilized preparation of $10^{4.7}$ ffu, $10^{5.2}$ ffu, or $10^{5.8}$ ffu of 89-12 HRV strain (RIX4414). The amount of DMEM, sucrose, dextran, sorbitol, and amino acids used as excipients were the same in Rota-023 and Rota-036. GSK's calcium carbonate buffer consisting of --- mg $CaCO_3$ and ------ xanthane ---------- was used as the diluent. Lots DRVC005A46 ($10^{4.7}$ ffu), DRVC010A48 ($10^{5.2}$ ffu), and DRVC004A46 ($10^{5.8}$ ffu) were used Rotarix. Lots 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent.

Placebo
The formulation was the same as for Rotarix but without RIX4414 virus. Lots DRVC014A48PL and DRVC006A46PL were used for placebo. Lots 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent.

Concomitant routine vaccines
Commercial lots of DTPw-HB + Hib and Polio Sabin (OPV) vaccines were used.

8.1.4.1.5 Endpoints

Primary Endpoints – 2-dose subset (amended May 3, 2002)
1. For 3 Rotarix concentrations ($10^{4.7}$, $10^{5.2}$, and $10^{5.8}$ ffu), occurrence of any RV GE from 2 weeks post-Dose 2 until end of 1st efficacy period (amended Sep 20, 2002)

Secondary Efficacy Endpoints – 2-dose subset (amended May 3 & Sep 20, 2002)
1. For 3 Rotarix concentrations, to assess if 2 doses of Rotarix given concomitantly with routine vaccinations can (amended Feb 12, 2001):
    a. Occurrence of severe RV GE from 2 weeks post-Dose 2 until end of 1st efficacy period
    b. Occurrence of RV GE due to virus types heterologous to vaccine strain from 2 weeks post-Dose 2 until end of 1st efficacy period (amended Feb 12, 2001)
    c. Occurrence of any and severe pure RV GE 2 weeks post-Dose 2 until end of 1st efficacy period
    d. Occurrence of mixed RV GE from 2 weeks post-Dose 2 until end of 1st efficacy period

e. Occurrence of hospitalization for RV GE 2 weeks post-Dose 2 until end of 1st efficacy period

Secondary Efficacy Endpoints – subset for 2nd efficacy period (amended Mar 26 & Aug 21, 2003)
1. For subset who received 2 doses of Rotarix/placebo:
   a. Occurrence of any and severe RV GE from end of 1st to end of 2nd efficacy period
   b. Occurrence of any and severe RV GE 2 weeks post-Dose 2 until end of 2nd efficacy period

Secondary Immunogenicity Endpoints – 2-dose subset
1. Serum RV IgA titers at Visit 1 and end of 1st efficacy follow-up period
2. In subset of 800 subjects, serum RV IgA titers at Visits 2 and 3
3. In subset of 800 subjects, proportion of subjects with vaccine take at Visits 2 and 3
4. In a subset of breast fed infants and formula fed infants, vaccine take and GMTs of RV IgA ELISA for each feeding subset for the following:
   a. No feeding 1 hour pre- and 30 minutes post-Dose 1 or 2
   b. Feeding 1 hour pre-Dose 1 or 2
   c. Feeding within 30 minutes post-Dose 1 or 2
5. In a subset of 400 subjects, viral shedding in the Rotarix groups
6. In a subset of 800 subjects, the following at 2 months post-Dose 2 and at Year 1:
   a. GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2, and 3, and anti-HBs
   b. Anti-PRP concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
   c. Anti-diphtheria toxoid concentrations ≥ 0.1 IU/ml
   d. Anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
   e. Anti-HBs concentrations ≥ 10 mcg/ml
   f. Anti-polio type 1 titers ≥ 8
   g. Anti-polio type 2 titers ≥ 8
   h. Anti-polio type 3 titers ≥ 8
   i. Anti-BPT concentrations ≥ 15 EL.U/ml

Reviewer Note: Vaccine take was calculated only for subjects with blood and stool samples.

Secondary Safety/Reactogenicity Endpoints
1. For each type of solicited symptom, occurrence of symptom within 15-day follow-up period after any dose of study vaccine
2. Occurrence of unsolicited symptoms within 42 days after Doses 1 and 2 (all subjects), according to WHO classification
3. Occurrence of SAEs throughout entire study period

Definitions
GE**:** diarrhea
Diarrhea: same as in Rota-004, Rota-023 and Rota-036
Vomiting: same as in Rota-004, Rota-023 and Rota-036
RV GE: same as in Rota-004 and Rota-036
Severe RV GE: same as in Rota-004, Rota-023 and Rota-036
Pure RV GE: RV GE with no other concurrent pathogen infection
Mixed RV GE: GE associated with RV and at least one other pathogen
1st year efficacy follow-up period: 2 weeks post-Dose 2 until 1 year of age (amended September 20, 2002)
2nd year efficacy follow-up period: end of 1st year efficacy follow-up period until maximum of 2 years of age; 2nd efficacy follow-up period ended in June 2003 after the end of the 2003 RV season (Mexico) and in October 2003 (Brazil, Venezuela)
Seroconversion: same as in Rota-004, Rota-023 and Rota-036
Seropositive: same as in Rota-004, Rota-023 and Rota-036
Seronegative: same as in Rota-004, Rota-023 and Rota-036

Vaccine take: (for subjects previously uninfected with RV pre-vaccination) anti-RV IgA ≥ 20 units/ml in post-vaccination sera *or* vaccine virus shedding in any stool sample collected from Visits 1 to 3

Summary of Significant Protocol Amendments

1. Amendment 1 – Feb 12, 2001
   a. Actual release titer of one of the lots (for $10^{5.8}$ ffu concentration) corrected
   b. Parents/guardiants directed to contact study personnel for every GE case
   c. Subsets for serum and stool analyses defined
   d. GE stool testing for cryptosporidia deleted
   e. Use of several routine vaccine commercial lots clarified
2. Modification 1 – Mar 14, 2001
   a. Changes in study personnel in Brazil and Venezuela implemented
3. Site-specific amendment for Venezuela – Oct 10, 2001
   a. Study added in a subset of subjects to evaluate fecal RV IgA immune response and the role of IgA antibodies as marker of protection against RV disease
4. Amendment 2 – Dec 11, 2001
   a. Termination of enrolment in Mexico by end of Dec 2001 allowed in order to avoid vaccinating subjects during the RV season
5. Amendment 3 – May 3, 2002
   a. Sample size decreased from 2640 to 2276 subjects because of enrolment difficulties
6. Amendment 4 – July 11, 2002
   a. Interim analysis allowed in order to provide early VE information against any and severe RV GE in Latin America
7. Amendment 5 – Sep 20, 2002
   a. Second efficacy follow-up period (until maximum of 24 months of age) added for subjects who had not completed the study as of Oct 31, 2002
8. Amendment 6 – Mar 26, 2003
   a. Use of Standard Verbal Autopsy Questionnaire per IDMC's recommendation
   b. Co-pathogen testing for all subjects during the 2nd efficacy follow-up period removed
   c. Termination of follow-up of Mexican subjects after the end of the 2003 RV season allowed
   d. Interim efficacy analysis at the end of the 2nd efficacy follow-up period in Mexico allowed
9. Amendment 7 – Aug 21, 2003
   a. Study end in Oct 2003 allowed by terminating the 2nd efficacy follow-up of subjects in Brazil and Venezuela

8.1.4.1.6 Surveillance

Follow-up visits

The table below summarizes the follow-up visits for safety/efficacy/immunogenicity.
2640 subjects were targeted for enrollment to obtain 2360 evaluable subjects (590 per arm).

Group	Visit 1 Day 0	Visit 2 Month 2	Visit 3 Month 4	Year 1 of age visit	Year 2 of age visit†
Rotarix $10^{4.7}$ ffu (Group A) (N=590)	X	X	X	X	X
Rotarix $10^{5.2}$ ffu (Group B) (N=590)	X	X	X	X	X
Rotarix $10^{5.8}$ ffu (Group C) (N=590)	X	X	X	X	X
Placebo (Group D) (N=590)	X	X	X	X	X

†for subset followed for 2 efficacy periods (target N ~1000 subjects, including subjects who did not complete their follow-up visit at 1 year of age by October 31, 2002); actual dates of final visits in 2003 for subjects from Mexico, Brazil, and Venezuela were April 21-May 14, September 21-November 8, and September 29-October 16, respectively

Vaccination with Rotarix or placebo took place at Visits 1 and 2 for all subjects. All subjects were co-administered DTPw-HB+Hib vaccine at Visits 1, 2, and 3.

Feeding practices (breast versus formula, fed within 60 minutes pre-vaccination and/or within 30 minutes post-vaccination) were recorded on the day of each study dose.

Safety diary cards for solicited and unsolicited symptoms were collected at Visits 2 and 3.

Pre-vaccination blood samples were obtained from all subjects at Visit 1. For all subjects receiving only 2 doses of Rotarix/placebo, a blood sample was obtained at Visit 5. For a subset of subjects receiving 2 doses of study vaccine/placebo (N=800), post-dose blood samples were drawn at Visits 2 and 3. This subset was comprised of the first 200 subjects enrolled in each country (200 x 3 countries = 600), with the remaining 200 coming from any of the participating countries according to the order of enrollment.

Stool samples (non-GE) were collected from a subset of 400 subjects (for vaccine take/viral shedding analyses) on the day of or 1 day prior to Dose 1 and Dose 2 and on Day 7 post-dose. This subset was comprised of the first 100 subjects enrolled in each country (100 x 3 countries = 300), with the remaining 100 coming from any participating country according to the order of enrollment.

GE Case Ascertainment

Active follow-up for GE was conducted via weekly visits to each subject by study personnel starting from 1 week post-Dose 1 until the end of the 1st efficacy period (and 2nd efficacy period for subjects followed during Year 2). Visits were done at the subject's home, health clinic, or other mutually convenient place. At these follow-up visits, study personnel inquired about the occurrence of GE episodes and AEs, and collected stool samples. Weekly visits were not required during weeks when study visits were scheduled.

Parents/guardians were also asked to contact study personnel for any symptoms suggestive of GE.

GE Case Follow-Up

For each GE episode, a diary card was provided by study personnel and completed daily by parents/guardians until symptoms resolved; cards were collected by study personnel when the episodes ended. The diary cards were similar to those used in Rota-023 and Rota-036 and assisted in clinically characterizing GE episodes.

The 20-point (Vesikari) scale was used to assess the intensity of each GE episode.

For each GE episode, stool samples were collected no later than 7 days after illness onset and brought to the study site as soon as possible or picked up by study personnel at weekly visits.

Stool samples were analyzed by RV antigen assay. Rapid screening at the study sites was performed using a commercial test (RotaClone, Meridian Diagnostics Inc.). Stool samples that tested RV positive by RotaClone were also tested locally for enteric pathogens; Enteroaggregative *E. coli* and Enteroinvasive *E coli* were tested at the laboratory of ---------- in Mexico City. All stool samples, regardless of RV results using RotaClone, were tested using ELISA to detect RV at the laboratory of Dr. R. Ward in Cincinnati. Only GE stool analysis performed at Dr. Ward's laboratory was considered for efficacy analyses.

All stool samples that tested positive for RV were tested by RT-PCR at GSK's laboratory in Belgium to determine G type. G1 RV detected in stool specimens between Visit 1 and Visit 3 was analyzed by sequencing to distinguish wild type from vaccine RV strains.

Stool analyses of 400 subjects for vaccine take and viral shedding

Provided that the subject had a negative RV ELISA test on Day 0, any detection of vaccine virus in any stool collected after vaccination up to Visit 3 was considered evidence of a vaccine take (i.e. vaccine response). Also, provided that a pre-vaccination stool sample tested ELISA negative, any detection of RV in a stool collected 7 days post-vaccination was considered evidence of a vaccine take. RV ELISA testing was performed at Dr. Ward's laboratory.

Site-specific study of anti-RV IgA in feces, Venezuela

Fecal RV IgA immune response and the role of IgA antibodies as a marker of protection were to have been evaluated in a subset of 200 infants from Venezuela. Stool samples were collected at

Days 0, 14, and 28 post-dose, then every 2 months from 6 months of age until Visit 4. For each GE episode, one stool sample each was collected 1-5 days and 14 days after symptom onset. All stool samples were tested by ELISA to determine fecal anti-RV IgA levels.

AE/SAE Monitoring, including IS
Solicited symptoms, unsolicited AEs, and SAEs were monitored similarly as in Rota-004.

SAE monitoring, including IS, was conducted using similar procedures in Rota-004, Rota-023 and Rota-036. Procedures for grading the intensity of unsolicited AEs/SAEs, assessing causality of AEs/SAEs to vaccination, follow-up of AEs/SAEs, and SAE reporting were also similar to those in Rota-004, Rota-023 and Rota-036.

Unsolicited symptoms were coded similarly as in Rota-004.

IS Case Ascertainment and Follow-up
Follow-up diagnostic procedures for IS cases were similar to Rota-004, Rota-023 and Rota-036.

Serology Analysis
Anti-RV IgA antibody concentrations were measured by ELISA at Dr. Ward's laboratory and/or GSK's laboratory in Belgium. Testing for RV was performed on samples collected at Visit 1 (pre-Dose 1), Visit 2 (post-Dose 1), Visit 3 (post-Dose 2), and Year 1.

Antibodies to PRP, diphtheria and tetanus toxoids, pertussis components, and HBsAg were measured by ELISA. Antibodies to polio viruses types 1, 2, and 3 were determined by ---------- test, with titers expressed in terms of the 50% inhibitory dose. Serological testing for routine childhood vaccine antigens was performed on samples collected at Visit 3 and Year 1 visit.

Forms
1. GE diary card
2. Safety diary card for solicited and unsolicited symptoms
3. Electronic Case Report Form (CRF)

Independent Data Monitoring Committee (IDMC)
An IDMC reviewed each case of suspected or confirmed intussusception and each SAE.

8.1.4.1.7 Statistical Considerations

Power Considerations - Primary Efficacy Objective
Due to difficulty in enrolling subjects, the targeted number of evaluable subjects was decreased from 2360 (590 per group) to 1840 (460 per group). Assuming a true VE of 70%, a frequency of RV GE of 12% in the placebo group from 2 weeks post-Dose 2 until the end of the 1st RV disease season, and 460 subjects in each treatment group, the study had 88.9% power to observe a lower limit of the VE 95% CI above 30%. Although the actual observed attack rate for any RV GE was 10.8%, the study still had 82% power to observe a lower limit of the VE 95% CI above 30%.

Power Considerations – Secondary Efficacy Objective (2nd follow-up period)
Assuming a true VE of 60%, a frequency of RV GE of 12% in the placebo group during the 2nd follow-up period, and 200 subjects in each treatment group, the study had 88% and 67% to detect a statistically significant vaccine effect in the pooled Rotarix group and each Rotarix group, respectively. However, the actual number of evaluable subjects for each group was substantially lower (<130), as was the observed RV GE attack rate (8.3%). Therefore, VE for this subset was not sufficiently powered to draw any conclusions.

Power Considerations – Secondary Immunogenicity Objective

Assuming seroprotection rates of between 90-98% and an anti-BPT GMT of 27.3 (standard deviation of 0.332), and assuming that rates/GMTs were the same in vaccine and placebo groups, 175 subjects per group provided the following:

- 80% global power that all the 95% CIs on the decrease in seroprotection rates in the vaccine group compared to placebo would be below 15%
- 80% global power that the 95% CIs on the fold decrease in anti-BPT in the vaccine group compared to placebo would be below 1.5

Study Cohorts

Total vaccinated cohorts (TVCs) consisted of all subjects for whom data (safety, efficacy, immunogenicity) were available, and underwent the following analyses:

- Secondary safety analysis (TVC for safety)
- Secondary immunogenicity analysis if needed (TVC for immunogenicity)
- Secondary efficacy analysis beyond 2 weeks post-Dose 2 (TVC for efficacy)

Criteria for inclusion in the ATP safety cohort were identical to Rota-004. The ATP safety cohort was to have been used if needed

Criteria for inclusion in the ATP efficacy cohort were identical to Rota-004. The ATP efficacy cohort was used for the primary efficacy analyses for Year 1, Year 2, and the combined period. It was also used to analyze the persistence of immune response at the end of the 1st efficacy follow-up period. The ATP efficacy cohort for the combined follow-up period included all subjects from the 1st Year ATP efficacy cohort who were enrolled in the 2nd efficacy follow-up period.

Criteria for inclusion in the ATP immunogenicity cohort were identical to Rota-004. In addition, intervals between Visits 1-2 and Visits 2-3 needed to be 49-83 days. The ATP immunogenicity cohort was used for the primary immunogenicity analysis.

Final Analyses

The following analyses were performed:

1. Demographics: age and height/weight (mean, range, SD, race, gender, feeding criteria
2. Efficacy:
    a. For subjects that received 2 doses
        - VE against any and severe RV GE 2 weeks post-Dose 2 to end of 1st efficacy period
        - VE against RV GE due to virus types heterologous to vaccine strain from 2 weeks post-Dose 2 toend of 1st efficacy period
        - VE against any and severe pure RV GE 2 weeks post-Dose 2 to end of 1st efficacy period
        - VE against mixed RV GE from 2 weeks post-Dose 2 to end of 1st efficacy period
        - VE against hospitalization for RV GE 2 weeks post-Dose 2 to end of 1st efficacy period

VE was initially calculated for pooled vaccine groups. If statistical significance favoring the Rotarix group was reached, then VE of Group C was calculated. If statistical significance was reached favoring Group C, then VE of Group B was calculated. If statistical significance was reached favoring Group B, then VE of Group A was calculated. For these analyses, the Cox proportional-hazard model was used to examine underlying assumptions that the period of follow-up was similar in the treatment groups.

VE by country and for seropositive subjects at study entry were also calculated as exploratory analyses.

    b. For the 2nd efficacy and combined follow-up periods (i.e. 2 weeks post-last dose to end of 2nd efficacy period)
        - VE against any, severe, and hospitalized RV GE
        - VE against any, severe, and hospitalized G1 RV GE

- VE against any, severe, and hospitalized RV GE due to heterologous strains

Analyses were performed for pooled vaccine groups and for each group.

3. Immunogenicity:
   a. For each antigen at each time point, seropositivity/seroprotection rates and GMCs/GMTs; for immunogenicity analyses of routine vaccinations, 2-sided 95% CIs for the differences in seroprotection/seropositivity rates and GMC/GMT ratios between groups were considered exploratory and clinical limits for non-inferiority were not pre-defined
   b. For subjects who received 2 study doses and had both planned blood and stool samples (N=400), vaccine take 2 months post-Dose 1 and post-Dose 2

RV shedding was evaluated by calculating the percentage of subjects with RV in stool samples collected at Days 0 and 7 after each study dose and after combined doses.

Anti-RV IgA GMCs were also calculated on subjects who had seroconverted after vaccination or natural infection.

The impact of feeding on vaccine take (on combined doses) at 2 months post-Dose 2 was explored using logistic regression. Immunogenicity of Rotarix at both doses, at Dose 1 only, at Dose 2 only, and for none of the doses were compared between Rotarix groups for the following categories: breast-fed only, breast-fed + formula-fed, fed within 1 hour before vaccination, and fed within 30 minutes after vaccination. Feeding factors that were significant in the regression were used to calculate vaccine take.

4. Safety
   a. Overall incidence of any AEs (solicited and unsolicited), by group, by dose, for overall doses, per subject; same calculations for Grade 3 and vaccine-related symptoms; calculations also done by country
   b. Incidence of each solicited general symptom, by group, from Days 0-14, after each dose, for all doses, per subject; same calculations for Grade 2/3, Grade 3 and vaccine-related symptoms
   c. % of subjects with unsolicited symptoms within Days 0-42 days, by WHO body system/WHO preferred terms; similar tabulations for Grade 3 and vaccine-related unsolicited symptoms
   d. % of subjects and doses reporting unsolicited gastrointestinal symptoms (WHO code 600) within Days 0-42; similar tabulations for Grade 3 and vaccine-related symptoms
   e. Number of SAEs occurring in each efficacy follow-up period; possible vaccine-associated SAEs, fatal SAEs, and IS cases were described
   f. % of subjects who took at least one concomitant medication during the solicited follow-up period, per group

As an exploratory analysis, pair-wise difference in the incidence of specific symptoms between the pooled Rotarix and placebo groups was performed using 2-sided Fisher exact test. Pair-wise differences among the 3 Rotarix groups were also assessed using 2-sided Fisher exact test. The following endpoints were used for pair-wise analyses:

- Each solicited symptom within Days 0-14 after any study dose
- Each solicited symptom within Days 0-7 after any study dose
- Each solicited Grade 3 symptom within Days 0-7 after any study dose
- Each solicited Grade 2 or 3 symptom within Days 0-7 after any study dose
- Each solicited vaccine-related symptom within Days 0-7after any study dose

<u>Final statistical analysis</u>
A final statistical analysis was performed at the end of the 1st efficacy follow-up period after all enrolled subjects completed the study visit at the end of the period. Data analyses from the end of the 1st efficacy follow-up period until the end of the 2nd efficacy follow-up period was presented as an annex. (Amended September 20, 2002)

Interim analysis
Two interim immunogenicity and reactogenicity analyses were performed to provide early information on dose selection of phase III studies (amended February 12, 2001). No study report was written, results were strictly controlled, and unblinding at the level of individual data was restricted to the statistician and database administration.

Two interim efficacy analyses against any and severe RV GE were performed to obtain early efficacy data (amended July 11, 2002, March 26, 2003). One of these analyses calculated VE at the end of the 2nd follow-up period in Mexico. Analyses were performed after 70 RV GE episodes occurred from 2 weeks after Dose 2. No study report was written, results were strictly controlled, and unblinding at the level of individual data was restricted to the statistician and database administrator.

In addition, an interim analysis for transplacental anti-RV IgG and transplancental anti-RV neutralizing antibodies were performed.

Results of all interim analyses were consistent with those presented in study reports.

Additional analyses/changes
Changes made to the planned analyses included the following:
- The TVC was used for analyses instead of the total cohort
- If RV was detected in stool samples from placebo subjects at pre-determined time points, G type was determined by RT-PCR
- Increase in incidence of specific symptoms post-vaccination between pooled Rotarix groups versus placebo was explored using 2-sided rather than 1-sided Fisher's exact test
- VE estimates against pure and mixed RV GE were not calculated because no concurrent pathogen was identified in the majority of RV GE episodes
- Vaccine take by feeding criteria was not calculated because none of the criteria had a significant effect in the logistic regression
- For the Year 2 efficacy cohort (ATP, TVC), VE against hospitalized GE was calculated

8.1.4.2 Results, by Trial (Objective information)

Study initiation date: May 25, 2001
Data lock point (for Final Study Report, Year 1): April 24, 2003
Date of Last Visit: November 8, 2003
Final Report date (Year 1): November 14, 2003
Annex Report date (Year 2): April 20, 2004

8.1.4.2.1 Populations enrolled/analyzed

Efficacy for 2-dose regimen - 1st Efficacy Follow-up Period (Year 1)

Study population by site
A total of 2155 subjects were in the TVC, summarized below by treatment group.

Country	Centre	Group					
		HRV $10^{4.7}$ n	HRV $10^{5.2}$ n	HRV $10^{5.8}$ n	Placebo n	All n	All %
Brazil	110	194	196	194	194	778	36.1
Mexico	210	101	101	102	101	405	18.8
Venezuela	310	243	243	244	242	972	45.1
All	All	538	540	540	537	2155	100

Source: Study Report Body Rota-006, pg 86

Drop-outs at end of Year 1
As depicted in the table below, 2004 out of 2155 (93%) subjects in the TVC completed the 1st efficacy follow-up period. Percentages were similar across groups.

	Groups				
	$10^{4.7}$	$10^{5.2}$	$10^{5.8}$	placebo	Total
Number of subjects enrolled	538	540	540	537	2155
Number of subjects completed	500	499	499	506	2004
Number of subjects dropped out	38	41	41	31	151
Reasons for drop-out:					
SAE	1	0	1	1	3
Non-serious AE	0	2	2	2	6
Protocol violation	0	0	1	1	2
Consent withdrawal (not due to an adverse event)	13	21	9	9	52
Migrated/moved from study area	21	17	24	18	80
Lost to follow-up (subjects with incomplete vaccination course)	1	0	1	0	2
Lost to follow-up (subjects with complete vaccination course)	1	0	0	0	1
Others	1	1	3	0	5

Enrolled = number of subjects who where entered in the study
Completed = number of subjects who completed Visit 4 at the end of the 1st efficacy follow-up period
Dropped-out = number of subjects who did not return for Visit 4 at the end of the 1st efficacy follow-up period
Source: Study Report Body Rota-006, pg 86

Protocol deviations – ATP safety cohort 1st follow-up period
The following protocol deviations led to subject exclusion from the ATP safety cohort:
- 38 (Rota $10^{4.7}$-10, Rota $10^{5.2}$-11, Rota $10^{5.8}$-8, placebo-9) received vaccinations forbidden by the protocol
- 4 (Rota $10^{4.7}$-1 Rota $10^{5.2}$-1, Rota $10^{5.8}$-2, placebo-1) had randomization failure
- 1 (placebo-1) had randomization code broken for SAE
- 96 (Rota $10^{4.7}$-20, Rota $10^{5.2}$-27, Rota $10^{5.8}$-19, placebo-30) received study vaccine not administered according to protocol (regurgitation within 30 minutes)
- 51 (Rota $10^{4.7}$-9, Rota $10^{5.2}$-14, Rota $10^{5.8}$-18, placebo-10) were either initially positive for RV or their RV status was unknown on day of Dose 1

Therefore, 1965 subjects were included in the ATP safety cohort.

Protocol deviations – ATP efficacy cohort
The following protocol deviations led to subject exclusion from the ATP efficacy cohort:
- 80 (Rota $10^{4.7}$-21, Rota $10^{5.2}$-26, Rota $10^{5.8}$-22, placeb-11) did not receive Dose 2
- 10 (Rota $10^{4.7}$-3, Rota $10^{5.8}$-3, placebo-4) dropped out before 1st efficacy period
- 29 (Rota $10^{4.7}$-7, Rota $10^{5.2}$-1, Rota $10^{5.8}$-4, placebo-17) had GE stool samples collected between Visit 1 to 2 that were positive for RV other than vaccine strain

Therefore, 1846 subjects were included in the ATP efficacy cohort.

Protocol deviations – ATP immunogenicity cohort
The following protocol deviations led to subject exclusion from the ATP immunogenicity cohort:
- 101 (Rota $10^{4.7}$-22, Rota $10^{5.2}$-27, Rota $10^{5.8}$-24, placebo-28) received medication forbidden in the protocol
- 45 (Rota $10^{4.7}$-7, Rota $10^{5.2}$-8, Rota $10^{5.8}$-5, placebo-25) had GE stool samples collected between Visits 1-3 that were positive for RV other than vaccine strain
- 88 (Rota $10^{4.7}$-18, Rota $10^{5.2}$-21, Rota $10^{5.8}$-26, placebo-23) were non-complaint with vaccination schedule (Dose 2 received outside of 49-83 day interval between vaccinations)
- 58 (Rota $10^{4.7}$-19, Rota $10^{5.2}$-9, Rota $10^{5.8}$-15, placebo-15) were non-complaint with blood sampling schedule
- 147 (Rota $10^{4.7}$-38, Rota $10^{5.2}$-45, Rota $10^{5.8}$-42, placebo-22) had missing immunogenicity data

Therefore, 1526 subjects were included in the ATP immunogenicity cohort.

Study demographics – ATP efficacy cohort (N=1846)

The median age at Dose 1 (8 weeks) was the same between groups. Most of the subjects in either group were either classified as Other or White/Caucasian. Female-to-male ratios were approximately 1:1 in the $10^{5.2}$ and placebo groups and 0.8:1 in the $10^{4.7}$and $10^{5.8}$ groups. Median height and weight measurements were also the same or similar between groups.

Characteristics	Parameters or Categories	HRV 10_4.7 N = 468		HRV 10_5.2 N = 460		HRV 10_5.8 N = 464		Placebo N = 454		Total N = 1846	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at first dose (weeks)	Mean	8.3	-	8.4	-	8.3	-	8.4	-	8.3	-
	SD	1.51	-	1.47	-	1.50	-	1.55	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	215	45.9	232	50.4	212	45.7	227	50.0	886	48.0
	Male	253	54.1	228	49.6	252	54.3	227	50.0	960	52.0
Race	Black	19	4.1	12	2.6	15	3.2	11	2.4	57	3.1
	White/Caucasian	98	20.9	116	25.2	124	26.7	111	24.4	449	24.3
	Oriental	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
	Other	351	75.0	332	72.2	325	70.0	331	72.9	1339	72.5
Height (cm)	Mean	57.4	-	57.5	-	57.5	-	57.6	-	57.5	-
	SD	2.75	-	2.59	-	2.90	-	2.92	-	2.80	-
	Median	57	-	58	-	57	-	58	-	57	-
	Unknown	2	-	1	-	1	-	1	-	5	-
Weight (kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.75	-	0.67	-	0.74	-	0.76	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Race "other" was reported as " Mestizo, Mestiza or Mixed"

Source: Study Report Body Rota-006, pg 93

Study demographics – TVC (N=2155)

Demographic characteristics were the same or similar as those described above for the ATP efficacy cohort.

Dose distribution – TVC

Ninety-nine subjects only received one dose.

Total number of doses received	HRV 10_4.7 (N = 538)		HRV 10_5.2 (N = 540)		HRV 10_5.8 (N = 540)		Placebo (N = 537)		Total (N = 2155)	
	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	28	5.2	31	5.7	25	4.6	15	2.8	99	4.6
2	510	94.8	509	94.3	515	95.4	522	97.2	2056	95.4
Any	538	100	540	100	540	100	537	100	2155	100

Source: Study Report Body Rota-006, pg 104

Study demographics – ATP immunogenicity cohort (N=1526)

With the exception of small differences in female:male ratios in each group, demographic characteristics were the same or similar as those described above for the ATP efficacy cohort and TVC. Feeding criteria on the day of Dose 1 or Dose 2 also were not substantially different across the 4 groups. Most subjects were breastfed or were both breastfed and formula fed.

Dose	Group	N	Feeding criteria		
			Breast milk	Infant formula	Both

			n	%	n	%	n	%
1	**HRV_4.7**	395	218	55.2	14	3.5	163	41.3
	HRV_5.2	377	192	50.9	15	4.0	170	45.1
	HRV_5.8	381	212	55.6	16	4.2	153	40.2
	Placebo	373	214	57.4	14	3.8	145	38.9
2	**HRV_4.7**	388	176	45.4	32	8.2	180	46.4
	HRV_5.2	369	171	46.3	36	9.8	162	43.9
	HRV_5.8	371	160	43.1	42	11.3	169	45.6
	Placebo	372	182	48.9	37	9.9	153	41.1

Source: Study Report Body Rota-006, pg 421

Concomitant vaccinations – TVC

Over 98% of subjects in each group received DTPw-HB+Hib vaccine with Dose 1 and Dose 2 of Rotarix/placebo.

Concomitant vaccinations – ATP immunogenicity cohort

Over 98% of subjects in each group received DTPw-HB+Hib with Dose 1 and Dose 2 of Rotarix/placebo. No subject was co-administered OPV. Of the subjects with available routine vaccination serology results at Visit 3, over 93% in each group received 2 doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3.

Efficacy for 2-dose regimen – 2nd Efficacy Follow-up Period (Year 2)

Study population by site

A total of 521 subjects in the TVC were planned to be followed during Year 2. Distribution by treatment group among the 3 countries is summarized below.

Center	**Country**	**HRV 10_4.7 n**	**HRV 10_5.2 n**	**HRV 10_5.8 n**	**Placebo n**	**Total**	
						n	**%**
110	Brazil	37	35	42	40	154	29.6
210	Mexico	66	66	71	69	272	52.2
310	Venezuela	26	25	22	22	95	18.2
All		129	126	135	131	521	100

Source: Study Report Body Rota-006 Annex, pg 41

Drop-outs at end of Year 2

As depicted in the table below, 505 of 521 (97%) subjects completed the 2nd efficacy follow-up period. Percentages were similar across groups.

	HRV 10_4.7	**HRV 10_5.2**	**HRV 10_5.8**	Placebo	Total
Total number of subjects enrolled in the subset to be followed during the second efficacy period	129	126	135	131	521
Number of subjects completed visit at the end of the second efficacy period	126	121	129	129	505
Number of subjects dropped-out during the second efficacy period	3	5	6	2	16
Reasons for drop-out:					
Serious Adverse Event	0	0	0	0	0
Non-serious adverse event	0	1	0	0	1
Protocol violation	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	0	0	0
Migrated/moved from study area	3	2	5	2	12
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	2	0	0	2
Others	0	0	1†	0	1

Enrolled = number of subjects who where enrolled in the second efficacy follow-up period; Completed = number of subjects who completed the final visit at the end of the 2nd efficacy period; Dropped-out = number of subjects who did not come at the final visit at the end of the 2nd efficacy period; † = The child was traveling in the period of the visit

Source: Study Report Body Rota-006 Annex, pg 42

Protocol deviations – ATP efficacy cohort for Year 2
The following protocol deviations led to subject exclusion from the ATP efficacy cohort:

- 9 (Rota $10^{4.7}$-2, Rota $10^{5.2}$-3, Rota $10^{5.8}$-3, placebo-1) received vaccinations forbidden by the protocol
- 32 (Rota $10^{4.7}$-4, Rota $10^{5.2}$-14, Rota $10^{5.8}$-5, placebo-9) received study vaccine not administered according to protocol (regurgitation of dose within 30 minutes)
- 27 (Rota $10^{4.7}$-4, Rota $10^{5.2}$-7, Rota $10^{5.8}$-12, placebo-4) were either initially positive for RV or their RV status was unknown on day of Dose 1
- 1 (Rota $10^{4.7}$-1) did not receive Dose 2
- 11 (Rota $10^{4.7}$-2, Rota $10^{5.2}$-0, Rota $10^{5.8}$-1, placebo-8) had GE stool samples collected between Visit 1 to 2 weeks post-Dose 2 that were positive for RV other than vaccine strain

Therefore, 441 subjects were included in the ATP efficacy cohort for Year 2 and combined periods.

Study demographics – ATP efficacy cohort (N=441)
The median age at Dose 1 (8 weeks) was the same between groups. Most of the subjects in either group were either classified as Other or White/Caucasian. Female-to-male ratios varied between groups. Median height and weight measurements were the same or similar between groups.

	Parameters or	HRV 10_4.7 N= 116		HRV 10_5.2 N= 102		HRV 10_5.8 N= 114		Placebo N= 109		Total N= 441	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean SD Median Minimum Maximum	8.5 1.63 8 6 12		8.6 1.64 8 6 12		8.4 1.77 8 6 12		8.5 1.71 8 6 12		8.5 1.70 8 6 12	
Gender	Female Male	49 67	42.2 57.8	62 40	60.8 39.2	58 56	50.9 49.1	45 64	41.3 58.7	214 227	48.5 51.5
Race	Black White/Caucasian Oriental Other	3 13 0 100	2.6 11.2 0.0 86.2	2 17 0 83	2.0 16.7 0.0 81.4	1 17 0 96	0.9 14.9 0.0 84.2	2 10 0 97	1.8 9.2 0.0 89.0	8 57 0 376	1.8 12.9 0.0 85.3
Height(cm)	Mean SD Median Unknown	56.5 2.57 57 0	- - - -	56.8 2.64 57 1	- - - -	56.5 2.86 57 0	- - - -	56.8 2.95 57 0	- - - -	56.7 2.80 57 1	- - - -
Weight(kg)	Mean SD Median	5.2 0.73 5.2	- - -	5.3 0.68 5.3	- - -	5.2 0.82 5.15	- - -	5.3 0.74 5.2	- - -	5.3 0.70 5.2	- - -

Race "other" was reported as " Mestizo, Mestiza or Mixed"
Source: Study Report Body Rota-006 Annex, pg 46

Study demographics – TVC (N=521)
Demographic characteristics were the same or similar as those described above for the ATP efficacy cohort, and were also similar to the TVC for Year 1.

8.1.4.2.2 Efficacy endpoints/outcomes

Year 1 Efficacy (2 weeks post-Dose 2 to Year 1 of age) – ATP efficacy cohort (2-dose cohort)

Reviewer Note: The median duration of follow-up during the Year 1 efficacy period was approximately 7 months in each group.

Summary of reported any RV GE and severe RV GE episodes – Year 1
RV was detected by ELISA in 58 Rotarix recipients ($10^{4.7}$-21, $10^{5.2}$-22,$10^{5.8}$-15) and 49 placebo recipients. No subject in any Rotarix group had more than one RV GE episode, while 2 subjects each had 2 RV GE episodes (one subject – 2 G1 wt episodes; one subject – 1 G1 wt episode and 1 G9 episode).

	HRV 10_4.7	HRV 10_5.2	HRV 10_5.8	Placebo
Total number of	**N= 468**	**N= 460**	**N= 464**	**N= 454**

Event	episode reported	n	%	n	%	n	%	n	%
GE	**1**	87	18.6	84	18.3	83	17.9	109	24.0
	2	54	11.5	45	9.8	55	11.9	44	9.7
	3	27	5.8	26	5.7	31	6.7	37	8.1
	4	15	3.2	12	2.6	10	2.2	14	3.1
	5	11	2.4	5	1.1	9	1.9	6	1.3
	6	2	0.4	4	0.9	1	0.2	3	0.7
	7	0	0.0	4	0.9	5	1.1	1	0.2
	8	1	0.2	1	0.2	1	0.2	0	0.0
	Any	197	42.1	181	39.3	195	42.0	214	47.1
RV GE	**1**	21	4.5	22	4.8	15	3.2	47	10.4
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	21	4.5	22	4.8	15	3.2	49	10.8

N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom
Source: Study Report Body Rota-006, pg 424

Of the RV GE episodes, 27 in the Rotarix group ($10^{4.7}$-12, $10^{5.2}$-10,$10^{5.8}$-5) and 34 in the placebo group were severe RV GE (Vesikari score ≥ 11 points).

		HRV 10_4.7		HRV 10_5.2		HRV 10_5.8		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
GE of any etiology (RV or not)	**Mild (1-6)**	190	46.2	202	52.5	214	51.0	185	44.2
	Moderate (7-10)	127	30.9	114	29.6	132	31.4	123	29.4
	Severe (≥11)	94	22.9	69	17.9	74	17.6	111	26.5
	Any	411	100	385	100	420	100	419	100
RV GE	**Mild (1-6)**	4	19.0	8	36.4	2	13.3	5	9.8
	Moderate (7-10)	5	23.8	4	18.2	8	53.3	12	23.5
	Severe (≥11)	12	57.1	10	45.5	5	33.3	34	66.7
	Any	21	100	22	100	15	100	51	100

n/% = number/percentage of GE or RV GE episodes reported in each group, by severity, among all GE or RV GE episodes reported in the first efficacy follow-up period; Any = any specified symptom, regardless of severity
Source: Study Report Body Rota-006, pg 95

Serotype G distribution is summarized below. G1 and G9 were the most prevalent types. RV G type could not be identified in 2 subjects from the Rota $10^{5.2}$ group.

	HRV 10_4.7 N = 468		HRV 10_5.2 N = 460		HRV 10_5.8 N = 464		Placebo N = 454	
Type	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any	21	4.5	22	4.8	15	3.2	49	10.8
G1 wild type	12	2.6	6	1.3	7	1.5	29	6.4
G2	0	0.0	0	0.0	1	0.2	3	0.7
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.7	4	3.0	7	1.5	15	3.3
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

n/% = number/percentage of subjects reporting at least once the specified type in each group
Source: Study Report Body Rota-006, pg 96

ELISA results were not available for 23.1-29.8% of GE episodes for each group. Results were unavailable due to non-collection of stool samples, invalid test results or non-testing of samples.

	HRV $10^{4.7}$ N'= 411		HRV $10^{5.2}$ N'= 385		HRV $10^{5.8}$ N'= 420		Placebo N'= 419	
Category	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
No stools collected	87	21.2	102	26.5	121	28.8	91	21.7
Stools collected but no results available	8	1.9	7	1.8	4	1.0	4	1.0
No stool results available	95	23.1	109	28.3	125	29.8	95	22.7

n/% = number/percentage of gastroenteritis episodes reported with the specified category
Source: Study Report Body Rota-006, pg 415

Mixed infections – Year 1

Three Rotarix recipients and 3 placebo recipients had mixed RV GE episodes**.** One episode ($10^{4.7}$group) was associated with salmonella, two episode ($10^{5.8}$-1, placebo-1) were associated with shigella, one episode (placebo group) was associated with Enteropathogenic E. Coli, and two episodes ($10^{5.8}$group-1, placebo-1) were associated with Enteroaggressive E coli, ($10^{4.7}$group).

Clinical characteristics of RV GE episodes – Year 1

The duration of looser than normal stools and vomiting were shorter in the Rotarix groups compared to the placebo group. The frequencies of fever ≥ 39.0°C, dehydration ≥6%, and hospitalizations were also less in the Rotarix groups compared to placebo. Nine Rotarix ($10^{4.7}$-5, $10^{5.2}$-1,$10^{5.8}$-3) and 14 placebo recipients required hospitalization.

Anti-RV IgA status at Visit 3 versus RV GE occurrence during Year 1, Rotarix groups

The percentages of subjects in the Rotarix group that reported at least one RV GE during the 1st efficacy follow-up period, by anti-RV IgA seropositive status at Visit 3, are included in the table below for each Rotarix group and for the groups pooled together. In each group, there were less seropositive subjects who had an RV GE episode than seronegative subjects.

Anti-RV Antibody status At Visit 3	HRV 10_4.7					HRV 10_5.2				
				95%CI					95%CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Negative	64	7	10.9	4.5	21.3	52	6	11.5	4.4	23.4
Positive	103	1	1.0	0.0	5.3	100	2	2.0	0.2	7.0
Unknown	301	13	4.3	2.3	7.3	308	14	4.5	2.5	7.5

Anti-RV Antibody status At Visit 3	HRV 10_5.8					Pooled HRV groups				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Negative	53	6	11.3	4.3	23.0	169	19	11.2	6.9	17.0
Positive	106	2	1.9	0.2	6.7	309	5	1.6	0.5	3.7
Unknown	305	7	2.3	0.9	4.7	914	34	3.7	2.6	5.2

N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2

n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2 reporting at least one RV GE episode from 2 weeks after Dose 2 up to the end of the first efficacy period

Source: Study Report Body Rota-006, pg 429

Vaccine efficacy against any RV GE – Year 1 (Primary endpoint)

VE of Rotarix against any RV GE during the 1st efficacy follow-up period was 58.4% for the $10^{4.7}$group, 55.7% for the $10^{5.2}$group, and 70.0% for the$10^{5.8}$group. VE for the pooled Rotarix group was 61.4%. The applicant stated that the Cox proportional-hazard model produced similar VE estimates.

				n/T	95%CI		n/N	95%CI		Vaccine Efficacy 95%CI			
Group	N	n	T (year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
HRV 10_4.7	468	21	276.4	0.076	0.050	0.117	4.5	2.8	6.8	58.4	29.4	76.3	<0.001
HRV 10_5.2	460	22	268.4	0.082	0.054	0.124	4.8	3.0	7.2	55.7	25.3	74.5	<0.001
HRV 10_5.8	464	15	272.2	0.055	0.033	0.091	3.2	1.8	5.3	70.0	45.7	84.4	<0.001
Pooled HRV Groups	1392	58	817.0	0.071	0.055	0.092	4.2	3.2	5.4	61.4	42.3	74.1	<0.001
Placebo	454	49	256.5	0.191	0.144	0.253	10.8	8.1	14.0	-	-	-	-

N = number of subjects included in each group; n = number of subjects reporting at least one RV GE episode in each group

T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group

% = percentage of subjects reporting at least one RV GE episode in each group; n/T = person-year rate of RV GE in each group

Source: Study Report Body Rota-006, pg 98

VE against severe RV GE – Year 1 (Secondary endpoint)

VE of Rotarix against any RV GE during the 1st efficacy follow-up period was 65.8% for the $10^{4.7}$group, 71.0% for the $10^{5.2}$group, and 85.6% for the$10^{5.8}$group. VE for the pooled Rotarix group was 74.1%.

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
HRV 10_4.7	468	12	279.7	0.043	0.024	0.076	2.6	1.3	4.4	65.8	32.2	83.9	<0.001
HRV 10_5.2	460	10	273.1	0.037	0.020	0.068	2.2	1.0	4.0	71.0	39.9	87.2	<0.001
HRV 10_5.8	464	5	276.1	0.018	0.008	0.044	1.1	0.4	2.5	85.6	63.0	95.6	<0.001
Pooled HRV Groups	1392	27	828.9	0.033	0.022	0.047	1.9	1.3	2.8	74.1	55.8	85.0	<0.001
Placebo	454	34	261.7	0.130	0.093	0.182	7.5	5.2	10.3	-	-	-	-

Source: Study Report Body Rota-006, pg 98

VE against any RV GE by main RV serotypes – Year 1 (Secondary endpoint)

VE of Rotarix against any wild type G1 RV GE during the 1st efficacy follow-up period was 59.9% for the $10^{4.7}$group, 79.6% for the $10^{5.2}$ group, 76.4% for the$10^{5.8}$ group, and 71.9% for the pooled group. VE estimates for any of the Rotarix groups or pooled Rotarix group were not statistically significant. VE against non-G1 RV GE was 60.9 (95% CI: 7.2-85.1%) for the$10^{5.8}$ group.

Group	N	n	n/N %	Vaccine Efficacy %	95% CI LL	95% CI UL	p-value
G1 wild type							
HRV 10_4.7	468	12	2.6	59.9	18.9	81.3	0.006
HRV 10_5.2	460	6	1.3	79.6	49.9	93.1	<0.001
HRV 10_5.8	464	7	1.5	76.4	44.9	91.3	<0.001
Pooled HRV Groups	1392	25	1.8	71.9	50.3	84.2	<0.001
Placebo	454	29	6.4	-	-	-	-
G9							
HRV 10_4.7	468	8	1.7	48.3	-30.0	81.0	0.141
HRV 10_5.2	460	14	3.0	7.9	-105	58.8	0.852
HRV 10_5.8	464	7	1.5	54.3	-19.0	84.3	0.086
Pooled HRV Groups	1392	29	2.1	36.9	-26.5	67.3	0.156
Placebo	454	15	3.3	-	-	-	-
Pooled non G1 (G2, G3, G4, G9)							
HRV 10_4.7	468	9	1.9	56.3	-0.3	82.5	0.037
HRV 10_5.2	460	14	3.0	30.9	-43.8	67.7	0.299
HRV 10_5.8	464	8	1.7	60.9	7.2	85.1	0.021
Pooled HRV Groups	1392	31	2.2	49.4	6.4	72.1	0.020
Placebo	454	20	4.4	-	-	-	-

Source: Study Report Body Rota-006, pg 430

VE against severe RV GE by main RV serotypes – Year 1 (Secondary endpoint)

VE of Rotarix against severe wild type G1 RV GE during the 1st efficacy follow-up period was 75.3% for the $10^{5.2}$ group, 87.8% for the$10^{5.8}$ group, and 73.5% for the pooled group. For the $10^{5.8}$ group, VE was 77.4% (95% CI: 17.8-95.9%) against severe G9 RV GE and 82.7% (95% CI: 40.3-96.8%) against severe non-G1 RV GE.

Group	N	n	n/N %	Vaccine Efficacy %	95% CI LL	95% CI UL	p-value
G1 wild type							
HRV 10_4.7	468	7	1.5	57.6	-9.0	85.2	0.057
HRV 10_5.2	460	4	0.9	75.3	23.5	94.0	0.006
HRV 10_5.8	464	2	0.4	87.8	48.0	98.6	<0.001
Pooled HRV Groups	1392	13	0.9	73.5	41.2	88.3	<0.001
Placebo	454	16	3.5	-	-	-	-

G9							
HRV 10_4.7	468	4	0.9	70.2	3.4	92.9	0.027
HRV 10_5.2	460	6	1.3	54.4	-28.5	85.8	0.109
HRV 10_5.8	464	3	0.6	77.4	17.8	95.9	0.011
Pooled HRV Groups	1392	13	0.9	67.4	23.6	86.1	0.005
Placebo	454	13	2.9	-	-	-	-
Pooled non G1 (G2, G3, G4, G9)							
HRV 10_4.7	468	5	1.1	71.5	19.4	91.8	0.009
HRV 10_5.2	460	6	1.3	65.2	7.4	88.8	0.020
HRV 10_5.8	464	3	0.6	82.7	40.3	96.8	0.001
Pooled HRV Groups	1392	14	1.0	73.1	42.1	87.7	<0.001
Placebo	454	17	3.7	-	-	-	-

Source: Study Report Body Rota-006, pg 431

VE against RV GE requiring hospitalization – Year 1 (Secondary endpoint)

VE of Rotarix against hospitalized RV GE during the 1st efficacy follow-up period was 93.0% for the $10^{5.2}$ group, 79.0% for the $10^{5.8}$ group, and 79.0% for the pooled group.

				n/T	95%CI		n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**T (year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV 10_4.7	468	5	281.4	0.018	0.007	0.043	1.1	0.3	2.5	65.4	-1.8	90.2	0.037
HRV 10_5.2	460	1	276.1	0.004	0.001	0.026	0.2	0.0	1.2	93.0	53.7	99.8	<0.001
HRV 10_5.8	464	3	276.8	0.011	0.003	0.034	0.6	0.1	1.9	79.0	24.9	96.1	0.007
Pooled HRV Groups	1392	9	834.3	0.011	0.006	0.021	0.6	0.3	1.2	79.0	48.0	92.0	<0.001
Placebo	454	14	267.7	0.052	0.031	0.088	3.1	1.7	5.1	-	-	-	-

Source: Study Report Body Rota-006, pg 101

VE against any RV GE and severe RV GE, by country – Year 1 (Exploratory)

For the $10^{5.8}$ group, VE against any RV GE was 63.5% (95% CI: 20.8-84.4%) in Brazil, 72.1% (95% CI: -3.3-95.0%) in Mexico, and 84.5% (95% CI: 31.4-98.3%) in Venezuela.

For the $10^{5.8}$ group, VE against severe RV GE was 81.5% (95% CI: 44.5-95.4%) in Brazil, 100% (95% CI: 22.6-100%) in Mexico, and 87.4% (95% CI: 5.9-99.7%) in Venezuela.

Year 1 Efficacy (2 weeks post-Dose 2 to Year 1 of age) – TVC for efficacy during the 1st efficacy period (2-dose cohort)

A total of 2044 subjects ($10^{4.7}$-507, $10^{5.2}$-508, $10^{5.8}$-512, placebo-517) were included in this cohort. The median duration of follow-up was 7.2 months for each group.

Summary of reported RV GE episodes

The numbers of subjects with any RV GE episode and numbers of episodes of severe RV GE for each group are provided in the tables below.

		HRV 10_4.7		HRV 10_5.2		HRV 10_5.8		Placebo	
	Total number of episode reported	**N= 507**		**N= 508**		**N= 512**		**N= 517**	
Event		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
RV GE	**1**	22	4.3	22	4.3	15	2.9	53	10.3
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	22	4.3	22	4.3	15	2.9	55	10.6

Source: Study Report Body Rota-006, pg 435

		HRV 10_4.7		HRV 10_5.2		HRV 10_5.8		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**

RV GE	**Mild (1-6)**	4	18.2	8	36.4	2	13.3 53.3	5	8.8
	Moderate (7-10)	5	22.7	4 10	18.2	8	33.3 100	12	21.1
	Severe (≥11)	13	59.1	22	45.5	5		40	70.2
	Any	22	100		100	15		57	100

Source: Study Report Body Rota-006, pg 435

Serotype distribution is summarized below.

Serotype	**HRV 10_4.7 N= 507**		**HRV 10_5.2 N= 508**		**HRV 10_5.8 N= 512**		**Placebo N= 517**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any	22	4.3	22	4.3	15	2.9	55	10.6
G1 wild type	13	2.6	6	1.2	7	1.4	31 3	6.0
G2	0	0.0	0	0.0	1	0.2		0.6
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.6	14	2.8	7	1.4	19	3.7
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

Source: Study Report Body Rota-006, pg 436

VE against any RV GE – Year 1
VE against any RV GE for the $10^{5.8}$ group was 72.5% (95% CI: 50.6-85.6%), similar to the VE estimate for the primary endpoint in the ATP cohort.

VE against severe RV GE – Year 1
VE against severe RV GE for the $10^{5.8}$ group was 87.4% (95% CI: 68.0-96.1%), similar to the VE estimate this endpoint in the ATP cohort.

VE against any RV GE by main RV serotypes – Year 1
For the $10^{5.8}$ group, VE against any wild type G1 RV GE was 77.2% (95% CI: 47.2-91.5%), VE against any G9 RV GE was 62.8% (95% CI: 7.6-86.8%), and VE against non-G1 RV GE was 66.3% (95% CI: 22.6-86.9%).

VE against severe RV GE by main RV serotypes – Year 1
For the $10^{5.8}$ group, VE against severe wild type G1 RV GE was 88.8% (95% CI: 53.1-98.7%), VE against severe G9 RV GE was 82.2% (95% CI: 38.4-96.7%), and VE against severe non-G1 RV GE was 85.6% (95% CI: 51.7-97.2%).

VE against RV GE requiring hospitalization – Year 1
VE of Rotarix against hospitalized RV GE during the 1st efficacy follow-up period was 81.1% (95% CI: 33.9-96.5%) for the $10^{5.8}$ group.

VE against any RV GE and severe RV GE, by country – Year 1 (Exploratory)
For the $10^{5.8}$ group, VE against any RV GE was 64.7% (95% CI: 25.0-84.7%) in Brazil, 76.9% (95% CI: 17.3-95.7%) in Mexico, and 84.6% (95% CI: 32.0-98.3%) in Venezuela.

For the $10^{5.8}$ group, VE against severe RV GE was 82.8% (95% CI: 49.6-95.7%) in Brazil, 100% (95% CI: 45.4-100%) in Mexico, and 87.5% (95% CI: 6.8-99.7%) in Venezuela.

Year 1 Efficacy (Day of Dose 1 to Year 1 of age) – TVC (2-dose cohort)

VE against any RV GE and severe RV GE – Year 1
VE of Rotarix against any (non-vaccine strain) RV GE during this interval was 72.2% (95% CI: 54.3-83.7%) for the $10^{5.8}$ group.

VE of Rotarix against (non-vaccine strain) severe RV GE during this interval was 88.1% (95% CI: 72.2-95.8%) for the $10^{5.8}$ group.

			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**p-value**

Any RV GE						
HRV 10_4.7	538	32	57.4	34.8	72.8	<0.001
HRV 10_5.2	540	28	62.9	42.0	76.8	<0.001
HRV 10_5.8	540	21	72.2	54.3	83.7	<0.001
Pooled HRV Groups	1618	81	64.2	50.3	74.1	<0.001
Placebo	537	75	-	-	-	-
Severe RV GE						
HRV 10_4.7	538	18	64.1	37.3	80.3	<0.001
HRV 10_5.2	540	12	76.1	54.5	88.4	<0.001
HRV 10_5.8	540	6	88.1	72.2	95.8	<0.001
Pooled HRV Groups	1618	36	76.1	62.6	84.9	<0.001
Placebo	537	50	-	-	-	-

Source: Study Report Body Rota-006, pg 451

Year 1 Efficacy (Day of Dose 1 to 2 weeks post-Dose 2) – TVC (2-dose cohort)

Summary of reported RV GE episodes

The numbers of subjects who reported at least one RV GE and at least one severe RV GE, by treatment group, are summarized below. Figures include both wild-type and vaccine strain RV GE.

Group	**N**	**n**	**%**
Any RV GE			
HRV 10_4.7	538	14	2.6
HRV 10_5.2	540	11	2.0
HRV 10_5.8	540	11	2.0
Pooled HRV Groups	1618	36	2.2
Placebo	537	20	3.7
Severe RV GE			
HRV 10_4.7	538	5	0.9
HRV 10_5.2	540	4	0.7
HRV 10_5.8	540	2	0.4
Pooled HRV Groups	1618	11	0.7
Placebo	537	10	1.9

Source: Study Report Body Rota-006, pg 449

VE against any RV GE – Dose 1 to 2 weeks post-Dose 2

VE of Rotarix against any (non-vaccine strain) RV GE during this interval was 70.2% (95% CI: 23.0-90.2%) for the $10^{5.2}$ group, 70.2% (95% CI: 23.0-90.2%) for the $10^{5.8}$ group, and 63.5% (95% CI: 29.5-81.0%) for the pooled group.

VE against severe RV GE – Dose 1 to 2 weeks post-Dose 2

VE of Rotarix against (non-vaccine strain) severe RV GE during this interval was 80.1% (95% CI: 6.7-97.9%) for the $10^{5.2}$ group, 90.1% (95% CI: 30.1-99.8%) for the $10^{5.8}$ group, and 73.4% (95% CI: 25.3-90.9%) for the pooled group.

Year 1 Immunogenicity (Visit 3 to Year 1 of age) – ATP immunogenicity cohort (2-dose cohort)

Anti-RV IgA response

Anti-RV IgA seroconversion rates at 2 months post-Dose 1, 2 months post-Dose 2, and at the end of Year 1 were similar between all Rotarix groups. GMC 2 months post-Dose 2 was higher in the $10^{5.8}$ group compared to the other groups. However, GMCs at the end of Year 1 were similar between all groups.

Group	**Timing**	**N**	**≥ 20 U/ml**				**GMC (U/ml)**		
					95% CI		**Value**	**95% CI**	
			n	**%**	**LL**	**UL**		**LL**	**UL**
HRV 10_4.7	Pre	395	0	0.0	0.0	0.9	<20.0	-	-
	PI(M2)	146	57	39.0	31.1	47.5	27.0	21.5	33.9
	PII(M4)	142	86	60.6	52.0	68.7	54.0	40.9	71.2
	PII(M10)	377	275	72.9	68.2	77.4	78.9	66.7	93.2

HRV 10_5.2	Pre	374	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	127	48	37.8	29.3	46.8	23.9	19.1	30.0
	PII(M4)	125	78	62.4	53.3	70.9	52.1	39.7	68.3
	PII(M10)	359	273	76.0	71.3	80.4	85.0	72.1	100.2
HRV 10_5.8	Pre	377	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	132	57	43.2	34.6	52.1	32.2	24.8	41.8
	PII(M4)	124	81	65.3	56.3	73.6	70.7	51.9	96.3
	PII(M10)	354	273	77.1	72.4	81.4	81.8	70.1	95.6
Placebo	Pre	368	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	139	3	2.2	0.4	6.2	<20.0	-	-
	PII(M4)	132	7	5.3	2.2	10.6	<20.0	-	-
	PII(M10)	360	149	41.4	36.3	46.7	43.2	35.4	52.8

N = number of subjects with available results; n/% = number/percentage of subjects with concentration above the cut-off
Pre = pre-vaccination; PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Comment: The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).
Source: Study Report Body Rota-006, pg 124

Seroconversion rates on combined doses (i.e. seroconverted at Visit 2 or Visit 3) were similar between Rotarix groups.

Group	N	Seroconversion on combined Dose 1 and Dose 2 at Visit 3			
				95% CI	
		n	%	LL	UL
HRV 10_4.7	145	89	61.4	52.9	69.3
HRV 10_5.2	130	86	66.2	57.3	74.2
HRV 10_5.8	127	85	66.9	58.0	75.0
Placebo	132	7	5.3	2.2	10.6

N = number of subjects with available anti-rotavirus IgA antibody results at Visit 3 and/or with seroconversion at Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or Visit 3
Source: Study Report Body Rota-006, pg 125

GMCs were similar between Rotarix groups, but less than the placebo group, indicating a stronger IgA response after natural infection than by Rotarix.

Group	Timing		GMC (U/ml)		
			Value	95% CI	
		N		LL	UL
HRV 10_4.7	PI(M2)	57	127.1	97.5	165.6
	PII(M4)	86	161.7	124.2	210.6
	PII(M10)	275	169.6	146.4	196.6
HRV 10_5.2	PI(M2)	48	100.6	75.2	134.5
	PII(M4)	78	140.7	111.0	178.5
	PII(M10)	273	166.8	144.8	192.1
HRV 10_5.8	PI(M2)	57	150.4	113.7	198.8
	PII(M4)	81	199.6	152.4	261.5
	PII(M10)	273	152.7	134.4	173.5
Placebo	PI(M2)	3	327.3	3.6	29783.1
	PII(M4)	7	464.9	81.0	2668.1
	PII(M10)	149	343.3	278.4	423.4

N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
Source: Study Report Body Rota-006, pg 125

Year 1 Immunogenicity (Visit 3 to Year 1 of age) – ATP immunogenicity cohort, stool analysis subset (2-dose cohort)

Anti-RV IgA response

Anti-RV IgA seroconversion rates at 2 months post-Dose 1, 2 months post-Dose 2, and at the end of Year 1 were similar between all Rotarix groups. GMC 2 months post-Dose 2 was higher in the $10^{5.8}$ group compared to the other groups. At the end of Year 1, GMC in the $10^{4.7}$ group was higher than the other two Rotarix groups, although 95% CIs were overlapping.

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV 10_4.7	Pre	118	0	0.0	0.0	3.1	<20.0	-	-
	PI(M2)	104	44	42.3	32.7	52.4	30.3	22.8	40.3
	PII(M4)	104	65	62.5	52.5	71.8	57.3	41.3	79.7
	PII(M10)	106	82	77.4	68.2	84.9	104.1	75.2	144.3
HRV 10_5.2	Pre	112	0	0.0	0.0	3.2	<20.0	-	-
	PI(M2)	94	33	35.1	25.5	45.6	21.7	17.0	27.8
	PII(M4)	96	58	60.4	49.9	70.3	51.9	37.9	71.2
	PII(M10)	97	67	69.1	58.9	78.1	70.7	51.1	97.8
HRV 10_5.8	Pre	111	0	0.0	0.0	3.3	<20.0	-	-
	PI(M2)	97	42	43.3	33.3	53.7	33.7	24.5	46.3
	PII(M4)	93	59	63.4	52.8	73.2	65.8	46.0	94.2
	PII(M10)	92	66	71.7	61.4	80.6	81.7	58.4	114.2
Placebo	Pre	104	0	0.0	0.0	3.5	<20.0	-	-
	PI(M2)	105	0	0.0	0.0	3.5	<20.0	-	-
	PII(M4)	99	4	4.0	1.1	10.0	<20.0	-	-
	PII(M10)	97	39	40.2	30.4	50.7	44.0	29.5	65.5

Source: Study Report Body Rota-006, pg 126

Vaccine virus shedding

The percentages of Rotarix recipients who shed vaccine RV in stools between Day 6 to Day 10 after Dose 1 were 36.2% for the $10^{4.7}$ group, 35.2% for the $10^{5.2}$ group, and 44.1% for the $10^{5.8}$ group. The percentages of Rotarix recipients who shed vaccine RV in stools between Day 6 to Day 10 after Dose 2 were 11.5% for the $10^{4.7}$ group, 21.3% for the $10^{5.2}$ group, and 16.5% for the $10^{5.8}$ group. Only one subject shed vaccine virus beyond Day 10 after either dose ($10^{5.8}$ group, approximately 2 months post-Dose 1).

Reviewer Note: Table 31 on page 128 indicates that 1 placebo recipient shed vaccine virus in stool collected between Day 6 to Day 10 post-Dose 2. However, on page 127, the applicant states that "None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV."

The percentages of Rotarix recipients who shed vaccine RV in at least one stool for at least one time point were 38.1% for the $10^{4.7}$ group, 45.2% for the $10^{5.2}$ group, and 47.8% for the $10^{5.8}$ group.

Vaccine take

Vaccine take rate after Dose 1 and Dose 2 was higher in the $10^{5.8}$ group than other groups, although 95% CIs were overlapping.

Group	Vaccine take after Dose 1, at Visit 2					Vaccine take after Dose 2, at Visit 3				
			95%CI					% 95%CI		
	N	n	%	L.L	U.L.	N	n	%	L.L.	U.L.
HRV 10_4.7	105	51	48.6	38.7	58.5	104	66	63.5	53.4	72.7
HRV 10_5.2	105	52	49.5	39.6	59.5	99	62	62.6	52.3	72.1
HRV 10_5.8	108	62	57.4	47.5	66.9	97	67	69.1	58.9	78.1
Placebo	105	0	0.0	0.0	3.5	99	4	4.0	1.1	10.0

Dose 1:
N = number of subject with available anti-rotavirus IgA antibody results at Visit 2 or with vaccine virus* in stools collected from after Visit 1 to Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or with vaccine virus* in stools collected after Visit 1 to Visit 2
Dose 2 – Visit 3:
N = number of subject with available anti-RV IgA antibody results at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
n/% = number/percentage of subjects who seroconverted at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
Comment: *RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode
Source: Study Report Body Rota-006, pg 129

Vaccine take rate after any dose was also higher in the $10^{5.8}$ group (75.5%) than the other groups ($10^{4.7}$group – 64.5%, $10^{5.2}$ group-72.5%, placebo-4%).

Reviewer Note: In the table above, the N for vaccine take after Dose 1 and Dose are described as "… or with vaccine virus in stools collected after Visit 1 to Visit 2" and "…or with vaccine virus in stools collected after Visit 2 to Visit 3," respectively. This appears to be an error, as each N should include the number of subjects with available stool results during these visit intervals.

Impact of feeding on vaccine take rates

Vaccine take rates by feeding criteria were not calculated because none of the pre-defined feeding criteria (exclusive breastfeeding, breastfeeding + formula feeding, feeding within 1 hour before vaccination, feeding within 30 minutes after vaccination) had a significant effect on vaccine take at 2 months post-Dose 2.

Year 1 Immunogenicity (Visit 3 to Year 1 of age) – ATP immunogenicity cohort, routine vaccination subset (2-dose cohort)

Immunogenicity analyses of routine vaccination were performed on the subset of subjects with documented receipt of at least 2 doses of routine vaccines between Visit 1 and the end of Year 1.

Among subjects with available routine vaccination serology results at Visit 3, over 93% in each group received 2 doses of DTPw-HIB+Hib and OPV between Visit 1 and before Visit 3.

Anti-diphtheria antibody response

Seroprotection rates against diphtheria at Visit 3 and the end of Year 1 appeared similar between the $10^{5.8}$ group and placebo group. GMCs were also similar between groups in all groups at both time points.

Group	Timing	N		≥ 0.1 IU/ml			GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV 10_4.7	PII(M4)	146	94	64.4	56.0	72.1	0.204	0.164	0.253
	PII(M10)	164	115	70.1	62.5	77.0	0.189	0.161	0.223
HRV 10_5.2	PII(M4)	136	80	58.8	50.1	67.2	0.183	0.146	0.230
	PII(M10)	149	102	68.5	60.3	75.8	0.186	0.156	0.221
HRV 10_5.8	PII(M4)	130	98	75.4	67.1	82.5	0.247	0.199	0.307
	PII(M10)	142	100	70.4	62.2	77.8	0.188	0.157	0.224
Pooled HRV Groups	PII(M4)	412	272	66.0	61.2	70.6	0.209	0.184	0.237
	PII(M10)	455	317	69.7	65.2	73.9	0.188	0.170	0.207
Placebo	PII(M4)	133	94	70.7	62.2	78.2	0.276	0.216	0.354
	PII(M10)	49	111	74.5	66.7	81.3	0.201	0.169	0.238

N = number of subjects with available results;
n/% = number/percentage of subjects with concentration above the considered protective level
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Source: Study Report Body Rota-006, pg 133

At Visit 3, the 95% CIs of the rate differences obtained from placebo minus the $10^{5.8}$ group and placebo minus the $10^{4.7}$ group included 0, while the rate difference from placebo minus the $10^{5.2}$ group did not include 0. At the end of Year 1, the 95% CIs of the rate differences from placebo minus each of the Rotarix groups included 0.

At Visit 3, the 95% CIs of the placebo/Rotarix GMC ratios included 1 for the $10^{5.8}$ group and $10^{4.7}$ group, but did not include 1 for the $10^{5.2}$ group. At the end of Year 1, the 95% CIs of the GMC ratios included 1 for all Rotarix groups.

Anti-tetanus antibody response

Seroprotection rates and GMCs at each time point appeared similar between placebo and each of the Rotarix groups.

Group	Timing	N		≥ 0.1 IU/ml			GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL

HRV 10_4.7	PII(M4)	147	145	98.6	95.2	99.8	1.106	0.925	1.321
	PII(M10)	166	166	100	97.8	100.0	1.230	1.106	1.368
HRV 10_5.2	PII(M4)	136	136	100	97.3	100.0	1.096	0.921	1.305
	PII(M10)	150	148	98.7	95.3	99.8	1.140	1.008	1.290
HRV 10_5.8	PII(M4)	131	128	97.7	93.5	99.5	1.051	0.868	1.274
	PII(M10)	143	143	100	97.5	100.0	1.179	1.040	1.337
Pooled HRV groups	PII(M4)	414	409	98.8	97.2	99.6	1.085	0.978	1.204
	PII(M10)	459	457	99.6	98.4	99.9	1.184	1.107	1.267
Placebo	PII(M4)	134	133	99.3	95.9	100.0	1.160	0.960	1.403
	PII(M10)	49	49	100	97.6	100.0	1.121	0.992	1.266

Source: Study Report Body Rota-006, pg 134

At both time points, the 95% CIs of the rate differences obtained from placebo minus Rotarix included 0 for all Rotarix groups.

At both time points, the 95% CIs of the placebo/Rotarix GMC ratios included 1 for all Rotarix groups.

Anti-BPT antibody response

Seropositivity rates and GMCs at each time point appeared similar between placebo and each of the Rotarix groups.

Group	Timing	N	≥ 15 EL.U/ml				GMC (EL.U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV 10_4.7	PII(M4)	44	94	65.3	56.9	73.0	19.4	17.0	22.2
	PII(M10)	165	124	75.2	67.8	81.5	22.5	20.1	25.2
HRV 10_5.2	PII(M4)	34	79	59.0	50.1	67.4	18.5	16.0	21.3
	PII(M10)	151	121	80.1	72.9	86.2	25.2	22.1	28.7
HRV 10_5.8	PII(M4)	131	84	64.1	55.3	72.3	18.4	16.1	21.0
	PII(M10)	144	101	70.1	62.0	77.5	22.2	19.3	25.5
Pooled HRV Groups	PII(M4)	409	257	62.8	58.0	67.5	18.8	17.4	20.3
	PII(M10)	460	346	75.2	71.0	79.1	23.2	21.6	25.0
Placebo	PII(M4)	30	80	61.5	52.6	69.9	17.6	15.4	20.2
	PII(M10)	48	106	71.6	63.6	78.7	22.4	19.4	25.7

Source: Study Report Body Rota-006, pg 135

At both time points, the 95% CIs of the rate differences obtained from placebo minus Rotarix included 0 for all Rotarix groups, while the 95% CIs of the placebo/Rotarix GMC ratios included 1 for all Rotarix groups.

Anti-HBs antibody response

Seroprotection rates at each time point appeared similar between placebo and each of the Rotarix groups. GMC at each time point appeared higher in the placebo group than in the Rotarix groups.

Group	Timing	N	≥ 10 mIU/ml				GMC (mIU/ml)		
			n		95% CI		Value	95% CI	
				%	LL	UL		LL	UL
HRV 10_4.7	PII(M4)	147	145	98.6	95.2	99.8	550.607	447.434	677.569
	PII(M10)	165	157	95.2	90.7	97.9	212.673	171.244	264.126
HRV 10_5.2	PII(M4)	136	134	98.5	94.8	99.8	595.706	470.668	753.960
	PII(M10)	150	145	96.7	92.4	98.9	214.367	174.033	264.050
HRV 10_5.8	PII(M4)	134	130	97.0	92.5	99.2	515.918	407.055	653.895
	PII(M10)	143	140	97.9	94.0	99.6	199.973	162.194	246.553
Pooled HRV groups	PII(M4)	417	409	98.1	96.3	99.2	553.237	485.976	629.806
	PII(M10)	458	442	96.5	94.4	98.0	209.166	185.198	236.237
Placebo	PII(M4)	133	131	98.5	94.7	99.8	674.888	527.372	863.667
	PII(M10)	149	144	96.6	92.3	98.9	238.668	193.571	294.271

Source: Study Report Body Rota-001336, pg 136

At both time points, the 95% CIs of the rate differences obtained from placebo minus Rotarix included 0 for all Rotarix groups. Also, at both time points, the 95% CIs of the placebo/Rotarix GMC ratios included 1 for all Rotarix groups.

Anti-PRP antibody response

For both titers, seroprotection rates at each time point appeared similar between placebo and each of the Rotarix groups. GMCs at each time point also appeared similar between groups.

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC (mcg/ml)		
					95% CI				95% CI			95% CI	
			n	%	LL	UL	n	%	LL	UL	Value	LL	UL
HRV 10_4.7	PII(M4)	143	143	100	97.5	100	138	96.5	92.0	98.9	6.420	5.359	7.691
	PII(M10)	165	164	99.4	96.7	100	155	93.9	89.1	97.1	3.987	3.477	4.571
HRV 10_5.2	PII(M4)	136	135	99.3	96.0	100	120	88.2	81.6	93.1	5.638	4.491	7.078
	PII(M10)	149	148	99.3	96.3	100	136	91.3	85.5	95.3	3.995	3.419	4.667
HRV 10_5.8	PII(M4)	133	132	99.2	95.9	100	121	91.0	84.8	95.3	5.114	4.158	6.288
	PII(M10)	143	143	100	97.5	100	131	91.6	85.8	95.6	3.592	3.107	4.152
Pooled HRV groups	PII(M4)	412	410	99.5	98.3	99.9	379	92.0	88.9	94.4	5.715	5.080	6.429
	PII(M10)	457	55	99.6	98.4	99.9	422	92.3	89.5	94.6	3.861	3.552	4.198
Placebo	PII(M4)	131	130	99.2	95.8	100	117	89.3	82.7	94.0	5.083	4.072	6.344
	PII(M10)	149	149	100	97.6	100	141	94.6	89.7	97.7	3.842	3.314	4.454

Source: Study Report Body Rota-006, pg 137

For each titer, the 95% CIs of the rate differences obtained from placebo minus Rotarix included 0 for all Rotarix groups at both time points. Also, at both time points, the 95% CIs of the placebo/Rotarix GMC ratios included 1 for all Rotarix groups.

Anti-poliovirus types 1, 2 and 3 antibody response

For each of the poliovirus types, seroprotection rates and GMTs at each time point appeared similar between placebo and each of the Rotarix groups.

Antibody	Group	Timing	N	≥ 1:8 dilution 95% CI				GMT Value 95% CI		
				n	%	LL	UL		LL	UL
Anti-poliotype 1	HRV 10_4.7	PII(M4)	147	145	98.6	95.2	99.8	1546.9	1207.7	1981.3
		PII(M10)	156	155	99.4	96.5	100	802.1	662.2	971.7
	HRV 10_5.2	PII(M4)	135	132	97.8	93.6	99.5	1120.1	852.6	1471.6
		PII(M10)	139	139	100	97.4	100	731.3	603.3	886.5
	HRV 10_5.8	PII(M4)	133	131	98.5	94.7	99.8	1261.4	979.9	1623.7
		PII(M10)	134	134	100	97.3	100	714.8	574.8	889.0
	Pooled HRV	PII(M4)	415	408	98.3	96.6	99.3	1304.5	1125.0	1512.7
	groups	PII(M10)	429	428	99.8	98.7	100	751.0	669.5	842.4
	Placebo	PII(M4)	130	129	99.2	95.8	100	1322.7	1039.4	1683.0
		PII(M10)	138	138	100	97.4	100	693.9	566.9	849.3
Anti-poliotype 2	HRV 10_4.7	PII(M4)	147	145	98.6	95.2	99.8	1138.6	913.3	1419.4
		PII(M10)	164	162	98.8	95.7	99.9	469.7	390.1	565.5
	HRV 10_5.2	PII(M4)	135	134	99.3	95.9	100	1042.7	838.3	1297.0
		PII(M10)	147	147	100	97.5	100	472.6	404.9	551.5
	HRV 10_5.8	PII(M4)	133	132	99.2	95.9	100	1346.2	1101.4	1645.3
		PII(M10)	140	140	100	97.4	100	523.6	445.3	615.7
	Pooled HRV	PII(M4)	415	411	99.0	97.6	99.7	1167.5	1032.4	1320.3
	groups	PII(M10)	451	449	99.6	98.4	99.9	486.8	441.6	536.6
	Placebo	PII(M4)	130	129	99.2	95.8	100	1112.1	892.9	1385.1
		PII(M10)	148	147	99.3	96.3	100	438.7	372.5	516.6
Anti-poliotype 3	HRV 10_4.7	PII(M4)	147	128	87.1	80.6	92.0	184.1	137.9	245.7
		PII(M10)	164	151	92.1	86.8	95.7	131.1	105.6	162.7
	HRV 10_5.2	PII(M4)	135	114	84.4	77.2	90.1	158.0	113.8	219.3
		PII(M10)	147	134	91.2	85.4	95.2	107.3	83.7	137.6
	HRV 10_5.8	PII(M4)	133	119	89.5	83.0	94.1	181.1	135.2	242.5
		PII(M10)	140	133	95.0	90.0	98.0	130.9	104.8	163.5
	Pooled HRV	PII(M4)	415	361	87.0	83.4	90.1	174.2	146.5	207.2
	groups	PII(M10)	451	418	92.7	89.9	94.9	122.8	107.6	140.0
	Placebo	PII(M4)	130	110	84.6	77.2	90.3	155.5	110.7	218.4
		PII(M10)	148	138	93.2	87.9	96.7	109.2	87.6	136.2

Source: Study Report Body Rota-006, pg 138

For each poliovirus type, the 95% CIs of the rate differences obtained from placebo minus Rotarix included 0 for all Rotarix groups at both time points. For each poliovirus type, the 95% CIs of the placebo/Rotarix GMT ratios included 1 for all Rotarix groups at both time points.

Year 1 Immunogenicity – TVC for immunogenicity(2-dose cohort)

A total of 2151 subjects ($10^{4.7}$ group-537, $10^{5.2}$ group-535, $10^{5.8}$ group-540, placebo-539) were included in this immunogenicity cohort.

Anti-RV IgA response

Seroconversion rates and GMC results were similar to the ATP immunogenicity cohort.

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	**PRE**	534	8	1.5	0.6	2.9	<20.0	-	-
	PI(M2)	187	74	39.6	32.5	47.0	28.2	22.8	35.0
	PII(M4)	180	110	61.1	53.6	68.3	53.6	42.0	68.3
	PII(M10)	472	343	72.7	68.4	76.6	79.9	68.8	92.8
HRV_5.2	**PRE**	529	8	1.5	0.7	3.0	<20.0	-	-
	PI(M2)	174	74	42.5	35.1	50.2	28.1	22.8	34.7
	PII(M4)	166	107	64.5	56.7	71.7	58.8	45.8	75.4
	PII(M10)	463	361	78.0	73.9	81.7	90.4	78.3	104.3
HRV_5.8	**PRE**	529	13	2.5	1.3	4.2	<20.0	-	-
	PI(M2)	184	80	43.5	36.2	51.0	31.4	25.3	38.9
	PII(M4)	173	117	67.6	60.1	74.5	67.9	53.1	86.9
	PII(M10)	459	356	77.6	73.5	81.3	88.6	76.7	102.3
Placebo	**PRE**	528	11	2.1	1.0	3.7	<20.0	-	-
	PI(M2)	192	13	6.8	3.7	11.3	<20.0	-	-
	PII(M4)	182	24	13.2	8.6	19.0	<20.0	-	-
	PII(M10)	488	236	48.4	43.8	52.9	53.0	44.6	62.9

Source: Study Report Body Rota-006, pg 570

Anti-RV IgA GMCs for seropositive subjects were similar to those in the ATP immunogenicity cohort.

Group	Timing		GMC		
			Value	95% CI	
		N		LL	UL
HRV_4.7	**PRE**	8	112.3	39.0	323.4
	PI(M2)	74	137.9	104.8	181.4
	PII(M4)	110	155.9	123.7	196.4
	PII(M10)	343	174.6	153.2	198.9
HRV_5.2	**PRE**	8	139.8	34.2	572.0
	PI(M2)	74	113.9	87.8	147.7
	PII(M4)	107	156.1	124.3	196.1
	PII(M10)	361	168.3	148.8	190.3
HRV_5.8	**PRE**	13	134.3	59.5	303.2
	PI(M2)	80	138.5	109.0	176.0
	PII(M4)	117	170.0	137.0	210.8
	PII(M10)	356	166.4	147.1	188.4
Placebo	**PRE**	11	282.5	101.5	786.8
	PI(M2)	13	299.4	132.5	676.7
	PII(M4)	24	287.2	154.4	534.3
	PII(M10)	236	314.2	268.4	367.9

Source: Study Report Body Rota-006, pg 571

Antibody responses to routine vaccine antigens

Antibody responses, as well placebo-Rotarix group comparisions of rate differences and GMC/GMT ratios, were consistent with results from the ATP immunogenicity cohort analyses for all vaccine antigens at both time points.

Year 2 Efficacy (end of 1st efficacy period to final visit at the end of 2nd efficacy period) – ATP efficacy cohort Year 2 (2-dose cohort)

Reviewer Note: The median duration of follow-up during the Year 2 efficacy period was approximately 10 months in each group.

Summary of reported any RV GE and severe RV GE episodes – Year 2
RV was detected by ELISA in 23 Rotarix recipients ($10^{4.7}$-5, $10^{5.2}$-7,$10^{5.8}$-11) and 9 placebo recipients. No subject in any group had more than one RV GE episode.

Event	Total number of episode reported	HRV 10_4.7 N= 116 n	%	HRV 10_5.2 N= 102 n	%	HRV 10_5.8 N= 114 n	%	Placebo N= 109 n	%
Second efficacy period									
RV GE	**1**	5	4.3	7	6.9	11	9.6	9	8.3
	Any	5	4.3	7	6.9	11	9.6	9	8.3

Source: Study Report Body Rota-006 Annex, pg 73

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 2 Rotarix episodes ($10^{4.7}$-1, $10^{5.2}$-1) and 3 placebo episodes.

Event	Severity	HRV 10_4.7 n	%	HRV 10_5.2 n	%	HRV 10_5.8 n	%	Placebo n	%
Second efficacy period									
GE	**Mild (1-6)**	64	52.5	72	63.2	70	56.0	51	51.5
	Moderate (7-10)	33	27.0	26	22.8	38	30.4	28	28.3
	Severe (≥11)	25	20.5	16	14.0	17	13.6	20	20.2
	Any	122	100	114	100	125	100	99	100
RV GE	**Mild (1-6)**	0	0.0	1	14.3	3	27.3	5	55.6
	Moderate (7-10)	4	80.0	5	71.4	8	72.7	1	11.1
	Severe (≥11)	1	20.0	1	14.3	0	0.0	3	33.3
	Any	5	100	7	100	11	100	9	100

Source: Study Report Body Rota-006 Annex, pg 49

Serotype G distribution is summarized below. G1 was the most prevalent circulating types. RV G type could not be identified in 1 subject (Rota $10^{4.7}$ group).

Serotype	HRV 10_4.7 N= 116 n	%	HRV 10_5.2 N= 102 n	%	HRV 10_5.8 N= 114 n	%	Placebo N= 109 n	%
Second efficacy period								
Any	5	4.3	7	6.9	11	9.6	9	8.3
G1 wild type	2	1.7	5	4.9	8	7.0	7	6.4
G2	1	0.9	0	0.0	1	0.9	0	0.0
G3	0	0.0	1	1.0	0	0.0	0	0.0
G4	1	0.9	0	0.0	0	0.0	0	0.0
G9	0	0.0	1	1.0	2	1.8	2	1.8
Unknown	1	0.9	0	0.0	0	0.0	0	0.0

Source: Study Report Body Rota-006 Annex, pg 50

ELISA results for GE stool samples were not available for 26.7% of GE episodes. Results were unavailable mainly because stool samples were not collected.

Anti-RV IgA status at the end of Year 1 vs. RV GE occurrence during Year 2, Rotarix groups
The percentages of subjects in the Rotarix group that reported at least one RV GE during the 2nd efficacy follow-up period, by anti-RV IgA seropositive status at the end of the 1st efficacy period, are included in the table below for each Rotarix group and for the groups pooled together. In each group except the $10^{4.7}$group, there were less seropositive subjects who had an RV GE episode than seronegative subjects.

Anti-rotavirus Antibody status At Visit 4	HRV 10_4.7 N	n	%	95%CI LL	UL	HRV 10_5.2 N	n	%	95%CI LL	UL
Negative	26	1	3.8	0.1	19.6	24	4	16.7	4.7	37.4
Positive	84	4	4.8	1.3	11.7	70	3	4.3	0.9	12.0
Unknown	6	0	0.0	0.0	45.9	8	0	0.0	0.0	36.9

Anti-rotavirus Antibody status At Visit 4	HRV 10_5.8			95%CI		Pooled HRV groups			95%CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Negative	20	4	20.0	5.7	43.7	70	9	12.9	6.1	23.0
Positive	86	7	8.1	3.3	16.1	240	14	5.8	3.2	9.6
Unknown	8	0	0.0	0.0	36.9	22	0	0.0	0.0	15.4

N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration at the end of the first efficacy follow-up period

n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration at end of first efficacy follow-up period reporting at least one RV GE episode in the second efficacy period

Source: Study Report Body Rota-006 Annex, pg 77

VE against any RV GE – Year 2 (Secondary endpoint)

VE estimates did not reach statistical significance for any of the Rotarix groups. Lack of statistical significance may have been impacted by a small sample size and lower than expected RV GE attack rate during this period.

Group	N	n	n/N 95%CI %	LL	UL	Vaccine Efficacy 95%CI %	LL	UL	P-value
Second efficacy period									
HRV 10_4.7	116	5	4.3	1.4	9.8	47.8	-73.5	86.3	0.274
HRV 10_5.2	102	7	6.9	2.8	13.6	16.9	-151	73.7	0.798
HRV 10_5.8	114	11	9.6	4.9	16.6	-16.9	-219	56.0	0.816
Pooled HRV	332	23	6.9	4.4	10.2	16.1	-106	62.6	0.671
Groups Placebo	109	9	8.3	3.8	15.1	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 53

VE against severe RV GE – Year 2 (Secondary endpoint)

VE estimates against severe RV GE during the 2nd efficacy follow-up period did not reach statistical significance for any of the Rotarix groups. Lack of statistical significance may have been impacted by a small sample size and lower than expected RV GE attack rate during this period, similar to that for VE against any RV GE.

Group	N	n	n/N 95%CI %	LL	UL	Vaccine Efficacy 95%CI %	LL	UL	P-value
Second efficacy period									
HRV 10_4.7	116	1	0.9	0.0	4.7	68.7	-290	99.4	0.357
HRV 10_5.2	102	1	1.0	0.0	5.3	64.4	-344	99.3	0.622
HRV 10_5.8	114	0	0.0	0.0	3.2	100.0	-131	100.0	0.115
Pooled HRV	332	2	0.6	0.1	2.2	78.1	-91.1	98.2	0.099
Groups Placebo	109	3	2.8	0.6	7.8	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 55

VE against any RV GE by main RV serotypes – Year 2

VE estimates against any wild type G1 RV GE or any non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

VE against severe RV GE by main RV serotypes – Year 2

VE estimates against severe wild type G1 RV GE or severe non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

VE against hospitalization due to GE – Year 2

VE estimates against GE of any etiology requiring hospitalization did not reach statistical significance for any of the Rotarix groups.

Year 2 Efficacy (end of 1st efficacy period to final visit at the end of 2nd efficacy period) – TVC for efficacy subset Year 2 (2-dose cohort)

Of the 521 subjects in the TVC, 4 were not included in the TVC for efficacy cohort Year 2 (3 did not receive Dose 2, 1 did not enter the 2nd efficacy follow-up period). Therefore, a total of 517 subjects ($10^{4.7}$-127, $10^{5.2}$-125, $10^{5.8}$-134, placebo-131) were included in this cohort. The median duration of follow-up was approximately 10 months for each group.

Summary of reported RV GE episodes

The numbers of subjects with any RV GE episode and numbers of episodes of severe RV GE for each group are provided in the tables below.

Event	Total number of episode reported	HRV 10_4.7 N= 127 n	%	HRV 10_5.2 N= 125 n	%	HRV 10_5.8 N= 134 n	%	Placebo N= 131 n	%
Second efficacy period									
RV GE	**1**	5	3.9	8	6.4	14	10.4	9	6.9
	Any	5	3.9	8	6.4	14	10.4	9	6.9

Source: Study Report Body Rota-006 Annex, pg 84

Event	Severity	HRV 10_4.7 n	%	HRV 10_5.2 n	%	HRV 10_5.8 n	%	Placebo n	%
Second efficacy period									
RV GE	**Mild (1-6)**	0	0.0	2	25.0	3	21.4	5	55.6
	Moderate (7-10)	4	80.0	5	62.5	10	71.4	1	11.1
	Severe (≥11)	1	20.0	1	12.5	1	7.1	3	33.3
	Any	5	100	8	100	14	100	9	100

Source: Study Report Body Rota-006 Annex, pg 85

Serotype distribution is summarized below.

Serotype	HRV 10_4.7 N= 127 n	%	HRV 10_5.2 N= 125 n	%	HRV 10_5.8 N= 134 n	%	Placebo N= 131 n	%
Second efficacy period								
Any	5	3.9	8	6.4	14	10.4	9	6.9
G1 wild type	2	1.6	5	4.0	10	7.5	7	5.3
G2	1	0.8	0	0.0	2	1.5	0	0.0
G3	0	0.0	1	0.8	0	0.0	0	0.0
G4	1	0.8	0	0.0	0	0.0	0	0.0
G9	0	0.0	2	1.6	3	2.2	2	1.5
Unknown	1	0.8	0	0.0	0	0.0	0	0.0

Source: Study Report Body Rota-006 Annex, pg 86

ELISA results for GE stool samples were not available for 27.2% of GE episodes. Percentages were similar between groups. Results were unavailable mainly because stools were not collected.

Anti-RV IgA status at the end of Year 1 versus RV GE occurrence during Year 2 - Rotarix groups

Similar to results in the ATP efficacy cohort Year 2, in each group except the $10^{4.7}$group, there were less seropositive subjects at the end of Year 1 who had an RV GE episode during Year 2 than seronegative subjects.

Anti-RV antibody status At Visit 4	HRV 10_4.7 N	n	%	95%CI LL	UL	HRV 10_5.2 N	n	%	95%CI LL	UL
Negative	27	1	3.7	0.1	19.0	26	5 3	19.2	6.6	39.4
Positive	93	4	4.3	1.2	10.6	91		3.3	0.7	9.3

Unknown	7	0	0.0	0.0	41.0	8	0	0.0	0.0	36.9

Anti-RV antibody status At Visit 4	**HRV 10_5.8**			**95%CI**		**Pooled HRV groups**			**95%CI**	
	N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Negative	21	4	19.0	5.4	41.9	74	10	13.5	6.7	23.5
Positive	102	9	8.8	4.1	16.1	286	16	5.6	3.2	8.9
Unknown	11	1	9.1	0.2	41.3	26	1	3.8	0.1	19.6

Source: Study Report Body Rota-006 Annex, pg 98

VE against any RV GE – Year 2
VE estimates did not reach statistical significance for any of the Rotarix groups.

VE against severe RV GE – Year 2
VE estimates did not reach statistical significance for any of the Rotarix groups.

VE against any RV GE by main RV serotypes – Year 2
VE estimates against any wild type G1 RV GE or any non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

VE against severe RV GE by main RV serotypes – Year 2
VE estimates against severe wild type G1 RV GE or severe non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

VE against hospitalization due to GE – Year 2
VE estimates against GE of any etiology requiring hospitalization did not reach statistical significance for any of the Rotarix groups.

Year 2 Efficacy (end of 1st efficacy period to final visit at the end of 2nd efficacy period) – TVC 3-dose subset Year 2

Summary of reported RV GE episodes
Thirteen subjects reported any RV GE ($10^{4.7}$-1 [3.7%], $10^{5.2}$-3 [10.3%], $10^{5.8}$-4 [14.3%], placebo-5 [17.2%]). Seven subjects reported severe RV GE ($10^{4.7}$-1 [3.7%], $10^{5.2}$-1 [3.4%], $10^{5.8}$-4 [14.3%], placebo-1 [3.4%]).

VE estimates for each group were not provided.

Combined Efficacy (2 weeks post-Dose 2 to final visit at the end of 2nd efficacy period) – ATP efficacy cohort Combined period (2-dose cohort)

Reviewer Note: The median duration of follow-up during the Year 2 efficacy period was approximately 10 months in each group.

Summary of reported any RV GE and severe RV GE episodes – Combined period
RV was detected by ELISA in 40 Rotarix recipients ($10^{4.7}$-10, $10^{5.2}$-13,$10^{5.8}$-17) and 25 placebo recipients. No subject in any Rotarix group had more than one RV GE episode, while 1 subject each had 2 RV GE episodes.

		HRV 10_4.7 N= 116		**HRV 10_5.2 N= 102**		**HRV 10_5.8 N= 114**		**Placebo N= 109**	
Event	**Total number of episode reported**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Combined efficacy periods									
RV GE	**1**	10	8.6	13	12.7	17	14.9	24	22.0
	2	0	0.0	0	0.0	0	0.0	1	0.9
	Any	10	8.6	13	12.7	17	14.9	25	22.9

Source: Study Report Body Rota-006 Annex, pg 73

Of the RV GE episodes, severe RV GE (Vesikari score ≥ 11 points) was reported in 10 Rotarix episodes ($10^{4.7}$-3, $10^{5.2}$-6,$10^{5.8}$-1) and 13 placebo episodes.

Event	Severity	HRV 10_4.7 n	HRV 10_4.7 %	HRV 10_5.2 n	HRV 10_5.2 %	HRV 10_5.8 n	HRV 10_5.8 %	Placebo n	Placebo %
Combined efficacy periods									
GE	**Mild (1-6)**	132	51.6	130	61.3	148	55.0	101	47.6
	Moderate (7-10)	71	27.7	51	24.1	86	32.0	58	27.4
	Severe (≥11)	53	20.7	31	14.6	35	13.0	53	25.0
	Any	256	100	212	100	269	100	212	100
RV GE	**Mild (1-6)**	2	20.0	1	7.7	4	23.5	6	23.1
	Moderate (7-10)	5	50.0	6	46.2	12	70.6	7	26.9
	Severe (≥11)	3	30.0	6	46.2	1	5.9	13	50.0
	Any	10	100	13	100	17	100	26	100

Source: Study Report Body Rota-006 Annex, pg 49

Serotype G distribution is summarized below. G1 and G9 were the most prevalent circulating types. RV G type could not be identified in 1 subject ($10^{4.7}$ group).

Serotype	HRV 10_4.7 N= 116 n	HRV 10_4.7 %	HRV 10_5.2 N= 102 n	HRV 10_5.2 %	HRV 10_5.8 N= 114 n	HRV 10_5.8 %	Placebo N= 109 n	Placebo %
Combined efficacy periods								
Any	10	8.6	13	12.7	17	14.9	25*	22.9
G1 wild type	5	4.3	9	8.8	11	9.6	21	19.3
G2	1	0.9	0	0.0	2	1.8	1	0.9
G3	0	0.0	1	1.0	0	0.0	0	0.0
G4	1	0.9	0	0.0	1	0.9	0	0.0
G9	2	1.7	3	2.9	4	3.5	4	3.7
Unknown	1	0.9	0	0.0	0	0.0	0	0.0

*One subject in the placebo reported 2 episodes of RV GE during the first efficacy period

Source: Study Report Body Rota-006 Annex, pg 50

ELISA results for GE stool samples were not available for 23.6% of GE episodes. Results were unavailable mainly because stool samples were not collected.

VE against any RV GE – Combined period (Secondary endpoint)

VE estimates reached statistical significance for the $10^{4.7}$group (62.4%) and pooled Rotarix group (47.5%). Lack of statistical significance in the other groups may have been impacted by a small sample size and lower than expected RV attack rate during the second efficacy follow-up period.

Group	N	n	n/N 95%CI %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy 95%CI %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Combined efficacy periods									
HRV 10_4.7	116	10	8.6	4.2	15.3	62.4	19.0	83.9	0.003
HRV 10_5.2	102	13	12.7	7.0	20.8	44.4	-12.8	73.9	0.072
HRV 10_5.8	114	17	14.9	8.9	22.8	35.0	-25.3	67.1	0.170
Pooled HRV Groups	332	40	12.0	8.7	16.0	47.5	9.7	68.9	0.008
Placebo	109	25	22.9	15.4	32.0	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 53

VE against severe RV GE – Combined period (Secondary endpoint)

VE estimates reached statistical significance for the $10^{4.7}$group (78.3%), the$10^{5.8}$group (92.6%), and the pooled Rotarix group was 74.7%.

Group	N	n	n/N 95%CI %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy 95%CI %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Combined efficacy periods									
HRV 10_4.7	116	3	2.6	0.5	7.4	78.3	21.1	96.0	0.008
HRV 10_5.2	102	6	5.9	2.2	12.4	50.7	-39.1	84.6	0.152
HRV 10_5.8	114	1	0.9	0.0	4.8	92.6	51.0	99.8	<0.001
Pooled HRV Groups	332	10	3.0	1.5	5.5	74.7	37.7	90.1	<0.001

Placebo	109	13	11.9	6.5	19.5	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 55

VE against any RV GE by main RV serotypes – Combined period

VE estimates against any wild type G1 RV GE reached statistical significance for the $10^{4.7}$group (77.6%) and the pooled Rotarix group (60.9%). VE estimates against any non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

			n/N	95%CI		Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
G1 wild type									
HRV 10_4.7	116	5	4.3	1.4	9.8	77.6	39.0	93.4	<0.001
HRV 10_5.2	102	9	8.8	4.1	16.1	54.2	-4.3	81.5	0.032
HRV 10_5.8	114	11	9.6	4.9	16.6	49.9	-8.7	78.2	0.055
Pooled HRV Groups	332	25	7.5	4.9	10.9	60.9	26.6	79.0	0.001
Placebo	109	21	19.3	12.3	27.9	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)									
HRV 10_4.7	116	4	3.4	0.9	8.6	24.8	-249	85.1	0.742
HRV 10_5.2	102	4	3.9	1.1	9.7	14.5	-297	83.0	1.000
HRV 10_5.8	114	6	5.3	2.0	11.1	-14.7	-375	70.8	1.000
Pooled HRV Groups	332	14	4.2	2.3	7.0	8.1	-226	68.7	0.792
Placebo	109	5	4.6	1.5	10.4	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 80

VE against severe RV GE by main RV serotypes – Combined period

VE estimates against severe wild type G1 RV GE reached statistical significance for the $10^{4.7}$group (81.2%), the $10^{5.8}$ group (90.4%), and the pooled Rotarix group (77.0%). VE estimates against severe non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
G1 wild type									
HRV 10_4.7	116	2	1.7	0.2	6.1	81.2	11.8	98.0	0.016
HRV 10_5.2	102	4	3.9	1.1	9.7	57.3	-48.2	90.2	0.168
HRV 10_5.8	114	1	0.9	0.0	4.8	90.4	32.8	99.8	0.004
Pooled HRV Groups	332	7	2.1	0.9	4.3	77.0	33.1	92.6	0.002
Placebo	109	10	9.2	4.5	16.2	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)									
HRV 10_4.7	116	1	0.9	0.0	4.7	68.7	-290	99.4	0.357
HRV 10_5.2	102	2	2.0	0.2	6.9	28.8	-522	94.0	1.000
HRV 10_5.8	114	0	0.0	0.0	3.2	100.0	-131	100.0	0.115
Pooled HRV Groups	332	3	0.9	0.2	2.6	67.2	-145	95.6	0.164
Placebo	109	3	2.8	0.6	7.8	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 81

VE against hospitalization due to RV GE – Combined period

VE against hospitalized RV GE did not reach statistical significance in any of the Rotarix groups; only three hospitalizations occurred ($10^{4.7}$group-1, $10^{5.8}$group-1, placebo-1).

VE against hospitalization due to GE – Combined period

VE estimates against GE of any etiology requiring hospitalization did not reach statistical significance for any of the Rotarix groups.

Combined Efficacy (2 weeks post-Dose 2 to final visit at the end of 2nd efficacy period) – TVC for efficacy subset Combined Period (2-dose cohort)

The TVC for efficacy cohort Combined Period was the same as the TVC for efficacy cohort Year 2 (N=517). The median duration of follow-up was 17.3-17.5 months for each group.

Summary of reported RV GE episodes

The numbers of subjects with any RV GE episode and numbers of episodes of severe RV GE for each group are provided in the tables below.

		HRV 10_4.7 N= 127		HRV 10_5.2 N= 125		HRV 10_5.8 N= 134		Placebo N= 131	
Event	**Total # of episode sreported**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Combined efficacy periods									
RV GE	**1**	10	7.9	14	11.2	20	14.9	26	19.8
	2	0	0.0	0	0.0	0	0.0	1	0.8
	Any	10	7.9	14	11.2	20	14.9	27	20.6

Source: Study Report Body Rota-006 Annex, pg 84

		HRV 10_4.7		HRV 10_5.2		HRV 10_5.8		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Combined efficacy periods									
RV GE	**Mild (1-6)**	2	20.0	2	14.3	4	20.0	6	21.4
	Moderate (7-10)	5	50.0	6	42.9	14	70.0	7	25.0
	Severe (≥11)	3	30.0	6	42.9	2	10.0	15	53.6
	Any	10	100	14	100	20	100	28	100

Source: Study Report Body Rota-006 Annex, pg 85

Serotype distribution is summarized below.

Serotype	**HRV 10_4.7 N= 127**		**HRV 10_5.2 N= 125**		**HRV 10_5.8 N= 134**		**Placebo N= 131**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Combined efficacy periods								
Any	10	7.9	14	11.2	20	14.9	27	20.6
G1 wild type	5	3.9	9	7.2	13	9.7	23	17.6
G2	1	0.8	0	0.0	3	2.2	1	0.8
G3	0	0.0	1	0.8	0	0.0	0	0.0
G4	1	0.8	0	0.0	1	0.7	0	0.0
G9	2	1.6	4	3.2	5	3.7	4	3.1
Unknown	1	0.8	0	0.0	0	0.0	0	0.0

Source: Study Report Body Rota-006 Annex, pg 86

ELISA results for GE stool samples were not available for 24.7% of GE episodes. Percentages were similar between groups. Results were unavailable mainly because stools were not collected.

VE against any RV GE – Combined period

VE estimates reached statistical significance for the $10^{4.7}$group (61.8%) and the pooled Rotarix group (44.7%).

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
HRV 10_4.7	127	10	7.9	3.8	14.0	61.8	18.6	83.5	0.004
HRV 10_5.2	125	14	11.2	6.3	18.1	45.7	-7.3	73.7	0.043
HRV 10_5.8	134	20	14.9	9.4	22.1	27.6	-34.0	61.5	0.261
Pooled HRV Groups	386	44	11.4	8.4	15.0	44.7	7.1	66.5	0.012
Placebo	131	27	20.6	14.0	28.6	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 90

VE against severe RV GE – Combined period

VE estimates against severe RV GE reached statistical significance for the $10^{4.7}$group (79.4%), the $10^{5.8}$ group (87.0%) and the pooled Rotarix group (75.1%).

			n/N	95%CI		Vaccine Efficacy	95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
HRV 10_4.7	127	3	2.4	0.5	6.7	79.4	27.1	96.2	0.006
HRV 10_5.2	125	6	4.8	1.8	10.2	58.1	-14.3	86.7	0.068
HRV 10_5.8	134	2	1.5	0.2	5.3	87.0	43.9	98.6	<0.001
Pooled HRV Groups	386	11	2.8	1.4	5.0	75.1	42.0	89.7	<0.001
Placebo	131	15	11.5	6.6	18.2	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 93

VE against any RV GE by main RV serotypes – Combined period

VE estimates against any wild type G1 RV GE reached statistical significance for the $10^{4.7}$group (77.6%), the $10^{5.2}$ group (59.0%) and the pooled Rotarix group (60.2%).

VE estimates against any non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

			n/N	95%CI		Vaccine Efficacy	95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
G1 wild type									
HRV 10_4.7	127	5	3.9	1.3	8.9	77.6	39.7	93.3	<0.001
HRV 10_5.2	125	9	7.2	3.3	13.2	59.0	8.0	83.3	0.014
HRV 10_5.8	134	13	9.7	5.3	16.0	44.7	-13.7	74.3	0.074
Pooled HRV Groups	386	27	7.0	4.7	10.0	60.2	27.3	78.0	<0.001
Placebo	131	23	17.6	11.5	25.2	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)									
HRV 10_4.7	127	4	3.1	0.9	7.9	17.5	-283	83.6	1.000
HRV 10_5.2	125	5	4.0	1.3	9.1	-4.8	-355	75.9	1.000
HRV 10_5.8	134	8	6.0	2.6	11.4	-56.4	-508	54.9	0.572
Pooled HRV Groups	386	17	4.4	2.6	7.0	-15.4	-300	59.1	1.000
Placebo	131	5	3.8	1.3	8.7	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 92

VE against severe RV GE by main RV serotypes – Combined period

VE estimates against severe wild type G1 RV GE reached statistical significance for the $10^{4.7}$group (82.8%), the $10^{5.8}$ group (91.9%) and the pooled Rotarix group (80.2%).

VE estimates against severe non-G1 RV GE when pooled together did not reach statistical significance for any of the Rotarix groups.

			n/N 95%CI			Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Combined efficacy periods									
G1 wild type									
HRV 10_4.7	127	2	1.6	0.2	5.6	82.8	22.8	98.1	0.011
HRV 10_5.2	125	4	3.2	0.9	8.0	65.1	-15.3	91.8	0.069
HRV 10_5.8	134	1	0.7	0.0	4.1	91.9	44.9	99.8	0.001
Pooled HRV Groups	386	7	1.8	0.7	3.7	80.2	45.5	93.4	<0.001
Placebo	131	12	9.2	4.8	15.5	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)									
HRV 10_4.7	127	1	0.8	0.0	4.3	65.6	-328	99.3	0.622
HRV 10_5.2	125	2	1.6	0.2	5.7	30.1	-510	94.2	1.000
HRV 10_5.8	134	1	0.7	0.0	4.1	67.4	-306	99.4	0.367
Pooled HRV Groups	386	4	1.0	0.3	2.6	54.7	-209	92.3	0.377
Placebo	131	3	2.3	0.5	6.5	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 95

VE against hospitalization due to RV GE – Combined period
VE against hospitalized RV GE did not reach statistical significance in any of the Rotarix groups; only three hospitalizations occurred ($10^{4.7}$group-1, $10^{5.8}$group-1, placebo-1).

VE against hospitalization due to GE – Combined period
VE estimates against GE of any etiology requiring hospitalization did not reach statistical significance for any of the Rotarix groups.
Combined Efficacy (Dose 1 to final visit at the end of 2nd efficacy period) – TVC (2-dose cohort)

VE against any RV GE – Dose 1 to end of Year 2
VE estimates against any RV GE (other than vaccine strain) reached statistical significance for the $10^{4.7}$group (60.5%), $10^{5.2}$ group (59.6%), and the pooled Rotarix group (52.4%). Although there were fewer subjects in the $10^{5.8}$ group compared to placebo who reported any RV GE, VE estimate did not reach statistical significance.

			n/N	95%CI		Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
From Dose 1 up to the end of second efficacy period									
HRV 10_4.7	129	14	10.9	6.1	17.5	60.5	25.0	80.3	<0.001
HRV 10_5.2	126	14	11.1	6.2	17.9	59.6	23.2	79.9	<0.001
HRV 10_5.8	135	23	17.0	11.1	24.5	38.0	-7.5	64.9	0.054
Pooled HRV Groups	390	51	13.1	9.9	16.8	52.4	24.9	69.5	<0.001
Placebo	131	36	27.5	20.0	36.0	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 99

VE against severe RV GE – Dose 1 to end of Year 2
VE estimates against severe RV GE (other than vaccine strain) reached statistical significance for all Rotarix groups, with the highest estimate in the $10^{5.8}$ group (86.1%).

			n/N	95%CI		Vaccine Efficacy 95%CI			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
From Dose 1 up to the end of first efficacy period									
HRV 10_4.7	129	6	4.7	1.7	9.8	71.0	25.7	90.4	0.004
HRV 10_5.2	126	6	4.8	1.8	10.1	70.3	23.9	90.2	0.004
HRV 10_5.8	135	3	2.2	0.5	6.4	86.1	53.6	97.4	<0.001
Pooled HRV Groups	390	15	3.8	2.2	6.3	76.0	51.2	88.5	<0.001
Placebo	131	21	16.0	10.2	23.5	-	-	-	-

Source: Study Report Body Rota-006 Annex, pg 100

Reviewer Note: In Supplement 31 on page 100, the second subheading "From Dose 1 up to the end of first efficacy period" appears to be mislabeled and should be "From Dose 1 up to the end of second efficacy period."

8.1.4.2.3 Safety outcomes

Year 1 Safety – TVC (2-dose subset)

Symptom sheets (SS) were completed for > 97% in each group after Dose 1 and >99% after Dose 2.

Dose	Group	Number of Doses	Doses NOT according to protocol	Number of general SS	Compliance % general
1	**HRV_4.7**	538	8	528	98.1
	HRV_5.2	540	10	528	97.8
	HRV_5.8	540	10	529	98.0
	Pooled HRV groups	1618	28	1585	98.0
	Placebo	537	16	532	99.1
2	**HRV_4.7**	510	13	506	99.2
	HRV_5.2	509	19	508	99.8
	HRV_5.8	515	10	512	99.4
	Pooled HRV groups	1534	42	1526	99.5

	Placebo	522	14	517	99.0
Total	**HRV_4.7**	1048	21	1034	98.7
	HRV_5.2	1049	29	1036	98.8
	HRV_5.8	1055	20	1041	98.7
	Pooled HRV groups	3152	70	3111	98.7
	Placebo	1059	30	1049	99.1

SS= symptom sheet; Doses not according to protocol = number of doses with regurgitation

Source: Study Report Body Rota-006, pg 413

Overall incidence of AEs, solicited or unsolicited – Day 0 to Day 14 post-dose

The percentages of subjects who reported at least one solicited/unsolicited symptom after Dose 1, Dose 2, and either dose, were similar between groups. An increase in symptoms from Dose 1 to Dose 2 was not observed for any group.

		Symptoms				
		N	**n**	**%**	**95% CI**	
					LL	**UL**
Dose 1	HRV 10_4.7	538	490	91.1	88.3	93.3
	HRV 10_5.2	540	491	90.9	88.2	93.2
	HRV 10_5.8	540	495	91.7	89.0	93.9
	Pooled HRV groups	1618	1476	91.2	89.7	92.6
	Placebo	537	500	93.1	90.6	95.1
Dose 2	HRV 10_4.7	510	437	85.7	82.3	88.6
	HRV 10_5.2	509	449	88.2	85.1	90.9
	HRV 10_5.8	515	451	87.6	84.4	90.3
	Pooled HRV groups	1534	1337	87.2	85.4	88.8
	Placebo	522	457	87.5	84.4	90.3
Overall/dose	HRV 10_4.7	1048	927	88.5	86.4	90.3
	HRV 10_5.2	1049	940	89.6	87.6	91.4
	HRV 10_5.8	1055	946	89.7	87.7	91.4
	Pooled HRV groups	3152	2813	89.2	88.1	90.3
	Placebo	1059	957	90.4	88.4	92.1
Overall/subject	HRV 10_4.7	538	514	95.5	93.4	97.1
	HRV 10_5.2	540	516	95.6	93.5	97.1
	HRV 10_5.8	540	515	95.4	93.2	97.0
	Pooled HRV groups	1618	1545	95.5	94.4	96.4
	Placebo	537	521	97.0	95.2	98.3

For each dose:

N = number of subjects having received the considered dose of HRV vaccine or placebo

n/% = number/percentage of subjects reporting at least one symptom for the considered dose of HRV vaccine or placebo

For overall/dose:

N = total number of doses of HRV vaccine or placebo administered

n/% = total number/percentage of doses of HRV vaccine or placebo reporting at least one symptom

For overall/subject:

N= number of subjects having received at least one dose of HRV vaccine or placebo

n/%= number percentage of subjects reporting at least one symptom

Source: Study Report Body Rota-006, pg 105

Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained the following figures, with differences from the applicant highlighted in bold italics. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

		N	**n**	**%**
Dose 1	HRV 10_5.8	540	***496***	***91.9***
Dose 2	HRV 10_5.2	509	***450***	***88.4***
Overall/dose	HRV 10_5.2	1049	***941***	***89.7***
	HRV 10_5.8	1055	***947***	***89.8***
Overall/subject	HRV 10_5.8	540	***516***	***95.6***

Overall incidence of Grade 3 AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects who reported at least one Grade 3 solicited or unsolicited symptom after Dose 1 and Dose 2 were slightly higher in the $10^{5.8}$ group compared to other groups, although 95% CIs overlapped. Increase in symptoms from Dose 1 to Dose 2 was not observed for any group.

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV_4.7	538	114	21.2	17.8	24.9
	HRV_5.2	540	128	23.7	20.2	27.5
	HRV_5.8	540	140	25.9	22.3	29.8
	Pooled HRV groups	1618	382	23.6	21.6	25.8
	Placebo	537	129	24.0	20.5	27.9
Dose 2	HRV_4.7	510	105	20.6	17.2	24.4
	HRV_5.2	509	111	21.8	18.3	25.7
	HRV_5.8	515	114	22.1	18.6	26.0
	Pooled HRV groups	1534	330	21.5	19.5	23.7
	Placebo	522	104	19.9	16.6	23.6
Overall/dose	HRV_4.7	1048	219	20.9	18.5	23.5
	HRV_5.2	1049	239	22.8	20.3	25.4
	HRV_5.8	1055	254	24.1	21.5	26.8
	Pooled HRV groups	3152	712	22.6	21.1	24.1
	Placebo	1059	233	22.0	19.5	24.6
Overall/subject	HRV_4.7	538	180	33.5	29.5	37.6
	HRV_5.2	540	204	37.8	33.7	42.0
	HRV_5.8	540	196	36.3	32.2	40.5
	Pooled HRV groups	1618	580	35.8	33.5	38.2
	Placebo	537	190	35.4	31.3	39.6

Source: Study Report Body Rota-006, pg 452

Overall incidence of vaccine-related AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects who reported at least one vaccine-related solicited or unsolicited symptom after Dose 2 were slightly higher in the $10^{5.8}$ group compared to other groups, although 95% CIs overlapped. Increase in symptoms from Dose 1 to Dose 2 was not observed for any group.

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV_4.7	538	275	51.1	46.8	55.4
	HRV_5.2	540	278	51.5	47.2	55.8
	HRV_5.8	540	271	50.2	45.9	54.5
	Pooled HRV groups	1618	824	50.9	48.5	53.4
	Placebo	537	276	51.4	47.1	55.7
Dose 2	HRV_4.7	510	218	42.7	38.4	47.2
	HRV_5.2	509	234	46.0	41.6	50.4
	HRV_5.8	515	240	46.6	42.2	51.0
	Pooled HRV groups	1534	692	45.1	42.6	47.6
	Placebo	522	223	42.7	38.4	47.1
Overall/dose	HRV_4.7	1048	493	47.0	44.0	50.1
	HRV_5.2	1049	512	48.8	45.7	51.9
	HRV_5.8	1055	511	48.4	45.4	51.5
	Pooled HRV groups	3152	1516	48.1	46.3	49.9
	Placebo	1059	499	47.1	44.1	50.2
Overall/subject	HRV_4.7	538	285	53.0	48.7	57.3
	HRV_5.2	540	289	53.5	49.2	57.8
	HRV_5.8	540	287	53.1	48.8	57.4
	Pooled HRV groups	1618	861	53.2	50.7	55.7
	Placebo	537	281	52.3	48.0	56.6

Source: Study Report Body Rota-006, pg 453

Reviewer Note: Based on analysis data provided by the applicant, the reviewer obtained the following figures, with differences from the applicant highlighted in bold italics. Because the numbers did not differ substantially from those provided by the applicant, the reviewer feels comfortable accepting the analysis submitted by the applicant.

		N	n	%
Dose 2	Placebo	522	***224***	***42.9***
Overall/dose	Placebo	1059	***500***	***47.2***

Solicited general AEs – Days 0-14 post-dose

In general, the incidence of any, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after Dose 1 were similar between the 3 Rotarix groups. There appeared to be slightly higher rates of any diarrhea (8.1%) in the $10^{5.8}$ group compared to other groups. Rates of any cough/runny nose, irritability/fussiness, loss of appetite, fever, and vomiting each exceeded 10% in each Rotarix group. The incidence of Grade 3 AEs was relatively low compared to the total number of AEs for each symptom. Grade 3 irritability/fussiness was reported at a rate ≥ 10% in each of the 3 Rotarix groups. Grade 3 AEs that were reported at a rate ≥ 1% and < 10% in each of the 3 Rotarix groups were cough/runny nose, diarrhea, loss of appetite, fever, and vomiting.

After Dose 1

Solicited symptom		HRV 10_4.7 N =538				HRV 10_5.2 N =540				HRV 10_5.8 N =540			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	325	60.4	56.1	64.6	316	58.5	54.2	62.7	322	59.6	55.4	63.8
	Grade 2 or 3	171	31.8	27.9	35.9	150	27.8	24.0	31.8	167	30.9	27.0	35.0
	Grade 3	45	8.4	6.2	11.0	51	9.4	7.1	12.2	53	9.8	7.4	12.6
	Related	109	20.3	16.9	23.9	102	18.9	15.7	22.4	91	16.9	13.8	20.3
Diarrhea	Total	33	6.1	4.3	8.5	34	6.3	4.4	8.7	44	8.1	6.0	10.8
	Grade 2 or 3	19	3.5	2.1	5.5	24	4.4	2.9	6.5	28	5.2	3.5	7.4
	Grade 3	8	1.5	0.6	2.9	11	2.0	1.0	3.6	11	2.0	1.0	3.6
	Related	16	3.0	1.7	4.8	20	3.7	2.3	5.7	29	5.4	3.6	7.6
Irritability/ fussiness	Total	381	70.8	66.8	74.6	380	70.4	66.3	74.2	391	72.4	68.4	76.1
	Grade 2 or 3	251	46.7	42.4	51.0	241	44.6	40.4	48.9	259	48.0	43.7	52.3
	Grade 3	65	12.1	9.4	15.1	69	12.8	10.1	15.9	75	13.9	11.1	17.1
	Related	236	43.9	39.6	48.2	227	42.0	37.8	46.3	241	44.6	40.4	48.9
Loss of appetite	Total	170	31.6	27.7	35.7	176	32.6	28.7	36.7	171	31.7	27.8	35.8
	Grade 2 or 3	50	9.3	7.0	12.1	50	9.3	7.0	12.0	70	13.0	10.2	16.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	11	2.0	1.0	3.6
	Related	74	13.8	11.0	17.0	78	14.4	11.6	17.7	78	14.4	11.6	17.7
Fever	Total	331	61.5	57.3	65.7	339	62.8	58.5	66.9	332	61.5	57.2	65.6
	Grade 2 or 3	127	23.6	20.1	27.4	110	20.4	17.1	24.0	126	23.3	19.8	27.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	8	1.5	0.6	2.9
	Related	205	38.1	34.0	42.4	189	35.0	31.0	39.2	189	35.0	31.0	39.2
Vomiting	Total	88	16.4	13.3	19.8	106	19.6	16.4	23.2	91	16.9	13.8	20.3
	Grade 2 or 3	35	6.5	4.6	8.9	61	11.3	8.8	14.3	43	8.0	5.8	10.6
	Grade 3	12	2.2	1.2	3.9	25	4.6	3.0	6.8	22	4.1	2.6	6.1
	Related	48	8.9	6.7	11.7	46	8.5	6.3	11.2	40	7.4	5.3	10.0

N = number of subjects with at least one solicited symptom sheet completed
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Source: Study Report Body Rota-006, pg 107

The incidence of total, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after Dose 1 were similar between the pooled Rotarix group and placebo. In addition, the rates for the $10^{5.8}$ group were similar to those of placebo, with overlapping 95% CIs.

After Dose 1

Solicited symptom		Pooled HRV groups N = 1618				Placebo N = 537			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL

Cough/ runny nose	Total	963	59.5	57.1	61.9	340	63.3	59.1	67.4
	Grade 2 or 3	488	30.2	27.9	32.5	182	33.9	29.9	38.1
	Grade 3	149	9.2	7.8	10.7	34	6.3	4.4	8.7
	Related	302	18.7	16.8	20.7	105	19.6	16.3	23.2
Diarrhea	Total	111	6.9	5.7	8.2	45	8.4	6.2	11.1
	Grade 2 or 3	71	4.4	3.4	5.5	27	5.0	3.3	7.2
	Grade 3	30	1.9	1.3	2.6	10	1.9	0.9	3.4
	Related	65	4.0	3.1	5.1	23	4.3	2.7	6.4
Irritability/ fussiness	Total	1152	71.2	68.9	73.4	408	76.0	72.1	79.5
	Grade 2 or 3	751	46.4	44.0	48.9	272	50.7	46.3	55.0
	Grade 3	209	12.9	11.3	14.6	82	15.3	12.3	18.6
	Related	704	43.5	41.1	46.0	243	45.3	41.0	49.6
Loss of appetite	Total	517	32.0	29.7	34.3	187	34.8	30.8	39.0
	Grade 2 or 3	170	10.5	9.1	12.1	65	12.1	9.5	15.2
	Grade 3	24	1.5	1.0	2.2	8	1.5	0.6	2.9
	Related	230	14.2	12.5	16.0	87	16.2	13.2	19.6
Fever	Total	1002	61.9	59.5	64.3	346	64.4	60.2	68.5
	Grade 2 or 3	363	22.4	20.4	24.5	126	23.5	19.9	27.3
	Grade 3	21	1.3	0.8	2.0	11	2.0	1.0	3.6
	Related	583	36.0	33.7	38.4	192	35.8	31.7	40.0
Vomiting	Total	285	17.6	15.8	19.6	89	16.6	13.5	20.0
	Grade 2 or 3	139	8.6	7.3	10.1	43	8.0	5.9	10.6
	Grade 3	59	3.6	2.8	4.7	13	2.4	1.3	4.1
	Related	134	8.3	7.0	9.7	54	10.1	7.6	12.9

Source: Study Report Body Rota-006, pg 108

Overall, the incidence of total, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after Dose 2 were similar between the 3 Rotarix groups. There appeared to be slightly higher rates of any (8.5%) diarrhea in the $10^{5.8}$ group compared to other groups. The incidence of Grade 3 AEs was relatively low compared to the total number of AEs for each symptom. In general, the rates of AEs after Dose 2 were similar to those after Dose 1. Rates of any cough/runny nose, irritability/fussiness, loss of appetite, fever, and vomiting each exceeded 10% in each Rotarix group. The incidence of Grade 3 AEs was relatively low compared to the total number of AEs for each symptom. Grade 3 symptoms reported at a rate ≥ 10% were cough runny nose (all Rotarix groups) and irritability/fussiness ($10^{4.7}$group). Grade 3 AEs that were reported at ≥ 1% and < 10% were diarrhea (all Rotarix groups), loss of appetite ($10^{4.7}$group and $10^{5.2}$group), fever (all Rotarix groups), and vomiting (all Rotarix groups). Grade 3 loss of appetite in the $10^{5.8}$group was reported at <1%.

After Dose 2

Solicited symptom		**HRV 10_4.7 N =510**				**HRV 10_5.2 N =509**				**HRV 10_5.8 N =515**			
		n	%	**95% CI** LL	UL	n	%	**95% CI** LL	UL	n	%	**95% CI** LL	UL
Cough/ runny nose	Total	310	60.8	56.4	65.0	323	63.5	59.1	67.7	334	64.9	60.6	69.0
	Grade 2 or 3	164	32.2	28.1	36.4	163	32.0	28.0	36.3	176	34.2	30.1	38.5
	Grade 3	51	10.0	7.5	12.9	51	10.0	7.6	13.0	56	10.9	8.3	13.9
	Related	97	19.0	15.7	22.7	110	21.6	18.1	25.4	109	21.2	17.7	25.0
Diarrhea	Total	38	7.5	5.3	10.1	34	6.7	4.7	9.2	44	8.5	6.3	11.3
	Grade 2 or 3	29	5.7	3.8	8.1	23	4.5	2.9	6.7	29	5.6	3.8	8.0
	Grade 3	8	1.6	0.7	3.1	12	2.4	1.2	4.1	13	2.5	1.4	4.3
	Related	19	3.7	2.3	5.8	23	4.5	2.9	6.7	21	4.1	2.5	6.2
Irritability/ fussiness	Total	292	57.3	52.8	61.6	303	59.5	55.1	63.8	313	60.8	56.4	65.0
	Grade 2 or 3	163	32.0	27.9	36.2	166	32.6	28.6	36.9	191	37.1	32.9	41.4
	Grade 3	53	10.4	7.9	13.4	43	8.4	6.2	11.2	49	9.5	7.1	12.4
	Related	168	32.9	28.9	37.2	173	34.0	29.9	38.3	177	34.4	30.3	38.6
Loss of appetite	Total	149	29.2	25.3	33.4	146	28.7	24.8	32.8	152	29.5	25.6	33.7
	Grade 2 or 3	67	13.1	10.3	16.4	62	12.2	9.5	15.3	61	11.8	9.2	15.0
	Grade 3	14	2.7	1.5	4.6	16	3.1	1.8	5.1	4	0.8	0.2	2.0
	Related	59	11.6	8.9	14.7	54	10.6	8.1	13.6	53	10.3	7.8	13.2
Fever	Total	275	53.9	49.5	58.3	272	53.4	49.0	57.8	279	54.2	49.8	58.5
	Grade 2 or 3	106	20.8	17.3	24.6	116	22.8	19.2	26.7	114	22.1	18.6	26.0

	Grade 3	9	1.8	0.8	3.3	13	2.6	1.4	4.3	14	2.7	1.5	4.5
	Related	139	27.3	23.4	31.3	127	25.0	21.2	28.9	143	27.8	23.9	31.9
Vomiting	Total	55	10.8	8.2	13.8	69	13.6	10.7	16.8	65	12.6	9.9	15.8
	Grade 2 or 3	27	5.3	3.5	7.6	41	8.1	5.8	10.8	37	7.2	5.1	9.8
	Grade 3	13	2.5	1.4	4.3	21	4.1	2.6	6.2	20	3.9	2.4	5.9
	Related	32	6.3	4.3	8.7	33	6.5	4.5	9.0	23	4.5	2.9	6.6

Source: Study Report Body Rota-006, pg 109

The incidence of total, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after Dose 2 were similar between the pooled Rotarix group and placebo. In addition, the rates for the $10^{5.8}$ group were similar to those of placebo, with overlapping 95% CIs.

After Dose 2

Solicited symptom		**Pooled HRV groups N = 1534**		**95% CI**		**Placebo N = 537**		**95% CI**	
		n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Cough/ runny nose	Total	967	63.0	60.6	65.5	331	63.4	59.1	67.6
	Grade 2 or 3	503	32.8	30.4	35.2	190	36.4	32.3	40.7
	Grade 3	158	10.3	8.8	11.9	46	8.8	6.5	11.6
	Related	316	20.6	18.6	22.7	103	19.7	16.4	23.4
Diarrhea	Total	116	7.6	6.3	9.0	46	8.8	6.5	11.6
	Grade 2 or 3	81	5.3	4.2	6.5	33	6.3	4.4	8.8
	Grade 3	33	2.2	1.5	3.0	15	2.9	1.6	4.7
	Related	63	4.1	3.2	5.2	20	3.8	2.4	5.9
Irritability/ fussiness	Total	908	59.2	56.7	61.7	305	58.4	54.1	62.7
	Grade 2 or 3	520	33.9	31.5	36.3	177	33.9	29.9	38.1
	Grade 3	145	9.5	8.0	11.0	42	8.0	5.9	10.7
	Related	518	33.8	31.4	36.2	164	31.4	27.5	35.6
Loss of appetite	Total	447	29.1	26.9	31.5	149	28.5	24.7	32.6
	Grade 2 or 3	190	12.4	10.8	14.1	69	13.2	10.4	16.4
	Grade 3	34	2.2	1.5	3.1	12	2.3	1.2	4.0
	Related	166	10.8	9.3	12.5	58	11.1	8.5	14.1
Fever	Total	826	53.8	51.3	56.4	288	55.2	50.8	59.5
	Grade 2 or 3	336	21.9	19.9	24.1	96	18.4	15.2	22.0
	Grade 3	36	2.3	1.6	3.2	11	2.1	1.1	3.7
	Related	409	26.7	24.5	29.0	125	23.9	20.3	27.8
Vomiting	Total	189	12.3	10.7	14.1	59	11.3	8.7	14.3
	Grade 2 or 3	105	6.8	5.6	8.2	30	5.7	3.9	8.1
	Grade 3	54	3.5	2.7	4.6	15	2.9	1.6	4.7
	Related	88	5.7	4.6	7.0	24	4.6	3.0	6.8

Source: Study Report Body Rota-006, pg 110

The incidence of doses or subjects reporting any, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after any dose were similar between the pooled Rotarix group and placebo.

For each solicited symptom after any dose, statistical analyses showed that the percentages of subjects reporting any symptom, Grade 2/3 symptom, Grade 3 symptom or vaccine-related symptom were not significantly different between any of the Rotarix groups or between the pooled Rotarix group and placebo.

There was no noticeable peak day in the prevalence of diarrhea from Day 0 to Day 14 after either dose for either group. A peak in the prevalence of fever occurred at Day 0 post-Dose 1 and post-Dose 2 for all groups. A peak in the prevalence of vomiting occurred at Day 1 post-Dose 1 and post-Dose 2. The median duration of diarrhea, vomiting, and fever during the 15-day period after each dose were similar between groups. Durations of each symptom after Dose 1 were also similar to those after Dose 2.

Solicited general AEs – Days 0-3, Days 0-7 post-dose
The applicant stated that the incidence of each individual symptom from Day 0-3 and Day 0-7 post-vaccination were similar between groups, with the majority of symptoms occurring within 8 days post-vaccination.

For each solicited symptom after any dose, statistical analyses demonstrated that the percentages of subjects reporting any symptom, Grade 2/3 symptom, Grade 3 symptom or vaccine-related symptom during Days 0-7 or Days 0-14 post-vaccination were not significantly different between any of the Rotarix groups or between the pooled Rotarix group and placebo. The only exception was Grade 2/3 vomiting During Day 0-7 post-vaccination, which occurred significantly more in the $10^{5.2}$ group compared to the $10^{4.7}$ group (12.4% vs. 8.4%; p=0.036). However, differences in rates of Grade 3 vomiting were not statistically significant.

Unsolicited AEs – Days 0-42 post-dose
The percentages of subjects with at least one unsolicited AE of any kind were similar between groups ($10^{4.7}$-65.1%, $10^{5.2}$-65.6%, $10^{5.8}$-60.7%, placebo-63.7%). The percentages of subjects in each Preferred Term also appeared similar between groups.
In the Rotarix groups, AE PTs reported in ≥ 10% of subjects were viral infection (all groups), and pharyngitis (all groups). AE PTs reported in ≥ 1% and <10% of Rotarix subjects were contact dermatitis ($10^{5.2}$ group), allergy ($10^{5.2}$ and $10^{5.8}$groups), fever (all groups), abdominal pain (all groups), anorexia, constipation, gastroesophageal reflux ($10^{5.2}$ and $10^{5.8}$groups), vomiting (all groups), nervousness (all groups), infection (all groups), moniliasis ($10^{4.7}$ and $10^{5.2}$groups), otitis media ($10^{5.2}$ group), upper respiratory infection (all groups), bronchitis (all groups), bronchospasm (all groups), coughing (all groups), pneumonia (all groups), respiratory disorder ($10^{5.2}$ group), rhinitis (all groups), skin disorder (all groups), and conjunctivitis (all groups).

The percentages of subjects with at least one unsolicited Grade 3 AE were also similar between groups ($10^{4.7}$-2.8%, $10^{5.2}$-5%, $10^{5.8}$-2.6%, placebo-3.2%). There were no major differences between groups for any WHO Preferred Term. Only Grade 3 PT pneumonia was reported in ≥ 1% of subjects in the Rotarix groups ($10^{5.2}$-1.5%, $10^{5.8}$-1.1%

Only 6 subjects, all from Brazil, reported a vaccine-related AE ($10^{4.7}$-2, placebo-4). One of the Rotarix recipients had *Fever*, while the other had *Bronchitis*.

The percentages of subjects with at least one unsolicited gastrointestinal AE (7.1-7.7% in each group), one vaccine-related GI AE (0.3-0.9% in each group) and one Grade 3 GI AE (0% in each group) were similar between groups. None of the gastrointestinal symptoms were assessed as vaccine-related.

Reactogenicity by country – Days 0-14 (solicited/unsolicited AEs), Days 0-42 (unsolicited AEs) post-dose
Overall, rates of solicited and unsolicited symptoms during these intervals after each dose were similar between groups for each country.

Concomitant medications/vaccinations – Days 0-14 post-dose
The percentages of subjects who started taking any medication and any antipyretics after each dose were comparable between groups. No increases in medication utilization occurred from Dose 1 to Dose 2. The percentages of subjects who took medications from Visit 1 to the end of Year 1 were also similar between groups.

SAEs – Dose 1 to end of Year 1
The numbers of subjects with at least one SAE were similar between groups ($10^{4.7}$-52, $10^{5.2}$-55, $10^{5.8}$-49, placebo-64). All SAEs were assessed as unrelated to study vaccination. The distributions of SAEs by WHO Body System or WHO Preferred Term were not provided in the report.
Reviewer Note: The reviewer did not observe a noticeable difference in distributions of SAEs by WHO Preferred Term. In the Rotarix groups, no SAE PTs were reported at a rate ≥ 10%, while

SAEs that occurred at ≥ 1% and <10% was bronchitis ($10^{4.7}$ -1.3%, $10^{5.2}$ -1.3%), gastroenteritis ($10^{4.7}$ -4.1%, $10^{5.2}$ -3.7%, $10^{5.8}$ -3.7%), pneumonia ($10^{4.7}$ -3.7%, $10^{5.2}$ -5.7%, $10^{5.8}$ -3.9%). None of the SAEs were as related to Rotarix vaccination.

One routine vaccine-related SAE (bronchitis) occurred in a Rotarix recipient ($10^{4.7}$group) from Brazil beginning on Day 0 post-Dose 2 of DTPw-HB+Hib vaccine. Treatment code was not broken.

One vaccine-unrelated IS case ($10^{4.7}$group) occurred 6 months post-Dose 2 in a 10-month male from Mexico. The subject recovered completely.

One subject, a 13 month-old male from Brazil, was diagnosed with Kawasaki's disease with onset approximately 7 months post-Dose 2 of Rotarix ($10^{4.7}$group).

Deaths – Dose 1 to end of Year 1
Three subjects died due to vaccine-unrelated SAEs. The first, a Mexican boy, died 13 days post-Dose 1 of placebo following cardio-respiratory failure. Treatment code for this subject was broken. The second, a Brazilian boy ($10^{4.7}$group), died 3 months post-Dose 2 from septicemia. The treatment code was not broken. The third, a Mexican boy ($10^{5.8}$group), died 1 month post-Dose 2 from a road traffic accident. The treatment code was not broken.

SAEs and non-serious AEs leading to drop-out at end of Year 1
Three subjects (Rota $10^{4.7}$-1, Rota $10^{5.8}$-1, placebo-1) dropped out due to SAEs (all deaths – see section above).

Six subjects (Rota $10^{5.2}$-2, Rota $10^{5.8}$-2, placebo-2) dropped out due to non-SAEs. One of these subjects (placebo) withdrew due to a Grade 2 allergic reaction starting 1 day post-Dose 1 that was assessed as possibly related to vaccination. The other 5 subjects dropped out due to non-vaccine-related AEs as follows: severe gastrointestinal reflux post-Dose 2 ($10^{5.8}$group), severe anemia 254 days post-Dose 2 ($10^{5.8}$group), severe reaction to BCG vaccination post-Dose 1 (placebo), Grade 1 hypothyroidism 108 days post-Dose 2 ($10^{5.2}$group), and Grade 2 cervical lymphangioma 117 days post-Dose 1 ($10^{5.2}$group).

Year 1 Safety – ATP cohort for safety (2-dose subset)

Note: Safety analyses on the ATP safety cohort were performed because more than 5% of subjects were eliminated from this cohort. The ATP safety cohort consisted of 1965 subjects ($10^{4.7}$-499, $10^{5.2}$-487, $10^{5.8}$-493, placebo-486) in the 2-dose subset.

Overall incidence of AEs, Grade 3 AEs, and vaccine-related AEs, solicited or unsolicited – Days 0-14 post-dose
The percentages of subjects, who reported at least one AE, one Grade 3 AE, and one vaccine-related AE after Dose 1, Dose 2, and either dose, were similar between groups. An increase in symptoms from Dose 1 to Dose 2 was not observed for any group.

Solicited general AEs – Days 0-14 post-dose
Overall, the incidence of total, Grade 2/3, Grade 3, and vaccine-related AEs for each symptom after each dose were similar between the groups. The incidence of Grade 3 AEs was relatively low compared to the total number of AEs for each symptom.

Unsolicited AEs – Days 0-42 post-dose
The percentages of subjects with at least one unsolicited AE of any kind were similar between groups. Results of other analyses were consistent with those for the TVC.

Year 2 safety – TVC (2-dose subset)

SAEs – Year 2

The numbers of subjects with at least one SAE were similar between groups ($10^{4.7}$-12, $10^{5.2}$-12, $10^{5.8}$-8, placebo-13). All SAEs were assessed as unrelated to study vaccination. The distributions of SAEs by WHO Body System or WHO Preferred Term were not provided in the report.
Reviewer Note: The reviewer did not observe a noticeable difference in distributions of SAEs by WHO Preferred Term. SAE PTs reported at a rate of ≥ 1% and <10% in Rotarix subjects were asthma ($10^{5.2}$and $10^{5.8}$ groups), bronchitis ($10^{5.2}$group), cachexia ($10^{4.7}$ group), convulsions ($10^{5.8}$group), dehydration ($10^{5.2}$group), dyspnea ($10^{5.2}$and $10^{5.8}$ groups), erythema multiforme ($10^{5.8}$group), fever ($10^{4.7}$ group), gastroenteritis (all groups), gastrointestinal disorder ($10^{4.7}$ group), bacterial infection ($10^{5.2}$group), injury ($10^{4.7}$and $10^{5.2}$ groups), laryngitis ($10^{5.2}$group), pharyngitis (all groups), pneumonia (all groups), and thinking abnormal ($10^{5.8}$group).

No cases of IS were reported during Year 2.

Deaths – Year 2
No deaths were reported during Year 2.

SAEs and non-serious AEs leading to drop-out between end of Year 1 and end of Year 2
Dropouts due to SAEs were not reported.

One subject dropped out due to chronic GE and renal disorder. This subject ($10^{5.2}$group) reported 1 non-RV GE episode during Year 2 (and also 3 non-RV GE episodes during Year 1).

Individual report forms reviewed

Individual case narratives were reviewed for IS and Kawasaki's Disease cases, vaccine-related SAEs, and deaths.

8.1.4.3 Comments & Conclusions

In Rota-006, two doses of Rotarix at a slightly higher concentration of vaccine virus ($10^{5.8}$ ffu of RIX4414) than that used in the 2 pivotal trials (Rota-023 and Rota-036), administered to children 6 to 12 weeks 2 months apart, resulted in an efficacy of 70% against any RV GE detected by ELISA during the 1st efficacy follow-up period, although the LL of the 95% CI was 45.7%. VE against severe RV GE during this period was 85.6%. VE estimates against any RV GE and severe RV GE detected by ELISA during the 2nd efficacy period did not reach statistical significance, possibly due to the smaller sample size and lower than expected RV GE attack rate during this period. Over the combined follow-up period, VE against severe RV GE was 92.6%.

Statistically significant VE against any RV GE and severe RV GE during Year 1 was observed for Rotarix at lower viral concentrations. In the $10^{4.7}$ group, VE against any and severe RV GE was 58.4% and 65.8%, respectively, although LLs of the 95% CI for both estimates were low. In the $10^{5.2}$ group, VE against any and severe RV GE was 55.7% and 71.0%, respectively. These VE estimates in both groups were lower than in the $10^{5.8}$ group, with LLs of the 95% CI less than 50%. In the $10^{4.7}$ group, VE estimates against any RV GE (62.4%) and severe RV GE (78.3%) during the combined period reached statistical significance, although the LLs of the 95% CI were less than 50%.

For all three groups, VE estimates against any wild-type G1 RV GE during Year 1 were statistically significant ($10^{4.7}$ - 59.5%, $10^{5.2}$ – 79.6%, $10^{5.8}$ – 76.4%), although LLs of the 95% CIs for all 3 estimates were less than 50%. VE estimates against any G9 RV GE did not reach statistical significance for any group, while VE against G2, G3, or G4 types were not calculated individually due to limited numbers of cases. When any non-G1 RV GE episodes were pooled together, VE was 60.9% for the $10^{5.8}$ group, although the lower 95% CI limit was only 7.2%.

VE estimates against severe wild-type G1 RV GE during year 1 were statistically significant for the $10^{5.2}$ group (75.3%) and $10^{5.8}$ group (87.8%); LLs of the 95% CI were below 50% for both estimates.

VE against severe G9 RV GE was also statistically significant for the $10^{4.7}$ and $10^{5.8}$ groups (70.2% and 77.4%, respectively; LLs of the 95% CI ≤ 50% for both). VE against pooled severe non-G1 RV GE reached statistically significance for all groups ($10^{4.7}$ - 71.5%, $10^{5.2}$ – 65.2%, $10^{5.8}$ – 82.7%); LLs of the 95% CI were all below 50%.

During Year 2, statistically significant VE was not observed against any wild-type G1 RV GE and severe G1 RV GE, or for any or severe pooled non-G1 RV GE. Over the combined period, statistically significant VE against any wild-type G1 RV GE was observed for the $10^{4.7}$ group (77.6%), while statistically significant VE against severe wild-type G1 RV GE was observed for the $10^{4.7}$ (81.2%) and the $10^{5.8}$ group (90.4%). All of these estimates were associated with LLs of the 95% CI less than 50%. VE estimates for any and severe pooled non-G1 RV GE did not reach statistical significance for either period.

Rotarix was efficacious during Year 1 against RV GE hospitalization in the $10^{5.8}$ group (79%; LL of 95% CI: 24.9%) and $10^{5.2}$ group (93.0%).

Analyses of immune responses to routine childhood vaccinations demonstrated that there were no significant differences between treatment groups in seroprotection rates, seropositivity rates, or GMC/GMTs to any of the vaccine antigens that did not favor any of the Rotarix groups. Although there appeared to be no impact of Rotarix at any concentration on the immune responses to routine co-administered and separately administered vaccine antigens, clinical limits for non-inferiority of Rotarix compared to placebo were not pre-defined for this study.

Safety was also demonstrated throughout the trial. No deaths were seen throughout the study. SAEs were relatively infrequent, and distributions by WHO Preferred Term were not noticeably different between groups. None of the SAEs were assessed as related to Rotarix/placebo vaccination. Only 1 case of IS was observed, occurring in a Rotarix recipient ($10^{4.7}$group) 6 months post-Dose 2.

Overall rates of subjects who experienced any solicited/unsolicited AE, Grade 2/3 AEs, Grade 3 AEs, or vaccine-related AEs from Day 0 to Day 14 post-dose were similar between treatment groups. Increases in symptoms between Dose 1 and Dose 2 were not observed. Rates for each solicited symptom were not significantly different between groups. The percentages of subjects with at least one unsolicited AE from Day 0 to Day 42 post-dose were similar between groups. The percentages of subjects with at least one Grade 3 unsolicited AE was less in the Rotarix group compared to the placebo group. Overall, there were no noticeable differences between groups for any unsolicited AE by WHO Preferred Term.

The validity of the results was strengthened by the double-blinded, placebo-controlled, study design. Efficacy, safety, and immunogenicity endpoints, case definitions, and study cohorts were clearly defined and appropriate. Overall, the study was well-conducted without any noticeable sources of biases. Data quality was acceptable, and appropriate data analyses were conducted as stated in the protocol and amendments. Protocol deviations were balanced between groups. Subject dropouts and missing data were handled appropriately and according to protocol.

Results from Rota-006 support the use of Rotarix in the prevention of any and RV GE. Efficacy data supports the use of Rotarix in the prevention of any and severe RV GE caused by G1 wild-type strains and severe G9 RV GE during Year 1, although LLs of the 95% CIs were all less than 50%. Except for G9, VE against other individual serotypes could not be adequately assessed due to limited GE cases caused by each non-G1 serotype. When non-G1 types were pooled together, efficacy against any and severe RV GE during Year 1 was demonstrated, although LLs of the 95% CIs for these estimates were low.

9 Overview of Efficacy Across Trials

9.1 Indication # I: Prevention of rotavirus gastroenteritis caused by G1 and non-G1 types

9.1.1 Methods

Four studies that contained efficacy data were reviewed: Rota-004, Rota-006, Rota-023, and Rota-036. Rota-023 and Rota-036 were pivotal Phase III studies that evaluated VE of two doses of Rotarix at $10^{6.5}$ $CCID_{50}$ per dose, the potency intended for licensure. Doses in both studies were administered either 1 or 2 months apart. In Rota-023, 17,867 infants 6-13 weeks of age from 11 Latin American countries were included in the Year 1 ATP efficacy cohort (see table below). In Rota-036, 3874 infants 6 to 14 weeks of age from 6 European countries were included in the Year 1 ATP efficacy cohort. Rota-004 and Rota-006 were Phase IIb studies conducted in infants 6-12 weeks of age that provided supportive efficacy data. Rota-004 evaluated two doses of Rotarix at $10^{5.3}$ $CCID_{50}$ per dose, administered 2 months apart. Rota-006 evaluated two doses of Rotarix at 3 different potencies ($10^{5.3}$ $CCID_{50}$, $10^{5.6}$ $CCID_{50}$, and $10^{6.6}$ $CCID_{50}$ per dose), administered 2 months apart. In addition, Rota-006 evaluated VE of three doses of Rotarix at each of the three potencies in subset of subjects. All four studies also evaluated anti-RV IgA immunogenicity of Rotarix in a subset of subjects. For further details of each study, please refer to sections 8.1.1, 8.1.2, 8.1.3, and 8.1.4 of this report.

Study #	Phase	TVC Year 1 Efficacy	TVC Year 2 Efficacy	ATP Year 1 Efficacy	ATP Year 2 Efficacy	ATP Combined Period Efficacy	ATP immunogenicity
Rota-004	IIb	Total-381* Rotarix-255 Placebo-126	Total-374 Rotarix-251 Placebo-123	Total-368 Rotarix-245 Placebo-123	Total-361 Rotarix-241 Placebo-120	Total-368 Rotarix-245 Placebo-123	Total-321 Rotarix-209 Placebo-112
Rota-006 (2-dose)	IIb	Total-2044* $10^{5.3}$/ 507 $10^{5.6}$/ 508 $10^{6.6}$/ 512 Placebo/ 517 Total-2155** $10^{5.3}$/ 538 $10^{5.6}$/ 540 $10^{6.6}$/ 540 Placebo/ 537	Total-517 $10^{5.3}$/ 127 $10^{5.6}$/125 $10^{6.6}$/ 134 Placebo/ 131	Total-1846 $10^{5.3}$/ 468 $10^{5.6}$/ 460 $10^{6.6}$/ 464 Placebo/ 454	Total-441 $10^{5.3}$/ 116 $10^{5.6}$/102 $10^{6.6}$/ 114 Placebo/ 109	Total-441 $10^{5.3}$/ 116 $10^{5.6}$/102 $10^{6.6}$/ 114 Placebo/ 109	Total-1526 $10^{5.3}$/ 395 $10^{5.6}$/377 $10^{6.6}$/ 381 Placebo/ 373
Rota-023	III	Total-20,169** Rotarix-10,159 Placebo-10,010	Total-15,813 Rotarix-7669 Placebo-7514	Total-17,867 Rotarix-9009 Placebo-8558	Total-14,237 Rotarix-7175 Placebo-7062	Total-14,286 Rotarix-7205 Placebo-7081	Total-734 Rotarix-393 Placebo-341
Rota-036	III	Total-3994** Rotarix-2646 Placebo-1348		Total-3874 Rotarix-2572 Placebo-1302	Total-3848 Rotarix-2554 Placebo-1294	Total-3874 Rotarix-2572 Placebo-1302	Total-1216 Rotarix-794 Placebo-422

*Follow-up from 2 weeks post-Dose 2; ***Follow-up from Dose 1

9.1.2 General Discussion of Efficacy Endpoints

Primary and secondary RV-related efficacy endpoints for each study are listed in the table below. In Rota-006 and Rota-036, the primary endpoint was the occurrence of any wild-type RV GE during the Year 1 efficacy period (i.e. 1st efficacy follow-up period). In Rota-023, the primary endpoint was the occurrence of severe wild-type RV GE during the Year 1 efficacy period. In Rota-004, primary endpoints included the occurrence of any and severe wild-type RV GE during the Year 1 efficacy period. Year 1 efficacy period for Rota-006 and Rota-023 was defined as the time from 2 weeks post-Dose 2 until 1 year of age. Year 1 efficacy period for Rota-004 and Rota-036 was defined as the time from 2 weeks post-Dose 2 until the end of the 1st RV season. In Rota-004, the 1st RV season covered December 1, 2000 to June 1, 2001. In Rota-036, the RV season covered the beginning of December 2004 to the end of May 2005.

Secondary endpoints common to Rota-004, Rota-006, and Rota-036 included severe RV GE during Year 1, any and severe RV GE due to heterologous types (i.e. G1 and non-G1) during Year 1, severe RV GE during Year 2, and any and severe RV GE during the combined period. Additional endpoints common to Rota-006 and Rota-036 included RV GE hospitalization during Year 1 and any RV GE during Year 2. Other endpoints specific to each study are noted in the table below.

Secondary endpoints for Rota-023 only involved severe RV GE: severe wild-type G1 RV GE during all 3 study periods, severe non-G1 RV GE during Year 1, and severe RV GE (all wild-type, wild G1, non-G1) from Dose 1 to the end of Year 1.

For secondary endpoints in Rota-004 and Rota-023, the Year 2 efficacy period was defined as the time from end of Year 1 until 2 years of age, while the combined period was the time from 2 weeks post-Dose 2 until 2 years of age. In Rota-006 and Rota-036, the Year 2 efficacy period went from the end of Year 1 until the end of the 2nd RV season, with the combined period extending from 2 weeks post-Dose 2 until the end of the 2nd RV season.

Study #	Primary Efficacy Endpoint	Secondary RV-related Efficacy Endpoints
Rota-004	Any/severe wild RV GE (ELISA) – Year 1	- Any/severe wild RV GE (RT-PCR) – Year 1 - Severe wild RV GE (ELISA, RT-PCR) – Year 2 - Any/severe wild RV GE (ELISA, RT-PCR) – combined period - Any/severe RV GE by G type – Year 1, Year 2, combined
Rota-006	Any wild RV GE – Year 1	- Severe wild RV GE – Year 1 - Any/severe wild RV GE due to heterologous types – Year 1 - Wild RV GE hospitalization – Year 1 - Any/severe wild RV GE – Year 2 - Any/severe wild RV GE – Combined period
Rota-023	Severe wild RV GE – Year 1	- Severe wild G1 RV GE – Year 1, Year 2, combined period - Severe non-G1 RV GE, pooled – Year 1 - Severe non-G1 RV GE, by individual type – Year 1 - Severe RV GE (wild, wild G1, non-G1 pooled, non-G1 individual) – Dose 1 to end of Year 1 - Severe wild RV GE, using Vesikari scale – Year 1
Rota-036	Any wild RV GE – Year 1	- Severe wild RV GE – Year 1, Year 2, combined period - Any/severe wild G1 RV GE – Year 1 - Severe wild G1 RV GE – Year 2, combined period - Any/severe non-G1 RV GE – Year 1 - Severe non-G1 RV GE – Year 2, combined period - Wild RV GE hospitalization – Year 1, Year 2, combined period - Wild RV GE medical – Year 1, Year 2, combined period - Any/severe wild RV GE – Dose 1 to end of Year 1

The choice of primary endpoints for all studies was appropriate because of the large burden of RV GE during the first year of life, and because the disease burden of severe RV disease (i.e. diarrhea and dehydration) is highest between 5-11 months of age. These endpoints therefore provided reasonable assessments of primary clinical benefit. Secondary endpoints were also appropriately chosen because they allowed assessment of cross-protection against other circulating heterologous serotypes, many of which had G and/or P components similar to those in the vaccine. Endpoints measured during Year 2 allowed the assessment of persistence of vaccine protection during a period when children remain susceptible to any and severe RV disease. In addition, an early Phase II placebo-controlled trial involving 2 doses of uncloned 89-12 RV strain (developed by Avant immunotherapeutics) used endpoints of any RV GE and very severe RV GE (Vesikari score >14 points) during Year 1, Year 2, and the 2-year combined period after vaccination.

In all studies, any RV GE and severe RV GE were accurately identified and reported using well-defined case definitions. Definitions for ***diarrhea*** and ***vomiting*** were identical in all studies. The definition of ***GE*** was diarrhea in Rota-004 and diarrhea with or without vomiting in Rota-006, Rota-

023, and Rota-036. The definition of ***RV GE*** (an episode of GE in which RV other than vaccine strain is identified in a stool sample collected no later than 7 days after GE symptom onset) was identical in Rota-004, Rota-006, and Rota-036. In Rota-023, the primary endpoint definition of ***severe RV GE*** was an episode of RV GE requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility. In all studies, including Rota-023 (secondary endpoint), ***severe RV GE*** was defined as an episode of RV GE with a Vesikari score ≥ 11 points. The Vesikari 20-point scale, which has been accepted internationally and widely used, measures the following: intensity/frequency and duration of diarrhea and vomiting, degree of fever and dehydration, and type of treatment. This scale, unlike the Clark scale used in the *RotaTeq* (Merck) development program, takes into account both the degree of dehydration and type of treatment.

Rota-004, Rota-006, and Rota-036 conducted active follow-up of subjects for GE case ascertainment. In Rota-004, subjects were contacted every 2 weeks by telephone from 2 weeks post-Dose 2 until the end of Year 2. In Rota-006, subjects were visited weekly by study personnel from 1 week post-Dose 1 until the end of Year 2. In Rota-036, subjects were contacted weekly from 1 week post-Dose 1 until the end of Year 1 (i.e. end of the 1st RV season), every two weeks from the end of Year 1 until the beginning of the Year 2 RV season and weekly from the beginning of the Year 2 RV season until the end of Year 2. Rota-23 conducted GE ascertainment by contacting hospitals and other medical facilities in the study area at least twice a week. Subjects were also contacted or visited at least every 4 days by non-medical study personnel to identify severe cases not identified by medical facility surveillance, such as cases treated in facilities outside the surveillance system.

Individual GE diary cards were used in each study to collect daily temperature, stool and emesis data for each GE episode. Parents were also instructed in the collection, labeling, storage, and submission of stool samples for each GE episode. All collected stools were laboratory tested for the presence of RV by ELISA. ELISA testing was performed at the laboratory of Dr. R. Ward, Children's Hospital Medical Center, Cincinnati (Rota-004, Rota-006) or at GSK's laboratory in Belgium using a commercial ELISA kit "RotaClone" (Rota-023, Rota-036). Stools that tested positive for RV by ELISA were further analyzed for G and P type determination by RT-PCR followed by Reverse Hybridization assay (or optional sequencing) at Delft Diagnostic Laboratory, the Netherlands (Rota-023, Rota-036), or by RT-PCR followed by ---------- (or optional sequencing) at the Laboratory of ---------- Finland (Rota-004) or at GSK laboratory, Belgium (Rota-006). The Reverse Hybridization assay was also able to differentiate G1 vaccine virus from wild-type G1 RV. G1 type detected by RT-PCR was sequenced to differentiate G1 vaccine virus from wild-type G1 RV if the stool sample was collected up to 2 weeks post-Dose 2 (Rota-004) or 2 months post-Dose 2 (Rota-006).

In all studies, serum anti-RV IgA response, considered a standard measure of immunity in most field studies and vaccine trials, was measured at pre- and post-vaccination time points (1-2 months post-Dose 2, end of Year 1) in a subset of subjects using well-defined parameters. Anti-RV IgA responses were measured in Rota-004 and Rota-006 by ELISA at the laboratory of Dr. R. Ward (Cincinnati), and in Rota-23 and Rota-036 using the GSK ELISA in Belgium. Based on results of retesting of available samples from Rota-004, Rota-006, and a third BLA study (Rota-033) with the GSK ELISA, an agreement of 98.5% was demonstrated between both ELISA methods. However, seroconversion rates were higher with GSK ELISA due to increased sensitivity of the GSK assay.

Seropositivity was defined as an anti-RV IgA antibody concentration ≥ 20 U/mL. Seroconversion was defined as an anti-RV IgA antibody concentration ≥ 20 U/mL in a subject who was seronegative for RV pre-Dose 1. The cut-off value of ≥ 20 U/mL has been previously used as evidence of natural RV infection[49]. For both the ATP and TVC immunogenicity cohorts, seroconversion rates and GMC values were obtained at each specified time point.

In Rota-006, RV immunogenicity was also measured by ***vaccine take***, which was defined as anti-RV IgA seropositivity in any post-vaccination blood sample ***or*** detection of RV antigen by ELISA in any post-vaccination stool sample (including GE stool sample) in a previously RV-uninfected subject. Stool antigen ELISA testing was performed at the laboratory of Dr. Ward (Cincinnati). Any RV detected in stools from GE episodes was further typed at GSK's laboratory (Belgium), and any

G1 RV was sequenced to differentiate vaccine virus from wild-type strains. Vaccine take rates were calculated after each dose. Vaccine take was included as an immunogenicity parameter because in some cases, serum IgA antibodies are not detected post-vaccination despite evidence of RV shedding (and hence viral replication) in stools several days after vaccination. In studies of RotaShield, the oral rhesus-human reassortant RV vaccine, a similar method of measuring vaccine take was utilized, except that stool IgA was also included[51].

9.1.3 Study Design

Adequate and well controlled studies

All four studies were adequately conducted in a randomized, double-blinded, placebo-controlled manner. A randomization blocking scheme ensured that balance between treatment groups was maintained. The control vaccine had the same composition and appearance as Rotarix except that it did not contain vaccine virus. Prospectively identified endpoints and statistical analysis plans were not significantly amended ad-hoc. These study design characteristics resulted in minimal biases as reflected by lack of major imbalances in baseline characteristics between treatment groups or lack of questionable endpoint analytic results.

Assessment of benefit

Adequacy of duration of follow-up
As previously mentioned in section 9.1.2, the duration of follow-up for primary and secondary efficacy endpoints in all the trials were adequate and provided reasonable assessments of primary and secondary clinical benefits of vaccine protection.

Entry criteria
For inclusion into any of the studies, parental/guardian written informed consent was required, and the subject was required to be free of obvious health problems as established by pre-enrollment medical history and clinical examination. Rota-023 and Rota-036 also required that parents/guardians were able to comply with study procedures. The required age ranges at Dose 1 were the same or similar between studies: 6-12 weeks (Rota-004, Rota-006, Rota-023 except Chile), 6-13 weeks (Rota-023, Chile only), and 6-14 weeks (Rota-036). Additional inclusion criteria consisted of birth between 36-42 weeks gestation (Rota-004, Rota-006) and birth weight > 2000 grams (Rota-006, Rota-036).

The following exclusion criteria were common to all 4 studies:
- Any clinically significant history of chronic gastrointestinal disease or other serious medical condition as determined by the investigator
- Any immunosuppressive or immunodeficient condition, including HIV infection
- Chronic administration (>14 days) of immunosuppressive or other immune-modifying drugs since birth
- Use of any investigational or non-registered drug/vaccine other than study vaccine within 30 days before study vaccine/placebo, or planned use during study period
- History of allergic disease/reaction likely to be exacerbated by any vaccine component
- Administration of immunoglobulins/blood products since birth or planned administration during study period

The following exclusion criteria were common to Rota-004, Rota-006, and Rota-036:
- Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol within 14 days before and after any study dose]
- GE within 7 days before Dose 1 (warranted deferral of vaccination)
- Acute disease at the time of enrollment, i.e. moderate/severe illness with or without fever (warranted deferral of vaccination)

The following exclusion criteria were common to Rota-004 and Rota-006:
- Previous confirmed occurrence of RV GE

Reviewer Note: On page 69 of the Summary of Clinical Efficacy report, the applicant states that the exclusion criterion “Previous confirmed occurrence of RV GE” was common to all studies except Rota-023. However, this criterion was not included in the protocol for Rota-036.

The following exclusion criteria applied to Rota-036:
- History of use of experimental RV vaccine

In addition, because Rota-006 and Rota-036 evaluated the immune response to co-administered routine vaccine antigens, the following exclusion criteria applied:
- Previous vaccination against diphtheria, tetanus, pertussis, and *H. flu* type b (for Rota-036, also previous vaccination against meningococcal group C in Spain and *S. pneumoniae* in France/Germany)
- History of vaccine-preventable diseases mentioned above

Overall, all 4 studies included healthy infants of relatively similar age ranges at Dose 1, while excluding infants with histories of gastrointestinal disorders or other serious medical conditions and infants who were immunosuppressed or immunodeficient. Therefore, the generalizability of Rotarix efficacy and immunogenicity results across studies is adequate.

In Rota-023 and Rota-036, previous confirmed RV GE was not an exclusion criterion, thereby potentially affecting efficacy and immunogenicity results if rates of pre-vaccination RV GE were different between vaccine and control groups. However, in Rota-023, pre-Dose 1 anti-RV IgA seropositivity rates in the TVC immunogenicity cohort were low (Rotarix-4.5%, placebo-3.5%). Similar pre-Dose 1 seropositivity results were seen in Rota-036 (TVC immunogenicity cohort: 2.1% in each group), indicating that previous exposure to RV infection was uncommon among Rotarix and placebo recipients in these two studies.

In Rota-004, Rota-006, and Rota-023, a history of experimental RV vaccination was not an exclusion criterion, thereby also potentially affecting efficacy and immunogenicity results. The applicant did not provide information on RV vaccination histories of subjects in these 3 studies. However, pre-Dose 1 anti-RV IgA seropositivity rates in the TVC immunogenicity cohorts in Rota-023, Rota-006 (1.5 - 2.5% in each arm), and Rota-004 (0% in each arm) indicate that previous RV vaccination was uncommon if not rare.

Adequacy of dose finding
As mentioned in section 9.1.2, a Phase II placebo-controlled trial of the 89-12 vaccine (Avant Immunotherapeutics) was conducted using any RV GE and very severe RV GE endpoints. In this trial, two doses of vaccine at $10^{5.0}$ffu/dose (<$10^{5.0}$ $CCID_{50}$/dose) were administered 6-10 weeks apart[49]. VE against any RV GE from post-Dose 2 to the end of the 1st RV season was 89% (95% CI: 65.4-96.5%) [49]. VE against very severe RV GE (>14 points) during the same interval was 100% (no CIs due to low numbers) [49].

In Rota-004, 2 doses of Rotarix ($10^{5.3}$ $CCID_{50}$ titer) administered 2 months apart demonstrated 73.0% efficacy against any RV GE and 90.0% efficacy against severe RV GE during Year 1, as well as 80.4% and 75.7% anti-RV IgA seroconversion rates at 1 month post-Dose 2 and at the end of Year 1, respectively (see section 9.1.4). Subsequently, Rota-006 ($10^{5.3}$ $CCID_{50}$, $10^{5.6}$ $CCID_{50}$, or $10^{6.6}$ $CCID_{50}$ titers; 2 doses 2 months apart) demonstrated a trend toward higher efficacy against any and severe RV GE with increasing titer (see section 9.1.4). Anti-RV IgA seroconversion rates at 2 months post-Dose 2 and at the end of Year 1 also increased with increasing vaccine titer. Based on these clinical results along with stability testing data, the applicant selected a titer of at least $10^{6.0}$ $CCID_{50}$ at the end of shelf-life for commercial use. In order to guarantee this end of shelf-life titer, the release specification was set at ------- $CCID_{50}$ per vial. The vaccine titer used in the two pivotal Phase III trials was $10^{6.5}$ $CCID_{50}$/dose, administered 1 or 2 months apart.

9.1.4 Efficacy Findings

As mentioned in section 9.1.3, subjects enrolled and vaccinated in these studies were healthy infants without significant past medical histories. In the ATP efficacy cohorts, the median age at

Dose 1, male:female ratio, and median height and weight were similar across studies. In Rota-004 and Rota-036, both conducted in Europe, nearly all subjects were Caucasian. In Rota-023, conducted in multiple Latin American countries, most of the subjects were Hispanic. Rota-006, also conducted in Latin America, enrolled nearly 75% of subjects who were of mixed ancestry.

The proportion of study dropouts and reasons for withdrawal were similar between treatment groups in each study, with most dropouts due to reasons other than SAEs or non-SAEs. The median duration of follow-up for Year 1 efficacy was 5.6 months for Rota-004, 7 months for Rota-006, 8 months for Rota-023, and 6 months for Rota-036.

Year 1 efficacy/immunogenicity – any RV GE
A summary of VE against RV GE-related endpoints and immunogenicity results for all four studies (ATP cohorts) can be found in Table 1 and Table 2 below. In Rota-036, the only pivotal Phase III trial that evaluated efficacy against any RV GE, Year 1 efficacy was 87.1% against any RV GE, 79.3% against any pooled non-G1 RV GE, 95.6% against any wild G1 RV GE, 88.3% against any G4 RV GE, and 75.6% against any G9 RV GE. Although VE against any G3 RV GE was 89.9%, the lower level of the 95% CI was only 9.5%. VE against any G2 RV GE was not statistically significant due to limited numbers of cases. Overall, these data indicate that Rotarix at the proposed licensing dose of $10^{6.5}$ $CCID_{50}$ was highly effective against any RV GE during Year 1 of follow-up, and provided good cross-protection against non-G1 strains when pooled together and analyzed individually.

Findings from Rota-036 were also supported by Rota-006 in the $10^{6.6}$ $CCID_{50}$cohort, where VE against any RV GE, any wild G1 RV GE, and any pooled non-G1 RV GE was 70.0%, 76.4%, and 60.9%, respectively. A smaller sample size in this subset compared to the Rota-036 study cohort may have contributed to the lower estimates and lower LLs of the 95% CIs. However, these results may also reflect previous findings with other live oral vaccines (OPV, *RotaShield*) that demonstrated lower immunogenicity in infants in developing countries (Rota-006 was conducted in Brazil, Mexico, and Venezuela) [52, 53]. Lower anti-RV IgA seroconversion rate (65.3%) and GMC (70.7 U/mL) post-Dose 2 in subjects from the $10^{6.6}$ $CCID_{50}$ cohort of Rota-006 were also lower than figures from Rotarix recipients in Rota-036 (86.5% and 197.2 U/mL, respectively).

Although subjects in Rota-004 and the $10^{5.3}$ $CCID_{50}$ and $10^{5.6}$ $CCID_{50}$ treatment arms in Rota-006 were administered vaccine titers less than the proposed licensure dose, Year 1 VE against any RV GE was 73.0%, 58.4%, and 55.7%, respectively. Year 1 VE against any wild G1 RV GE was 64.9%, 59.9%, and 79.6%, respectively. For these 6 estimates, LLs of the 95% CIs were low. Differences in efficacy and IgA seroconversion rates and GMCs post-Dose 2, were observed between Rota-004 and the $10^{5.3}$ $CCID_{50}$ cohort of Rota-006 (see Table 2). These differences could have been influenced by sample sizes and ethnic/environmental factors mentioned above.

VE against any G2 RV GE was also calculated in a post-hoc analysis by pooling cases for each endpoint together from all studies, including cases from the lower potency groups in Rota-004 and Rota-006. As a result, pooled VE was 78.3% (LL 95% CI: 18.4%) against any G2 RV GE. However, upon further consultation with the CBER biostatistical reviewer, these results will not be acceptable to demonstrate efficacy against G2 RV GE.

In Rota-036 and Rota-006, VE from Dose 1 to the end of Year 1 follow-up was calculated using TVCs. VE against any RV GE was 87.3% in Rota-036 and 72.2% in Rota-006 ($10^{6.6}$group).

The impact of breastfeeding on VE and immunogenicity was evaluated in Rota-036.
The percentages of subjects who were breastfed at the time of vaccination (one dose and both doses) were similar between groups. VE against any RV GE among subjects that breastfed at the

time of at least one dose was similar to VE among subjects not breastfed at any of the doses (86.0% vs. 90.8% respectively). Post-Dose 2 seroconversion rates and GMCs were comparable between the 2 feeding strata (85.5% vs. 89.2% and 185.8 U/mL vs 231.5 U/mL; overlapping 95% CIs for both comparisons were present). These results indicate that breastfeeding did not impact either VE or immunogenicity.

As mentioned in section 9.1.2, vaccine take as a measure of immunogenicity was assessed in Rota-006. At post-Dose 1 and post-Dose 2 time points, vaccine take rates were slightly higher than seroconversion rates. Vaccine take after any dose was 75.5% in the $10^{6.6}$group.

Year 1 efficacy/immunogenicity – severe RV GE

Rota-036, Rota-004, and Rota-006 evaluated all severe RV GE efficacy endpoints using the Vesikari scale. In contrast, Rota-023 based all but one endpoint (severe RV GE using the Vesikari scale) on a clinical case definition of severe RV GE. In Rota-023, VE was 84.7% (84.8% using the Vesikari scale) against severe RV GE, 91.8% against severe wild G1 RV GE, 75.4% against severe pooled non-G1 RV GE, 87.7% against severe G3 RV GE (LL of 95% CI: 8.3%), and 90.6% against severe G9 RV GE. Cross-protection against non-G1 strains when pooled and analyzed individually was thus demonstrated. VE against severe G2 RV GE did not reach statistical significance, and VE against severe G4 RV GE was not calculated, both due to limited case numbers. VE against hospitalized RV GE was 85.0%.

In Rota-036, VE against severe RV GE was 95.8%, higher than in Rota-023. Higher efficacy was also demonstrated against severe G1 RV GE (96.4%), severe pooled non-G1 RV GE (95.4%), severe G3 RV GE (100%; (LL of 95% CI: 44.8%), severe G4 RV GE (100%), severe G9 RV GE (94.7%), and hospitalized RV GE (91.8%). VE against RV GE leading to any medical attention, evaluated only in Rota-036, was 91.8%. Seroconversion rate and GMC one to two months post-Dose 2 were also higher in Rota-036 than in Rota-023 (86.5% vs 76.8% and 197.2 U/mL vs 102.6 U/mL). These differences suggest that although Rotarix vaccination resulted in high efficacy in both Latin America and Europe, protection and immunogenicity among subjects may be higher in developed countries as compared to less developed countries, consistent with previous observations using other live oral vaccines[52, 53].

Rota-036 also evaluated VE using the Clark scale, previously used in the evaluation of *RotaShield*. VE against severe RV GE (93.3%), severe G1 (93.7%), severe pooled non-G1 (92.8%), and severe G9 (91.6%) RV GE were slightly lower than the same VE estimates using the Vesikari scale.

Efficacy against severe RV GE was also seen in Rota-004 and Rota-006. In the$10^{6.6}$ $CCID_{50}$ group from Rota-006, VE was 85.6% against severe RV GE, 87.8% (LL 95% CI: 48.0%) against severe G1 RV GE, 82.7% (LL 95% CI: 40.3%) against severe pooled non-G1 RV GE, 77.4% (LL 95% CI: 17.8%) against severe G9 RV GE, and 79.0% (LL 95% CI: 24.9%) against hospitalized RV GE. Despite using lower vaccine potency ($10^{5.3}$ $CCID_{50}$) and a smaller sample size, Rota-004 showed a VE of 90% (LL 95% CI: 10.3%) against severe RV GE. VE against severe RV GE in the $10^{5.3}$ $CCID_{50}$ group from Rota-006 was 65.8% (LL 95% CI: 32.2%).

VE against severe G2 RV GE was also calculated in a post-hoc analysis by pooling cases for each endpoint together from all studies, including cases from the lower potency groups in Rota-004 and Rota-006. Using the Vesikari scale for all cases (including cases from Rota-023), pooled VE was 71.4% (95% CI: 20.1-91.1%) against severe G2 RV GE. As stated above, these results will not be acceptable to demonstrate efficacy against G2 RV GE.

In Rota-023, Rota-036, and Rota-006, VE from Dose 1 to the end of Year 1 follow-up was calculated using TVCs. VE against severe RV GE was 81.1% in Rota-023, 96.0% in Rota-036, and

88.1% in Rota-006 ($10^{6.6}$group).

Year 2 efficacy – any RV GE
In Rota-036, statistically significant vaccine protection during the Year 2 follow-up period was demonstrated against any RV GE (71.9%), any wild G1 RV GE (83.5%), any pooled non-G1 RV GE (68.2%), and any G9 RV GE (71.2%). Protective efficacy against any RV GE (72.8%) and any wild G1 RV GE (77.4%) was also seen in Rota-004, although LLs of the 95% CIs were low. None of the estimates in Rota-006 reached statistical significance due to limited numbers of cases.

Year 2 efficacy/immunogenicity – severe RV GE
Protective efficacy against severe RV GE endpoints during Year 2 follow-up was observed in both pivotal trials, with all VE estimates being higher in Rota-036 than Rota-023 (see Table 1). In Rota-023, VE against severe RV GE was 79.0% (81.5% using the Vesikari scale), while in Rota-036, VE against the same endpoint was 85.6%. VE against hospitalized RV GE was 81.5% in Rota-023 and 92.2% in Rota-036. In Rota-023, VE was 81.5% against severe G1 RV GE, 80.1% against severe pooled non-G1 RV GE, 63.1% against severe G4 RV GE, and 87.7% against severe G9 RV GE. However, the LL of the 95% CI for VE against severe G4 RV GE was low (34.5% and 0.7%, respectively). In Rota-036, VE was 96.5% against severe G1 RV GE, 80.8% against severe pooled non-G1 RV GE, and 77.7% against severe G9 RV GE. In addition, VE against severe G2 RV GE (89.9%; LL 95% CI = 9.4%) was demonstrated, the first time an endpoint involving G2 type resulted in statistically significant VE in any of the studies.

In Rota-004, VE efficacy against severe RV GE (83.4%; LL 95% CI: 7.2%) and severe G1 RV GE (91.7%; LL 95% CI: 31.6%) was observed. Although immunogenicity analyses indicated a drop in seroconversion rates and GMCs from Year 1 to Year 2, 67.2% of Rotarix subjects were seropositive for anti-RV IgA antibodies at the end of Year 2. VE against these same endpoints did not reach statistical significance in Rota-006.

Combined period efficacy (Year 1 and Year 2) – any RV GE
VE against RV GE was demonstrated for the combined efficacy follow-up period. In Rota-036, VE was 78.9% against any RV GE and 89.8% against any G1 RV GE. In addition, VE against any pooled non-G1 RV GE was 72.9% and VE estimates against G2 (58.3%; LL 95% CI: 10.1%), G3 (84.8%; LL 95% CI: 41.0%), G4 (83.1%), and G9 (72.9%) types were all statistically significant. In Rota-004, VE against any RV GE and any G1 RV GE was 71.6% and 72.6%, respectively. In Rota-006, VE against any RV GE and any G1 RV GE was 62.4% and 77.6%, respectively. The LLs of the 95% CIs for the estimates from Rota-004 and Rota-006 were less than 50%.

In Rota-036 and Rota-006, VE from Dose 1 to the end of Year 2 follow-up was calculated using TVCs. VE against any RV GE was 79.4% in Rota-036 and 38.0% (LL 95% CI = -7.5%) in Rota-006 ($10^{6.6}$group).

Combined period efficacy (Year 1 and Year 2) – severe RV GE
Protective efficacy against severe RV GE was also demonstrated during the combined efficacy period. In Rota-023, VE against severe RV GE was 80.5% (82.5% using the Vesikari scale), while in Rota-036, VE against the same endpoint was 90.4%. VE against hospitalized RV GE was 83.0% in Rota-023 and 96.0% for Rota-036. In Rota-023, statistically significant VE was observed against severe G1 (82.1%), severe pooled non-G1 (77.5%), severe G3 (78.9; LL 95% CI: 24.5%), severe G4 (61.8%; LL 95% CI: 4.1%), and severe G9 RV GE (86.6%). In Rota-036, efficacy was observed against severe G1 (96.4%), severe pooled non-G1 (87.7%), severe G2 (85.5%; LL 95% CI: 24.0%), severe G3 (93.7%), severe G4 (95.4%), and severe G9 RV GE (85.0%).

In Rota-006 ($10^{6.6}$group), VE was 92.6% against severe RV GE and 90.4% (LL 95% CI: 32.8%) against severe G1 RV GE, figures similar to Rota-036 and higher than Rota-023. In Rota-004, VE against these two endpoints were 84.9% (LL 95% CI: 41.5%) and 90.0%, respectively.

In Rota-023, Rota-036 and Rota-006, VE from Dose 1 to the end of Year 2 follow-up was calculated using TVCs. VE against any RV GE was 80.3% in Rota-023, 90.7% in Rota-036 and 86.1% in Rota-006 ($10^{6.6}$group).

RV immunogenicity – other BLA studies
Anti-RV IgA responses were also measured in all or a subset of subjects from Rota-005, Rota-007, Rota-014 and Rota-033 by ELISA at the laboratory of Dr. R. Ward (Cincinnati), and in Rota-039, Rota-048, and Rota-060 by GSK ELISA in Belgium. Vaccine take rates were calculated in all studies except Rota-060.

Among subjects in Rota-005, Rota-007, Rota-039, Rota-048, and Rota-060 who were administered Rotarix at a potency of at least $10^{6.6}CCID_{50}$ per dose, anti-RV IgA rates at 1 to 2 months post-Dose 2 ranged from 78.2- 88.3%, comparable to seroconversion rates for Rota-023 and Rota-036 (see Tables 3 and 4 below). GMCs at 1-2 months post-Dose 2 ranged from 117.0- 188.2 U/mL, also similar to GMCs for Rota-023 and Rota-036; the only exception was in Rota-048, where 1 month post-Dose 2 GMC was 360.6 U/mL.

In Rota-005, where most of the subjects were from the U.S., 1-2 month post-Dose 2 seroconversion rate (78.2%) and GMC (117.0 U/mL) were less than estimates from Rota-036 (86.5% and 197.2 U/mL). Although the sample size of the ATP immunogenicity cohort was larger in Rota-036 than in Rota-005 (794 vs 209), the median age at Dose 1 was also higher in Rota-036 than in Rota-005 (11.0 weeks vs 9 weeks)
Reviewer Note: On page 57 of the Summary of Clinical Efficacy, the applicant labeled Table 18 as "Anti-HRV IgA seroconversion rates and GMCs two months after dose 2 in study Rota-007 (ATP cohort for immunogenicity)." However, on page 107 of the Rota-007 Study Report, the same rate and GMC were listed on line PII(M2) which meant "one month after the second dose of HRV vaccine or placebo (Visit 3)."

Vaccine take rates at 1-2 months after any dose (i.e. combined Dose 1 and Dose 2 take rate) ranged from 88.0- 97.8% (Rota-005: 88.0%), higher than in Rota-006 (75.5%). The highest vaccine take rate was observed in Rota-007 (97.8%), the study with the oldest aged cohort (11-17 weeks at Dose 1).

<u>Rota-014</u>
Among the BLA studies, only Rota-014 allowed co-administration of OPV. Although Rotarix potency in this study ($10^{5.6}$ $CCID_{50}$ per dose) was below that of the licensure dose, interference of the anti-RV IgA immune response post-Dose 1 was observed in the Rotarix-OPV co-administered group compared to the Rotarix-IPV co-administered group. In the subset (ATP immunogenicity cohort) vaccinated before the RV season, the seroconversion rate for the HRV+OPV group was 13.3% (95% CI: 5.9-24.6%), lower than the 32.8% (95% CI: 21.0-46.3%) in the HRV+IPV group. GMC was <20 U/mL in the HRV+OPV group compared to 23.9 U/mL in the HRV+IPV group.

However, in this same subset, 1 month post-Dose 2 rates in the Rotarix+OPV group increased to 35.8% (95% CI: 23.1-50.2%) compared to 42.9% (28.8-57.8%) in the Rotarix+IPV group. Post-Dose 2 GMC was 28.1 U/mL in the HRV+OPV group compared to 32.6 U/mL in the HRV+IPV group. The GMC ratio (HRV+IPV/ HRV+OPV) was 1.2 (95% CI: 0.6-2.2). Seroconversion rates for the combined Rotarix doses were 40.7% (95% CI: 27.6-55.0%) for the HRV+OPV group and 50.0% (95% CI: 36.1-63.9%) for the HRV+IPV group. Vaccine take rates on combined Rotarix doses were

43.8% for the HRV+OPV group and 50.0% for the HRV+IPV group; the rate difference between the two groups was not statistically significant

Rota-033

Lot-to-lot consistency of 3 consecutive production lots of Rotarix ($10^{6.6}$group potency) was evaluated. The following lots were used:

Lot A: RVC018A42 (used in Rota-023 and Rota-036)
Lot B: RVC019A43 (used in Rota-023)
Lot C: RVC021A44 (used in Rota-023)

Subjects in each Rotarix lot group received 2 doses 2 months apart. Lots were considered to be consistent at 2 months post-Dose 2 if all 90% CIs for the ratio of GMCs between two lots were within the pre-specified interval (0.5-2.0). Post-hoc analyses were also performed using the following FDA criteria: 95% CIs of GMC ratios with the same pre-specified interval.

Anti-RV IgA seroconversion rates for each group using the Ward ELISA are summarized in the table below. Seroconversion rates appeared similar between all Rotarix groups. GMC of Lot B appeared lower compared to the other 2 lots.

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV lot A	**Pre**	154	0	0.0	0.0	2.4	<20	-	-
	PII(M4)	154	112	72.7	65.0	79.6	83.0	63.9	107.9
HRV lot B	**Pre**	166	0	0.0	0.0	2.2	<20	-	-
	PII(M4)	167	116	69.5	61.9	76.3	59.4	47.5	74.2
HRV lot C	**Pre**	173	0	0.0	0.0	2.1	<20	-	-
	PII(M4)	173	127	73.4	66.2	79.8	81.2	63.6	103.7
Placebo	**Pre**	91	0	0.0	0.0	4.0	<20	-	-
	PII(M4)	91	9	9.9	4.6	17.9	<20	-	-

N = number of subjects with available results; n/% = number/percentage of subjects with concentration above the cut-off
Pre = pre-vaccination; PII (M4) = two months after the second dose (Visit 3)
Adapted from Study Report Body Rota-033, pg 61

Using the GSK ELISA, 2-month post-Dose 2 seroconversion rates and GMCs were higher for each Rotarix lot compared to placebo. GMC of Lot B remained lower compared to the other 2 lots.

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV lot A	**PII(M4)**	147	126	85.7	79.0	90.9	142.8	110.0	185.5
HRV lot B	**PII(M4)**	162	132	81.5	74.6	87.1	119.1	93.1	152.3
HRV lot C	**PII(M4)**	176	149	84.7	78.5	89.6	152.0	118.7	194.8
Placebo	**PII(M4)**	87	12	13.8	7.3	22.9	<20	--	--

Adapted from Study Report Body Rota-033 Annex, pg 10

Comparison of seroconversion rates and GMCs between the two ELISA methods among subjects tested with both assays also demonstrated higher rates GMCs with the GSK ELISA than Ward ELISA.

		WARD assay								GSK assay							
			≥ 20 U/ml				GMC (U/ml)				≥20 U/ml				GMC (U/ml)		
					95% CI			95% CI				Value	95% CI				
Group	Timing	N	n	%	LL	UL	Value	LL	UL	N	n	%	LL	UL		LL	UL
HRV lot A	PRE	132	0	0.0	0.0	2.8	<20	-	-	132	0	0.0	0.0	2.8	<20	-	-
	PII(M4)	132	95	72.0	63.5	79.4	75.5	57.5	99.1	132	112	84.8	77.6	90.5	150.6	113.4	199.9

HRV lot B	**PRE**	157	0	0.0	0.0	2.3	<20	-	-	157	0	0.0	0.0	2.3	<20	-	-
	PII(M4)	157	110	70.1	62.2	77.1	61.6	48.9	77.7	157	127	80.9	73.9	86.7	120.7	93.7	155.4
HRV lot C	**PRE**	162	0	0.0	0.0	2.3	<20	-	-	162	0	0.0	0.0	2.3	<20	-	-
	PII(M4)	162	120	74.1	66.6	80.6	81.1	63.2	104.1	162	135	83.3	76.7	88.7	156.6	120.3	204.0
Pooled HRV	**PRE**	451	0	0.0	0.0	0.8	<20	-	-	451	0	0.0	0.0	0.8	<20	-	-
	PII(M4)	451	325	72.1	67.7	76.2	72.2	62.5	83.4	451	374	82.9	79.1	86.3	141.4	121.3	164.8
Placebo	**PRE**	84	0	0.0	0.0	4.3	<20	-	-	84	0	0.0	0.0	4.3	<20	-	-
	PII(M4)	84	9	10.7	5.0	19.4	<20	--	--	84	11	13.1	6.7	22.2	<20	-	-

Adapted from Study Report Body Rota-033 Annex, pg 16

Vaccine take rates (using the Ward ELISA) on combined Dose 1 and Dose 2 at Visit 3 were similar between lots as shown below.

Group	**Vaccine take on combined doses 1 and 2 at Visit 3**				
				95% CI	
	N	**n**	**%**	**L.L.**	**U.L.**
HRV lot A	7	5	71.4	29.0	96.3
HRV lot B	7	5	71.4	29.0	96.3
HRV lot C	12	9	75.0	42.8	94.5
Placebo	6	2	33.3	4.3	77.7

N = number of subjects with available anti-rotavirus IgA antibody result at visit 3, or who seroconverted at Visit 2, or with vaccine virus* in stools collected after Visit 1 to Visit 3
n/% = number/percentage of subjects who seroconverted at visit 2 or 3, or with vaccine virus* in stools collected after Visit 1 to Visit 3
*rotavirus in stools collected at pre-specified time points or vaccine virus in stools collected in case of gastroenteritis episode
Adapted from Study Report Body Rota-033, pg 68

GMC ratios (Ward ELISA) between pairs of lots are summarized in the table below. For each of the 3 ratios, the 90% CIs were within the 0.5-2.0 pre-specified interval defining consistency.

						Ratio of GMCs		**90 %CI**	
Group	**N**	**GMC**	**Group**	**N**	**GMC**	**groups**	**Value**	**LL**	**UL**
HRV lot A	154	83.0	**HRV lot B**	167	59.4	**HRV Lot A over HRV Lot B**	1.40	1.05	1.87*
HRV lot A	154	83.0	**HRV lot C**	173	81.2	**HRV Lot A over HRV Lot C**	1.02	0.77	1.36*
HRV lot B	167	59.4	**HRV lot C**	173	81.2	**HRV Lot B over HRV Lot C**	0.73	0.55	0.97*

N = number of subjects with available data
*lower and upper limits of the 90% CI within the pre-specified [0.5; 2] clinical limits interval for consistency
Source: Study Report Body Rota-033, pg 62

As noted in the table below, seroconversion rate differences (Ward ELISA) were not statistically significant, as the 90% CIs all included 0.

						Difference in seroconversion rate			
							Value	**90% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**groups**	**%**	**LL**	**UL**
HRV lot A	154	72.7	**HRV lot B**	167	69.5	**HRV lot A minus HRV lot B**	3.3	-5.1	11.5
HRV lot A	154	72.7	**HRV lot C**	173	73.4	**HRV lot A minus HRV lot C**	-0.7	-8.8	7.4
HRV lot B	167	69.5	**HRV lot C**	173	73.4	**HRV lot B minus HRV lot C**	-3.9	-12.0	4.1

N = number of subjects with available results; % = percentage of subjects who seroconverted at visit 3
Source: Study Report Body Rota-033, pg 62

Using FDA criteria of 95% CI for GMC ratio comparisons (Ward ELISA), the applicant was still able to demonstrate that the 95% CIs for each of the paired lot ratios fell within the 0.5-2.0 pre-specified limit interval defining consistency (see table below).

						Ratio of GMCs			
								95% CI	
Group	**N**	**GMC**	**Group**	**N**	**GMC U/mL**	**groups**	**Value**	**LL**	**UL**
HRV lot A	154	83.0	**HRV lot B**	167	59.4	**HRV Lot A over HRV Lot B**	1.40	0.99	1.98

HRV lot A	154	83.0	**HRV lot C**	173	81.2	**HRV Lot A over HRV Lot C**	1.02	0.72	1.44
HRV lot B	167	59.4	**HRV lot C**	173	81.2	**HRV Lot B over HRV Lot C**	0.73	0.52	1.02

Lower and upper limit of the 95% CI within the prespecified limit interval (0.5; 2) for consistency
Source: Summary of Clinical Efficacy, pg 112

Lot-to-lot consistency using the same FDA criteria was also demonstrated when the GSK ELISA was used to measure GMCs, as noted below.

Group	**N**	**GMC U/ml**	**Group**	**N**	**GMC U/ml**	**Ratio of GMCs**			
						groups	**Value**	**95% CI**	
HRV lot A	147	142.8	**HRV lot B**	162	119.1	**HRV lot A over HRV lot B**	1.20	0.83	1.72
HRV lot A	147	142.8	**HRV lot C**	176	152.0	**HRV lot A over HRV lot C**	0.94	0.66	1.34
HRV lot B	162	119.1	**HRV lot C**	176	152.0	**HRV lot B over HRV lot C**	0.78	0.55	1.11

Adapted from Study Report Body Rota-033 Annex, pg 10

Seroconversion rate differences (Ward or GSK ELISA) were also not statistically significant using 95% CIs.

Ward ELISA

Group	**N**	**%**	**Group**	**N**	**%**	**Difference in seroconversion rate**			
						groups	**Value %**	**95% CI**	
								LL	**UL**
HRV lot A	154	72.7	**HRV lot B**	167	69.5	**HRV lot A minus HRV lot B**	3.3	-6.7	13.1
HRV lot A	154	72.7	**HRV lot C**	173	73.4	**HRV lot A minus HRV lot C**	-0.7	-10.4	8.9
HRV lot B	167	69.5	**HRV lot C**	173	73.4	**HRV lot B minus HRV lot C**	-3.9	-13.5	5.7
HRV pooled	494	71.9	**Placebo**	91	9.9	**HRV pooled minus Placebo**	62.0	53.3	68.2

Source: Study Report Body Rota-033 Annex, pg 8

GSK ELISA

Group	**N**	**%**	**Group**	**N**	**%**	**Difference in seroconversion rate**			
						groups	**Value %**	**95% CI**	
								LL	**UL**
HRV lot A	147	85.7	**HRV lot B**	162	81.5	**HRV lot A minus HRV lot B**	4.2	-4.2	12.5
HRV lot A	147	85.7	**HRV lot C**	176	84.7	**HRV lot A minus HRV lot C**	1.1	-7.0	8.8
HRV lot B	162	81.5	**HRV lot C**	176	84.7	**HRV lot B minus HRV lot C**	-3.2	-11.3	4.8
HRV pooled	485	83.9	**Placebo**	87	13.8	**HRV pooled minus Placebo**	70.1	60.8	76.8

Adapted from Study Report Body Rota-033 Annex, pg 11

Reviewer Note: To explore the reasons for the low GMC in Lot B, additional statistical analyses were performed. GMCs and seroconversion rates were higher in Mexico than Peru and Colombia as a result of older age at vaccination (9 weeks vs 8 weeks and 8 weeks) and longer interval between Dose 1 and Dose 2 (64 days vs 51 and 58 days). Among the lots in Peru and Colombia, Lot B had the lowest GMC. Among the lots in Mexico, Lot B and Lot C had similarly low GMCs compared to Lot A.

When the applicant performed a second analysis using a 2-way ANOVA model to adjust for country effect, the adjusted GMCs were slightly higher than the unadjusted GMCs (Lot A- 93.4 U/mL, Lot B- 67.9 U/mL, Lot C – 90.2 U/mL). However, when analyses were performed using the adjusted GMCs (for country effect), criteria for consistency was still met for all 3 pair-wise comparisons. The applicant concluded that the lower GMC for lot B could be explained by random variability.

Rota-060

Seroconversion rates and GMC for the group co-administered Rotarix ($10^{6.5}$potency) and routine vaccines (co-ad group) and the group administered Rotarix separately from routine vaccines (sep-

ad group) are summarized in Table 3 below. Although blood samples were obtained at different time points (2 months post-Dose 2 for the sep-ad group; 3 months post-Dose 2 for the co-ad group), seroconversion rates were similar between groups, and the rate difference between the co-ad group minus the sep-ad group was not statistically significant (-7.16%, 95% CI: -15.84-1.98). The GMC ratio (co-ad/sep-ad) was statistically significant (0.58; 95% CI: 0.40-0.86), and may have been due to differences in blood collection time points and age at Rotarix vaccination (co-ad group: 2 and 4 months; sep-ad group: 3 and 5 months).

In the sep-ad group, the seroconversion rate (86.0%) and GMC (188.2 U/mL) measured at 2 months post-Dose 2 were similar to the 1-2 month post-Dose 2 seroconversion rate and GMC in Rota-036 (86.5% and 197.2 U/mL). Although the seroconversion rate (78.8%) and GMC (110.0 U/mL) in the co-ad group were lower than the sep-ad group and the subset in Rota-036, these measurements were taken 3 months post-Dose 2. These figures were also comparable to 1-2 month immunogenicity data from Rota-023 (76.8% and 102.6 U/mL) and 2-month post-Dose 2 estimates from Rota-005 (78.2% and 117 U/mL), and higher than 2-month post-Dose 2 data from the $10^{6.6}CCID_{50}$ group in Rota-006 (65.3% and 70.7 U/mL).

Breastfeeding and RV immunogenicity
The impact of breastfeeding on RV immunogenicity was evaluated in Rota-005, Rota-006, Rota-007, and Rota-036. All studies allowed unrestricted feeding prior to vaccination.

Rota-006
As mentioned in section 8.1.4, none of the 4 feeding criteria (exclusive breastfeeding, breastfeeding + formula feeding, feeding within 1 hour pre-vaccination, feeding within 30 minutes post-vaccination) had a significant effect on vaccine take.

Rota-036
The impact of breastfeeding on VE was evaluated only in Rota-036. As reviewed in section 8.1.2, feeding patterns were similar between treatment groups. VE against any RV GE for the 2 feeding strata (breastfed for at least one dose, not breastfed at any of the doses) were similar (86.0% versus 90.8%). Similarly, VE against severe RV GE was similar for each of the feeding strata (95.7% vs. 96.2%, respectively), indicating that breastfeeding had no impact on Rotarix VE. Visit 3 (1-3 months post-Dose 2) seroconversion rates and GMCs were similar by feeding category. Among subjects who were breastfed at one or more doses, the anti-RV IgA seroconversion rate and GMC in Rotarix recipients were 85.5% and 185.8 U/ml, respectively. Among non-breastfed subjects, the seroconversion rate and GMC in Rotarix recipients were 89.2% and 231.5 U/ml, respectively. 95% CIs for seroconversion rates and GMCs both overlapped between feeding strata.

Rota-005
The frequencies of different feeding criteria by dose number and by potency group for the ATP Immunogenicity Cohort are summarized below.

Dose	Group (CCID_50)	Feeding criteria						
		N	Breast milk		Infant formula		Both	
			n	%	n	%	n	%
1	HRV_5.6	170	70	41.2	78	45.9	22	12.9
	HRV_6.8	161	74	46.0	67	41.6	20	12.4
	Placebo	79	35	44.3	26	32.9	18	22.8
2	HRV_5.6	165	53	32.1	86	52.1	26	15.8
	HRV_6.8	155	53	34.2	82	52.9	20	12.9
	Placebo	76	26	34.2	35	46.1	15	19.7

N=number of subjects with available data
Adapted from Study Report Body Rota-005, pg 122

Immunogenicity analyses suggested that vaccine take rates were lower in subjects exclusively breastfed compared to subjects not breastfed. Among subjects that were only breastfed, the vaccine take rate on combined Doses 1 and 2 at Visit 3 (2 months post-Dose 2) was 72.3% (95% CI: 57.4-84.4%) in the $10^{5.6}CCID_{50}$ group and 83.7% (70.3-92.7%) in the $10^{6.8}CCID_{50}$ group. Among subjects not breastfed, the combined vaccine take rate was 89.9% (95% CI: 81.7-95.3%) in the $10^{5.6}CCID_{50}$ group and 89.3% (80.6-95.0%) in the $10^{6.8}CCID_{50}$ group. Among subjects both breastfed and formula fed, the combined vaccine take rate was 66.7% (95% CI: 43.0-85.4%) in the $10^{5.6}CCID_{50}$ group and 94.1% (71.3-99.9%) in the $10^{6.8}CCID_{50}$ group.
Results of an exploratory logistic regression analysis demonstrated that vaccine take was significantly lower in breastfed Rotarix recipients at both potencies (p=0.03). When other additional factors, such as formula feeding and timing of feeding, were added to breastfeeding exposure, the prediction of vaccine take did not improve (all p-values were >0.1)

Rota-007
No reliable conclusions about the impact of breastfeeding on RV immunogenicity could be made from this study because most of the subjects in the ATP cohort for immunogenicity were formula fed after Dose 1 ($10^{5.3}CCID_{50}$ - 78.7%, $10^{5.6}CCID_{50}$ - 75.9%, $10^{6.6}CCID_{50}$ - 73.7%) and Dose 2 ($10^{5.3}CCID_{50}$ - 84.4%, $10^{5.6}CCID_{50}$ - 79.7%, $10^{6.6}CCID_{50}$ - 79.6%). However, the combined anti-RV IgA seroconversion rate at Visit 2 (1 month post-Dose 1), Visit 3 (1 month post-Dose 2), or Visit 4 (2 months post-Dose 2) was similar between formula-fed and breastfed Rotarix recipients pooled from all dose potencies (93.3% vs 85.7%; overlapping 95% CIs).

In addition, among all Rotarix recipients, frequencies of feeding within 30 minutes after vaccination were low (after Dose 1 - 10%, after Dose 2 - 10%, after both doses - 3%); none of these subjects fed within 1 hour before vaccination. The combined anti-RV IgA seroconversion rate (i.e. seroconversion at Visit 2, Visit 3, or Visit 4) was 97.5% in subjects that fed within 30 minutes after Dose 1 only, 80% in subjects that fed within 30 minutes after Dose 2 only, 90.9% in subjects that fed within 30 minutes after both doses, and 93.2% in subjects not in the previous 3 categories (95% CIs of all 4 estimates were overlapping).

Maternal antibodies and RV immunogenicity
The effect of maternally acquired anti-RV antibodies on immunogenicity was assessed in a subset of subjects from Rota-004, Rota-006, and Rota-014. The levels of pre-vaccination maternal antibodies were higher in vaccine non-responders compared to responders after 2 doses. In general, subjects with seroconversion after Dose 1 had lower levels of maternal serum antibodies (anti-RV IgA and anti-RV neutralizing antibody) prior to vaccination than vaccine non-responders. However, it was also shown that seroconversion could be induced after administration of a second vaccine dose despite high levels of maternal antibodies.

Table 1: ATP efficacy summary (%, 95% CI)

Endpoint - RV GE	Rota-023 $10^{6.5}$ $CCID_{50}$	Rota-036 $10^{6.5}$ $CCID_{50}$	Rota-004 $10^{5.3}$ $CCID_{50}$#	Rota-006 (2-dose subset)		
				$10^{5.3}$ $CCID_{50}$	$10^{5.6}$ $CCID_{50}$	$10^{6.6}$ $CCID_{50}$
Year 1						
Any		87.1 (79.6, 92.1)	73.0 (27.1, 90.9)	58.4 (29.4, 76.3)	55.7 (25.3, 74.5)	70.0 (45.7, 84.4)
Any wild G1		95.6 (87.9, 98.8)	64.9 (-2.3, 88.6)	59.9 (18.9, 81.3)	79.6 (49.9, 93.1)	76.4 (44.9, 91.3)
Any non-G1 pooled		79.3 (64.6, 88.4)	NC	56.3 (-0.3, 82.5)	30.9 (-43.8, 67.7)	60.9 (7.2, 85.1)
Any G2		62.0 (-124.4, 94.4)	**	NC	NC	NC
Any G3		89.9 (9.5, 99.8)	NC	NC	NC	NC
Any G4		88.3 (57.5, 97.9)	NC	NC	NC	NC
Any G9		75.6 (51.1, 88.5)	**	48.3 (-30.0, 81.0)	7.9 (-105, 58.8)	54.3 (-19.0, 84.3)
Severe †	84.7 (71.7, 92.4)					

Severe ‡	84.8 (71.1, 92.7)	95.8 (89.6, 98.7)	90.0 (10.3, 99.8)	65.8 (32.2, 83.9)	71.0 (39.9, 87.2)	85.6 (63.0, 95.6)
Severe G1 §	91.8 (74.1, 98.4)	96.4 (85.7, 99.6)	87.4 (-26.8, 99.7)	57.6 (-9.0, 85.2)	75.3 (23.5, 94.0)	87.8 (48.0, 88.3)
Severe non-G1 pooled§	75.4 (50.0, 89.0)	95.4 (85.3, 99.1)	NC	71.5 (19.4, 91.8)	65.2 (7.4, 88.8)	82.7 (40.3, 96.8)
Severe G2 §	41.0 (-79.2, 82.4)	74.7 (-386.2, 99.6)	**	NC	NC	NC
Severe G3 §	87.7 (8.3, 99.7)	100 (44.8, 100)	NC	NC	NC	NC
Severe G4 §	NC	100 (64.9, 100)	NC	NC	NC	NC
Severe G9 §	90.6 (61.7, 98.9)	94.7 (77.9, 99.4)	NC	70.2 (3.4, 92.9)	54.4 (-28.5, 85.8)	77.4 (17.8, 95.9)
Hospitalized	85.0 (69.6, 93.5)	100 (81.8, 100)		65.4 (-1.8, 90.2)	93.0 (53.7, 99.8)	79.0 (24.9, 96.1)
Medical attention		91.8 (84.0, 96.3)				
Year 2						
Any		71.9 (61.2, 79.8)	72.8 (19.9, 91.8)	47.8 (-73.5, 86.3)	16.9 (-151, 73.7)	-16.9 (-219, 56.0)
Any wild G1		83.5 (69.3, 91.7)	77.4 (29.3, 93.8)	73.2 (-41.0, 97.3)	23.7 (-179, 80.9)	-9.3 (-254, 65.4)
Any non-G1 pooled		68.2 (52.6, 78.9)*	NC	**	**	**
Any G2		57.1 (-3.7, 82.6)	NC	NC	NC	NC
Any G3		79.7 (-23.8, 98.1)	NC	NC	NC	NC
Any G4		69.6 (-56.2, 95.3)	NC	NC	NC	NC
Any G9		71.2 (51.9, 83.1)	**	NC	NC	NC
Severe †	79.0 (66.4, 87.4)					
Severe ‡	81.5 (69.6, 89.3)	85.6 (75.8, 91.9)	83.4 (7.2, 98.4)	68.7 (-290, 99.4)	64.4 (-344, 99.3)	100 (-131, 100)
Severe G1 §	72.4 (34.5, 89.9)	96.5 (86.2, 99.6)	91.7 (31.6, 99.8)	68.7 (-290, 99.4)	64.4 (-344, 99.3)	100 (-131, 100)
Severe non-G1 pooled §	80.1 (65.6, 89.1)	80.8 (63.7, 90.4)*	NC	NC	NC	NC
Severe G2 §	**	89.9 (9.4, 99.8)	NC	NC	NC	NC
Severe G3 §	71.9 (-47.7, 97.1)	83.1 (-110.3, 99.7)	NC	NC	NC	NC
Severe G4 §	63.1 (0.7, 88.2)	87.3 (-28.0, 99.7)	NC	NC	NC	NC
Severe G9 §	87.7 (72.9, 95.3)	77.7 (53.0, 90.1)	**	NC	NC	NC
Hospitalization	81.5 (67.7, 90.1)	92.2 (65.6, 99.1)				
Medical attention		76.2 (63.0, 85.0)				
Combined period						
Any		78.9 (72.7, 83.8)	71.6 (41.6, 86.8)	62.4 (19.0, 83.9)	44.4 (-12.8, 73.9)	35.0 (-25.3, 67.1)
Any wild G1		89.8 (82.9, 94.2)	72.6 (42.2, 87.6)	77.6 (39.0, 93.4)	54.2 (-4.3, 81.5)	49.9 (-8.7, 78.2)
Any non-G1 pooled		72.9 (62.9, 80.5)*	NC	24.8 (-249, 85.1)	14.5 (-297, 83.0)	-14.7 (-375, 70.8)
Any G2		58.3 (10.1, 81.0)	**	NC	NC	NC
Any G3		84.8 (41.0, 97.3)	NC	NC	NC	NC
Any G4		83.1 (55.6, 94.5)	NC	NC	NC	NC
Any G9		72.9 (59.3, 82.2)	**	NC	NC	NC
Severe †	80.5 (71.3, 87.1)					
Severe ‡	82.1 (73.1, 88.5)	90.4 (85.1, 94.1)	84.9 (41.5, 97.3)	78.3 (21.1, 96.0)	50.7 (-39.1, 84.6)	92.6 (51.0, 99.8)
Severe G1 §	82.1 (64.6, 91.9)	96.4 (90.4, 99.1)	90.0 (52.9, 98.9)	81.2 (11.8, 98.0)	57.3 (-48.2, 90.2)	90.4 (32.8, 99.8)
Severe non-G1 pooled §	77.5 (64.7, 86.2)	87.7 (78.9, 93.2)*	NC	68.7 (-290, 99.4)	28.8 (-522, 94.0)	100 (-131, 100)
Severe G2 §	38.6 (-112.9, 84.2)	85.5 (24.0, 98.5)	**	NC	NC	NC
Severe G3 §	78.9 (24.5, 96.1)	93.7 (52.8, 99.9)	NC	NC	NC	NC
Severe G4 §	61.8 (4.1, 86.5)	95.4 (68.3, 99.9)	NC	NC	NC	NC
Severe G9 §	86.6 (73.0, 94.1)	85.0 (71.7, 92.6)	NC	NC	NC	NC
Hospitalization	83.0 (73.1, 89.7)	96.0 (83.8, 99.5)				
Medical attention		83.8 (76.8, 88.9)				

† Defined as requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility

‡ Defined as ≥ 11 points on the Vesikari scale

§ Severe RV GE is defined as ≥ 11 points on the Vesikari scale for Rota-004, Rota-006, and Rota-036

RV detected by ELISA for all endpoints

* Pooled non-G1 included G12; ** 95% CI extremely wide due to limited number of cases

NC = not calculated due to absence or limited numbers of cases

Note: Table prepared by reviewer from data in study reports of Rota-023, Rota-036, Rota-004, and Rota-006

Table 2: ATP Immunogenicity summary of efficacy studies

Endpoint	Rota-023 $10^{6.5}$ $CCID_{50}$	Rota-036 $10^{6.5}$ $CCID_{50}$	Rota-004 $10^{5.3}$ $CCID_{50}$	Rota-006		
				$10^{5.3}$ $CCID_{50}$	$10^{5.6}$ $CCID_{50}$	$10^{6.6}$ $CCID_{50}$
Seroconversion rate – % (95% CI)						
2 months post-Dose 1				39.0 (31.1, 47.5)	37.8 (29.3, 46.8)	43.2 (34.6, 52.1)
1 month post-Dose 2			80.4 (74.3, 85.5)			
1-2 months post-Dose 2	76.8 (72.4, 80.9)	86.5 (83.9, 88.8)				
2 months post-Dose 2				60.6 (52.0, 68.7)	62.4 (53.3, 70.9)	65.3 (56.3, 73.6)
End of Year 1			75.7 (68.9, 81.6)	72.9 (68.2, 77.4)	76.0 (71.3, 80.4)	77.1 (72.4, 81.4)

End of Year 2			67.2 (60.8, 73.3)*			
Vaccine take rate – % (95% CI)						
2 months post-Dose 1				48.6 (38.7, 58.5)	49.5 (39.6, 59.5)	57.4 (47.5, 66.9)
2 months post-Dose 2				63.5 (53.4, 72.7)	62.6 (52.3, 72.1)	69.1 (58.9, 78.1)
2 months post-any dose				64.5 (54.6, 73.5)	72.5 (63.1, 80.6)	75.5 (66.2, 83.3)
GMC – U/mL (95% CI)						
2 months post-Dose 1						
1 month post-Dose 2			164.0 (129.7, 207.3)			
1-2 months post-Dose 2	102.6 (86.3, 122.0)	197.2 (175.2, 222.0)				
2 months post-Dose 2				54.0 (40.9, 71.2)	52.1 (39.7, 68.3)	70.7 (51.9, 96.3)
End of Year 1			83.2 (67.2, 103.0)			
End of Year 2			53.1 (43.9, 64.4)*			

*Performed on the TVC for immunogenicity cohort only (Rotarix-269, placebo-135)

Note: Table prepared by reviewer from data in study reports of Rota-023, Rota-036, Rota-004, and Rota-006

Table 3: ATP immunogenicity summary of studies conducted in the US

Endpoint	Rota-005 $10^{6.8}$ $CCID_{50}$ N=123-133 n=150	Rota-060 $10^{6.6}$ $CCID_{50}$	
		Co-Ad group N=165	Sep-Ad group N=121
Seroconversion rate – % (95% CI)			
2 months post-Dose 1			
1 month post-Dose 2			
1-2 months post-Dose 2			
2 months post-Dose 2	78.2 (70.2-84.9)		86.0 (78.5-91.6)
3 months post-Dose 2		78.8 (71.8-84.8)	
6 months post-Dose 2	72.4 (63.6-80.0)		
Vaccine take rate – % (95% CI)			
2 months post-Dose 1			
2 months post-Dose 2	80.6 (73.0-86.8)		
1-2 months post-any dose	88.0 (81.7-92.7)		
GMC – U/mL (95% CI)			
2 months post-Dose 1			
1 month post-Dose 2			
1-2 months post-Dose 2			
2 months post-Dose 2	117.0 (88.3-154.9)		188.2 (139.6-253.5)
3 months post-Dose 2		110.0 (85.8-141.1)	
6 months post-Dose 2	77.7 (59.5-101.5)		

N= Number of subjects for seroconversion rate and GMC calculations; n= Number of subjects included in vaccine take rate calculations

Note: Table prepared by reviewer from data in study reports of Rota-005 and Rota-060

Table 4: ATP Immunogenicity summary of other BLA studies

Endpoint	Rota-007 $10^{6.6}$ $CCID_{50}$ N=154-160 n=46	Rota-039 $10^{6.5}$ $CCID_{50}$ N=157* n=167*	Rota-048 $10^{6.5}$ $CCID_{50}$ N=94** n=94**
Seroconversion rate – % (95% CI)			
2 months post-Dose 1			
1 month post-Dose 2	88.3 (82.2-92.9)		83.7 (74.2-90.8)
1-2 months post-Dose 2			
2 months post-Dose 2	85.0 (78.5-90.1)	84.7 (78.1-90.0)	
End of Year 1			
End of Year 2			
Vaccine take rate – % (95% CI)			
2 months post-Dose 1			
1 month post-Dose 2	88.9 (76.0-96.3)		84.1 (74.8, 91.0)
2 months post-Dose 2	89.1 (76.4-96.4)	88.0 (82.1-92.5)	
1-2 months post-any dose	97.8 (88.5-100.0)		89.4 (81.3-94.8)
GMC – U/mL (95% CI)			
2 months post-Dose 1			
1 month post-Dose 2	171.2 (135.0-217.1)		360.6 (236.4-549.8)

1-2 months post-Dose 2			
2 months post-Dose 2	112.1 (89.0-141.1)	134.4 (104.5-172.9)	
End of Year 1			
End of Year 2			

N= Number of subjects for seroconversion rate and GMC calculations; n= Number of subjects included in vaccine take rate calculations
*Includes only group receiving Rotarix with buffer and not stored at 37°C; **Includes only group receiving Rotarix in lyophilized formulation
Note: Table prepared by reviewer from data in study reports of Rota-007, Rota-039, and Rota-048

9.1.5 Efficacy/Immunogenicity Conclusions

Rotarix, administered at a titer of $10^{6.5}$ $CCID_{50}$ and as a 2-dose series (1 to 2 months apart) to healthy infants 6 to 14 weeks of age, was effective in preventing RV GE of any severity and in preventing severe RV GE caused by naturally-occurring RV strains during the first year of follow-up. In Rota-006, point estimates for any and severe VE were lower for $10^{5.3}$ $CCID_{50}$ and $10^{5.6}$ $CCID_{50}$ titers. In Rota-004, point estimates for any and severe VE at $10^{5.3}$ $CCID_{50}$ were lower than in Rota-036 ($10^{6.5}$ $CCID_{50}$). Protective efficacy was also observed during the second year of follow-up. Although not evaluated in the US, VE was observed across heterogeneous geographical populations. In general, VE estimates were higher in the European study cohorts (Rota-036, Rota-004) than the Latin American cohorts (Rota-023, Rota-006). Based on pivotal study Rota-036, breastfeeding did not appear to impact Rotarix VE.

Statistically significant protection was demonstrated against any RV GE and severe RV GE caused by circulating G1 and non-G1 types when pooled together. VE for these endpoints were also statistically significant for G3, G4, and G9 subtypes during Year 1 and the combined period. Although efficacy against any and severe G2 RV GE was not demonstrated during Year 1 in any of the studies, statistically significant VE against these G2 endpoints was reached when all cases were pooled together in a post-hoc analysis. However, CBER views these results as unacceptable to demonstrate efficacy against G2 RV GE during Year 1. Post-marketing surveillance for vaccine failures associated with G2 RV GE, along with other individual non-G1 types, should be conducted.

Two doses of Rotarix at a potency of ≥ $10^{6.5}$ $CCID_{50}$ per dose were also immunogenic in infants, as demonstrated by post-Dose 2 anti-RV IgA seroconversion rates, GMCs, and vaccine take rates. In Rota-006, GMC was lower in the $10^{5.6}$ $CCID_{50}$ group compared to the $10^{6.6}$ $CCID_{50}$ group. Immunogenicity results from Rota-006 and Rota-036 indicated that breastfeeding did not significantly impact anti-RV IgA seroconversion post-vaccination.

Overall, efficacy data from these trials support the proposed indication of prevention of RV GE.

10 Overview of Safety Across Trials

10.1 Safety Database - Number of Subjects, Types of Subjects and Extent of Exposure

Numbers and characteristics of subjects in each of the 11 BLA studies are summarized in Table 1 and Table 2 in Appendix 1. A total of 75,353 infants received at least one dose of Rotarix or placebo. Of these infants, 40,614 infants received at least one dose of Rotarix and 34,739 infants received at least one dose of placebo. A total of 78,980 doses of Rotarix and 67,349 doses of placebo were administered.

Among the Rotarix recipients, 37,214 subjects received vaccine at the potency (≥ $10^{6.0}$ $CCID_{50}$ per dose), formulation (lyophilized, buffered), and storage temperature (2° to 8°C) intended for commercial use in the U.S. A total 72,242 doses were administered.

Among the Rotarix recipients, 3076 subjects received vaccine at a potency less than $10^{6.0}$ $CCID_{50}$ per dose. A total 6098 doses were administered.

Across the studies, 90.5-99.1% of Rotarix recipients and 90.3-100% of placebo recipients received two study doses.

In Rota-006, 30 subjects in the ≥ $10^{6.0}$ $CCID_{50}$ group, 61 subjects in the < $10^{6.0}$ $CCID_{50}$ group, and 30 subjects in the placebo received a third dose. These doses were not included in the Integrated Safety Summary (ISS) analyses described below. However, the safety of Dose 3 has been reviewed in section 8.1.4.
All enrolled and vaccinated subjects were healthy male or female infants without obvious health problems. The age range at the time of Dose 1 was 5-17 weeks. Male-to-female ratio, height, and weight were generally similar between studies. In each study, the majority of subjects were White/Caucasian, Hispanic, Black, Mixed ancestry, or Oriental.

Seven of the studies enrolled only infants who were born at ≥ 36 weeks of gestation, while three studies included only infants who had a birth weight > 2000 grams.

10.2 Safety Assessment Methods

The table below summarizes the categories of safety data collected during each study.

Overview of Safety Data Collection

Study #	ISS analysis group	Solicited general AEs	Solicited AE period (days)	Unsolicited AEs	Unsolicited AE period (days)	SAEs	Unsolicited AE & SAE coding	Weight & Height	Concomitant meds
Rota-004	Supplementary	Yes (except cough/runny nose)	15	Yes	43	Yes	WHO, MedDRA	First visit	Yes
Rota-005	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-006*	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-007	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-014	Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-023	Core	NC	NA	No§	NA	Yes	MedDRA	First visit	NT
Rota-033	Core	Yes (except cough/runny nose)	8	Yes	31	Yes	MedDRA	First visit	Yes
Rota-036	Core	Yes (subset) (also type of medical attention)	8	Yes	31 (also: type of medical attention)	Yes	MedDRA	First visit	Yes
Rota-039†	Core	Yes	15	Yes	31	Yes	MedDRA	First visit	Yes
Rota-048‡	Core	Yes	15	Yes	31	Yes	MedDRA	First visit	Yes
Rota-060	Not included	NC	NA	Yes¶	Throughout study	Yes	MedDRA	First visit	Yes

ISS = Integrated Safety Summary; NC=not collected; NA= not applicable
Core ISS analysis: at least $10^{6.0}CCID_{50}$ potency versus placebo
Supplementary ISS analysis: less than $10^{6.0}CCID_{50}$ potency versus placebo
*safety data after 3rd dose in subset of 121 infants not included in ISS
†safety data not included in ISS for the following study groups: Rotarix without buffer, Rotarix stored at 37°C
‡safety data not included in ISS for the following study group: Rotarix in liquid formulation
¶Specific AEs included new onset of chronic illness(es) that were not congenital anomalies and conditions prompting emergency room visits; also AEs leading to drop-out
§Only AEs leading to drop-out
Note: table prepared by reviewer

Solicited General AEs

Solicited general AEs were collected from all or a subset of subjects in 9 of the 11 studies (data not collected for Rota-023 and Rota-060). AEs consisted of diarrhea, fussiness/irritability, loss of appetite, fever, and vomiting. Cough/runny nose was included as an AE except in Rota-004 and Rota-033. In Rota-036, data on the type of medical attention (i.e. medical personnel contact, advice, or visit; emergency room contact/visit; hospitalization) received for AEs was also collected.

In Rota-033 and Rota-036, AE data was collected from Day 0 to Day 7 post-vaccination, while in the remaining studies, data was collected from Day 0 to Day 14. In all studies, AEs were recorded on diary cards by parents/guardians.

For each AE, a standard scale was used for all studies to grade AE intensity (see table below).

Solicited general AE	**Intensity grade**	**Parameter**	
Recorded and scored by infant subject's parents/guardians			
Fussiness/Irritability	0	Behavior as usual	
(Rota-004, Rota-005, Rota-006,	1	Crying more than usual/ no effect on normal activity	
Rota-007, Rota-014, Rota-033,	2	Crying more than usual/ interferes with normal activity	
Rota-036, Rota-039, Rota-048)	3	Crying that cannot be comforted/ prevents normal activity	
Loss of appetite	0	Normal	
(Rota-004, Rota-005, Rota-006,	1	Eating less than usual/ no effect on normal activity	
Rota-007, Rota-014, Rota-033,	2	Eating less than usual/ interferes with normal activity	
Rota-036, Rota-039, Rota-048)	3	Not eating at all	
Cough/runny nose	0	Normal	
(Rota-005, Rota-006, Rota-007,	1	Cough/runny nose which is easily tolerated	
Rota-014, Rota-036, Rota-039,	2	Cough/runny nose which interferes with daily activity	
Rota-048)	3	Cough/runny nose which prevents daily activity	
Numbers of loose stools, episodes of vomiting and maximum temperature were recorded daily by subjects' parents/guardians on the diary card. The maximum intensity was scored at GSK Biologicals using the scale below.			
Diarrhea	0	0-2 looser than normal stools/day	
(Rota-004, Rota-005, Rota-006,	1	3 looser than normal stools/day	
Rota-007, Rota-014, Rota-033,	2	4-5 looser than normal stools/day	
Rota-036, Rota-039, Rota-048)	3	≥ 6 looser than normal stools/day	
Fever		Measured rectally	Measured orally/axillary
(Rota-004, Rota-005, Rota-006,	0	< 38.0°C	< 37.5°C
Rota-007, Rota-014, Rota-033,	1	≥ 38.0 – ≤ 38.5°C	≥ 37.5 – ≤ 38.0°C
Rota-036, Rota-039, Rota-048)	2	> 38.5 – ≤ 39.5°C	> 38.0 – ≤ 39.0°C
	3	> 39.5°C	> 39.0°C
Vomiting	0	No emesis	
(Rota-004, Rota-005, Rota-006,	1	1 episode of vomiting/day	
Rota-007, Rota-014, Rota-033,	2	2 episodes of vomiting/day	
Rota-036, Rota-039, Rota-048)	3	≥ 3 episodes of vomiting/day	

Source: Summary of Clinical Safety, pg 20

Unsolicited AEs

Unsolicited AEs were collected from all subjects in 10 of the 11 studies (data not collected for Rota-023). AEs were coded and reported using MedDRA in Rota-023, Rota-033, Rota-036, Rota-039, Rota-048, and Rota-060. AEs were initially coded and reported using the WHO dictionary for adverse reaction terminology in the remaining 5 studies, but were re-coded using MedDRA. In Rota-036, data on type of medical attention (i.e. medical personnel, contact, advice, or vist; emergency room contact or visit; hospitalization) received for AEs was also collected.

In Rota-033, Rota-036, Rota-039, and Rota-048, AE data was collected from Days 0 to 30 post-vaccination, while in the other studies, data was collected from Days 0 to 42. In Rota-060, only new onset of chronic illness(es) that were not congenital anomalies and conditions prompting emergency room visits were considered as unsolicited AEs.

For each AE, the following standard scale was used for all studies to grade AE intensity:

Grade 1 = Easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
Grade 2 = Sufficiently discomforting to interfere with normal everyday activities
Grade 3 = Prevented normal, everyday activities (In a young child, for example, prevented attendance at a day-care center and caused parents/guardians to seek medical advice)

Serious Adverse Events (SAEs)

SAEs were collected and reported in all studies throughout the study period and coded using the same methods (MedDRA, WHO dictionary) as for unsolicited AEs. Any SAE was reported to GSK within 24 hours using the SAE Report Form. The following definition of an SAE was applied:

- Any untoward medical occurrence that resulted in death, was life-threatening, resulted in persistent or significant disability/incapacity, required in-patient hospitalization or prolongation of existing hospitalization. In addition, important medical events that may have jeopardized the subject or may have required intervention to prevent one of the other outcomes listed above were considered serious.

An IDMC consisting of external clinical experts and a biostatistician was established in May 2002 to independently monitor safety aspects of the Rotarix vaccine clinical development. In addition, two other independent committees, a Clinical Events Committee and a Safety Review Committee, were formed to review data in Rota-023 (see section 8.1.1.1.6).

Intussusception (IS)

Special procedures were planned and implemented to rapidly identify and treat IS in all studies. Rota-023 was specifically designed and powered to assess the risk of IS following Rotarix vaccination, and has already been described in detail in section 8.1.1. In the other studies (except Rota-060), parents/guardians were made aware of the symptoms of IS (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating, high fever) and were instructed to inform the investigator and seek medical advice at the nearest hospital. Investigators were also aware of a possible increased risk of IS, and took appropriate diagnostic and therapeutic measures. Cases of IS were diagnosed by radiography. All studies (except Rota-004 and Rota-060) required completion of an IS Form in addition to documentation in the CRF.

Causality of AEs

In studies where co-administration of routine vaccines was allowed (all except Rota-004 and Rota-048), the investigators assessed whether the AE was causally related to vaccination rather than to individual vaccines.

Concomitant medications

Numbers and percentages of subjects in each treatment group who received any concomitant medication (medication except for vitamins or dietary supplements), any antipyretic medication, any prophylactic antipyretic medication, and any antibiotic post-vaccination were tabulated in each study except Rota-023.

Statistical analyses

Integrated safety summary
An integrated safety summary (ISS) analysis based on TVC (i.e. subjects who received at least one Rotarix or placebo vaccine) safety data from 10 of the 11 clinical studies (only Rota-060 not included) was conducted after an agreement between CBER and GSK at a pre-BLA meeting on June 21, 2006. The ISS analysis involved the pooling of subjects from the 10 studies into the following two analysis groups to allow for precise estimation of Rotarix safety at the licensing potency for the US (≥ $10^{6.0}$ $CCID_{50}$ per dose):

- Core ISS group: pooled subjects who received Rotarix at ≥ $10^{6.0}$ $CCID_{50}$ per dose or placebo (subjects pooled from Rota-005, Rota-006, Rota-007, Rota-023, Rota-033, Rota-036, Rota-039, and Rota-048)

- Supplementary ISS group: pooled subjects who received Rotarix at < $10^{6.0}$ $CCID_{50}$ per dose or placebo (subjects pooled from Rota-004, Rota-005, Rota-006, Rota-007, and Rota-014)

Core ISS analysis
A total of 36,755 subjects received 71,320 doses of Rotarix at a potency ≥ $10^{6.0}$ $CCID_{50}$ per dose. The distribution by individual study is summarized in the table below. Of note, in both the Core ISS and Supplementary ISS analyses, the same numbers of placebo subjects and doses were used (i.e. Rota-005, Rota-006, and Rota-007).

Study	Core ISS: HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo							
	HRV 10_6.5 CCID50		HRV 10_6.6 CCID50		HRV 10_6.8 CCID50		Placebo	
	N subjects	N doses	N subjects	N doses	N subjects	N doses	N subjects	N doses
Rota-005	_	_			209	400	108	209
Rota-006†	_	_	570	1115	_	_	567	1119
Rota-007	_	_	653	1292	_	_	653	1295
Rota-023	31673	61289	_	_	_	_	31552	61017
Rota-033	730	1413	_	_	_	_	124	236
Rota-036	2646	5267	_	_	_	_	1348	2686
Rota-039	174	345	_	_	_	_	52	104
Rota-048	100	199	_	_	_	_	50	99
Total	**36,755 subjects (71,320 doses)**						**34,454 subjects (66,765 doses)**	

N subjects = number of subjects receiving at least one dose
N doses = total number of doses administered
†In study Rota-006, 30 subjects in group HRV $10^{6.6}$ CCID50 and 30 subjects in group placebo received a third dose of HRV vaccine or placebo. The third dose administered was not counted under N doses in this table and any AEs reported after the third dose were not included in the ISS.
Placebo group for study Rota-039 includes Placebo group (N=26) and Placebo group without buffer (N=26)
Placebo group for study Rota-048 includes Placebo group (N=25) and Placebo group for the liquid formulation (N=25)
(Source: Summary of Clinical Safety, pg 32)

For all studies combined, the median age at Dose 1 was 8 weeks, the percentage of males was 51.1%, the percentage of Hispanics was 73.4% (followed by 16.2% Caucasians), the median height was 60 cm, and the median weight was 5.8 kg.

Supplementary ISS analysis

A total of 3076 subjects received 6037 doses of Rotarix at a potency < $10^{6.0}$ $CCID_{50}$ per dose. The distribution by individual study is summarized in the table below.

Study	Supplementary ISS: HRV vaccine (less than 10_6.0 CCID50 per dose) versus placebo					
	HRV 10_5.3 CCID50		HRV 10_5.6 CCID50		Placebo	
	N subjects	N doses	N subjects	N doses	N subjects	N doses
Rota-004	270	526	–	–	135	261
Rota-005	–	–	212	415	108	209
Rota-006†	569	1110	570	1109	567	1119
Rota-007	510	1011	648	1287	653	1295
Rota-014	–	–	297	579	150	293
Total	**3,076 subjects (6,037 doses)**				**1,613 subjects (3,177 doses)**	

N subjects = number of subjects receiving at least one dose
N doses = total number of doses administered
†In study Rota-006, 31 subjects in group HRV 105.3 CCID50, 30 subjects in group HRV 105.6 CCID50 and 30 subjects in group placebo received a third dose of HRV vaccine or placebo. The third dose administered was not counted under N doses in this table and the AEs reported after the third dose, were not included in the ISS.
(Source: Summary of Clinical Safety, pg 33)

For all studies combined, the median age at Dose 1 was 10 weeks, the percentage of males was 50.6%, the percentage of Orientals was 36.1% (followed by 29.9% Other and 23.8% Caucasians), the median height was 59 cm, and the median weight was 5.6 kg.

TVC Core and Supplementary ISS groups - Subject and dose distribution

For each study in the ISS, the numbers and percentages of subjects who received one dose, two doses, or at least one dose, by treatment group, are tabulated below.

Study	Group	N	Subjects receiving the specified number of doses					
			One dose		Two doses		At least one dose	
			n	%	n	%	n	%
Rota-004	HRV 10_5.3 CCID50	270	14	5.2	256	94.8	270	100
	Placebo	135	9	6.7	126	93.3	135	100
Rota-005	HRV 10_5.6 CCID50	212	9	4.2	203	95.8	212	100
	HRV 10_6.8 CCID50	209	18	8.6	191	91.4	209	100
	Placebo	108	7	6.5	101	93.5	108	100
Rota-006*	HRV 10_5.3 CCID50	569	28	4.9	541	95.1	569	100
	HRV 10_5.6 CCID50	570	31	5.4	539	94.6	570	100
	HRV 10_6.6 CCID50	570	25	4.4	545	95.6	570	100
	Placebo	567	15	2.6	552	97.4	567	100
Rota-007	HRV 10_5.3 CCID50	510	9	1.8	501	98.2	510	100
	HRV 10_5.6 CCID50	648	9	1.4	639	98.6	648	100
	HRV 10_6.6 CCID50	653	14	2.1	639	97.9	653	100
	Placebo	653	11	1.7	642	98.3	653	100
Rota-014	HRV 10_5.6 CCID50 + OPV	91	5	5.5	86	94.5	91	100
Part I	HRV 10_5.6 CCID50 + IPV	90	7	7.8	83	92.2	90	100
	Placebo	90	6	6.7	84	93.3	90	100

Rota-014 Part 2†	HRV 10_5.6 CCID50 + OPV	57	2	3.4	55	93.2	57	100
	HRV 10_5.6 CCID50 + IPV	59	1	1.7	58	96.7	59	100
	Placebo	60	1	1.7	59	98.3	60	100
Rota-023	HRV 10_6.5 CCID50	31673	2057	6.5	29616	93.5	31673	100
	Placebo	31552	2087	6.6	29465	93.4	31552	100
Rota-033	HRV 10_6.5 CCID50 (Lot A)	243	23	9.5	220	90.5	243	100
	HRV 10_6.5 CCID50 (Lot B)	241	17	7.1	224	92.9	241	100
	HRV 10_6.5 CCID50 (Lot C)	246	7	2.8	239	97.2	246	100
	Placebo	124	12	9.7	112	90.3	124	100
Rota-036	HRV 10_6.5 CCID50	2646	25	0.9	2621	99.1	2646	100
	Placebo	1348	10	0.7	1338	99.3	1348	100
Rota-039	HRV 10_6.5 CCID50	174	3	1.7	171	98.3	174	100
	Placebo	52	0	0.0	52	100	52	100
Rota-048	HRV 10_6.5 CCID50	100	1	1.0	99	99.0	100	100
	Placebo	50	1	2.0	49	98.0	50	100

N = number of subjects in each group
n/% = number/percentage of subjects who received the specified number of doses of HRV vaccine/placebo
*A subset of 121 subjects received three doses of HRV vaccine or placebo
†In study Rota-014 Part 2, three additional subjects were enrolled (2 subjects in HRV + OPV group and 1 subject in HRV + IPV group) but did not receive any dose of HRV
Placebo group for study Rota-039 includes Placebo group (N=26) and Placebo without buffer group (N=26)
Placebo group for study Rota-048 includes Placebo group (N=25) and Placebo group for the liquid formulation (N=25)
(Source: Summary of Clinical Safety, pg 34)

Safety Endpoints

The following safety endpoints were analyzed for each ISS group:

- Individual solicited AEs (any intensity and Grade 3) from Days 0-7 post-vaccination
- Unsolicited AEs (any intensity and Grade 3) from Days 0-30 post-vaccination
- Fatal events from Days 0-30 post-vaccination and during the entire study course
- SAEs from Days 0-30 post-vaccination and during the entire study course
- Discontinuation due to non-SAE or SAE (discontinuation defined as missing a study visit/planned concluding visit/study dose due to an AE/SAE)
- Concomitant medication use (any medication, any antipyretic, prophylactic antipyretic, any antibiotic) post-vaccination

The relative risk (RR; percentage in Rotarix group/percentage in placebo group), along with 95% CIs, was calculated for each safety endpoint based on exact conditional likelihood approach adjusted for the study effect.

For both ISS groups, post-Dose 2 safety data from 121 subjects in the 3-dose subset of Rota-006 were excluded. Analysis of solicited AEs included only subjects and doses with a completed solicited AE CRF/eCRF. Subjects not reporting unsolicited AEs were treated as subjects without an unsolicited AE. Also, analysis of SAEs coded to the MedRA PT *Intussusception* was based on the onset date and not diagnosis (as in Rota-023), and included cases besides those categorized as "definite IS."

Results of individual studies

In addition to ISS analyses, the Summary of Clinical Safety report also presented TVC safety results from the following individual studies: Rota-023 (pivotal Phase III), Rota-005 (Phase II, US/Canada), Rota-033 (lot-to-lot consistency study), and Rota-036 (pivotal Phase III)

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

A total of 128 post-vaccination deaths (≥ $10^{6.0}$ $CCID_{50}$ -68, < $10^{6.0}$ $CCID_{50}$ -5, placebo-55), were reported from the 10 studies in the ISS. In addition, no deaths were reported from Rota-060. The distribution of deaths by individual study is tabulated below.

Deaths

Study	HRV vaccine at least 10_6.0 CCID50 per dose		HRV vaccine less than 10_6.0 CCID50 per dose		Placebo	
	N	n	N	n	N	n
Rota-004	-	-	270	0	135	0
Rota-005	209	0	212	0	108	0
Rota-006	570	1	1139	1	567	1
Rota-007	653	2	1158	1	653	0
Rota-014	-	-	297	3	150	5
Rota-023	31673	62	-	-	31552	49
Rota-033	730	3	-	-	124	0
Rota-036	2646	0	-	-	1348	0
Rota-039	174	0	-	-	52	0
Rota-048	100	0	-	-	50	0
All studies	36755	68	3076	5	34739	55

N = number of subjects that received at least one dose; n = number of fatal cases
(Source: Summary of Clinical Safety, pg 50)

Core ISS analysis

Deaths – Day 0 to Day 30 post-vaccination
A total of 53 deaths (pooled Rotarix group-33, pooled placebo-20) were reported from Days 0-30 post-vaccination. The RR was 1.64 (95% CI: 0.92-3.02). For each MedDRA SOC or PT, there were no significant differences between groups (i.e. 95% CIs of RR did not include 1.0). Among the SOCs, the highest number of deaths was coded under the SOC *Infections and infestations* (Rotarix-14, placebo-9; RR=1.55, 95% CI: 0.62-4.06). Among the PTs, the highest number of deaths was coded under the PT *Pneumonia* (Rotarix-7, placebo-5; RR-1.39, 95% CI: 0.38-5.57).

Deaths – entire study period
A total of 118 deaths (pooled Rotarix group-68, pooled placebo-50) were reported throughout the course of the studies. The RR was 1.31 (95% CI: 0.89-1.93). There were no significant differences between groups for each MedDRA SOC or PT. Among the SOCs, the highest number of deaths was coded under the SOC *Infections and infestations* (Rotarix-31, placebo-21; RR=1.40, 95% CI: 0.78-2.57). Among the PTs, the highest number of deaths was coded under the PT *Pneumonia* (Rotarix-19, placebo-10; RR-1.74, 95% CI: 0.76-4.23).

Supplementary ISS analysis

Deaths – Day 0 to Day 30 post-vaccination
A total of 7 deaths (Rotarix-3, placebo-4) were reported from Day 0-30 post-vaccination. The RR was 0.38 (95% CI: 0.06-2.27). For each MedDRA SOC or PT, there were no significant differences between groups. Among the SOCs, the highest number of deaths was coded under the SOC *Infections and infestations* (Rotarix-2, placebo-3; RR=0.34, 95% CI: 0.03-3.01). Only one death was coded under PT *Pneumonia* (Rotarix group).

Deaths – study period
A total of 11 deaths (Rotarix-5, placebo-6) were reported throughout the course of the studies. The RR was 0.42 (95% CI: 0.10-1.67). There were no significant differences between groups for each MedDRA SOC or PT. Among the SOCs, the highest number of deaths was coded under the SOC *Infections and infestations* (Rotarix-4, placebo-5; RR=0.41, 95% CI: 0.08-1.90). There were 2 deaths coded under the PT *Pneumonia* (Rotarix-1, placebo-1).

Individual studies – Rota-023 (pivotal Phase III, Latin America plus Finland)
Study deaths, including pneumonia deaths, were reviewed in detail in section 8.1.1.

Individual studies - Rota-036 (pivotal Phase III, Europe)
Death analysis results were reviewed in detail in section 8.1.2.

Individual studies – Rota-005 (Phase II, US and Canada)
A total of 529 infants from the US (N=448) and Canada (N=81) received at least one dose of Rotarix or placebo (Rotarix $10^{5.3}$ $CCID_{50}$ -212, Rotarix $10^{6.8}$ $CCID_{50}$ -209, placebo-108). Two study doses were given 2 months apart. US infants were co-administered Infanrix, OmniHIB or ActHIB or Combax, IPOL, and Prevnar, while Canadian infants were co-administered Pentacel. Subjects were followed for 10 months post-Dose 1.

No deaths were reported in any of the treatment groups during the study.

Individual studies – Rota-033 (Phase III, Lot-to-lot consistency, Latin America)
A total of 854 infants from Colombia, Mexico and Peru received at least one dose from one of three $10^{6.5}$ $CCID_{50}$/dose lots of Rotarix or placebo (lot A -243, lot B-241, lot C-246, placebo-124). Two study doses were given 2 months apart. Although co-administration of routine DTwP-HepB/Hib vaccine was allowed, over 80% of subjects were not co-administered routine vaccine with study vaccine. Subjects were followed for 4 months post-Dose 1.

Three deaths were reported during the study as follows:
1. Death 1 – 5 month female, Mexico, cardiorespiratory arrest due to bronchial aspiration 72 days post-Dose 1 of Lot A Rotarix; not related to study vaccine
2. Death 2 – 5 month male, Mexico, multiple foci pneumonia beginning 37 days post-Dose 2 of Lot C Rotarix; not related to study vaccine
3. Death 3 – 4 month male, Colombia, bronchiolitis beginning 58 days post-Dose 1 of Lot B Rotarix, later developed seizures and septic shock/DIC possibly due to shigellosis, final diagnoses - pneumonia, GE possibly due to shigellosis; not related to study vaccine

Individual studies – Rota-060 (Phase III, US, concomitant routine vaccination)
A total of 484 infants from the US received at least one dose of the study vaccine (Rotarix $10^{6.5}$ $CCID_{50}$/dose, *Pediarix, Prevnar* or *ActHIB*). From the total, 249 subjects were assigned to the co-administration group (Rotarix co-administered with routine vaccines) and 235 were assigned to the separately administered group (Rotarix administered separately from routine vaccines). Two doses of Rotarix were given 2 months apart. Subjects were followed for 8-9 months post-Dose 1.

No deaths were reported in any of the treatment groups during the study.

10.3.2 Other Significant/Potentially Significant Events

Serious adverse events (SAEs)

A total of 4814 subjects reported at least 1 SAE (≥ $10^{6.0}$ $CCID_{50}$ -2219, < $10^{6.0}$ $CCID_{50}$ -279, placebo-2316) from the 10 studies in the ISS. The distribution of SAEs by study is tabulated below.

SAEs

Study	HRV vaccine at least 10_6.0 CCID50			HRV vaccine less than 10_6.0 CCID50 per dose			Placebo		
	N	n	%	N	n	%	N	n	%
Rota-004	-	-	-	270	28	10.37	135	9	6.67
Rota-005	209	7	3.35	212	8	3.77	108	6	5.56
Rota-006	570	68	11.93	1139	146	12.82	567	84	14.81
Rota-007	653	58	8.88	1158	86	7.43	653	40	6.13
Rota-014	-	-	-	297	11	3.70	150	7	4.67
Rota-023	31673	1775	5.60	-	-	-	31552	1989	6.30
Rota-033	730	16	2.19	-	-	-	124	1	0.81
Rota-036	2646	290	10.96	-	-	-	1348	176	13.06
Rota-039	174	4	2.30	-	-	-	52	4	7.69
Rota-048	100	1	1.00	-	-	-	50	0	0.0
All studies	36755	2219	6.04	3076	279	9.07	34739	2316	6.67

(Source: Summary of Clinical Safety, pg 56)

Core ISS analysis

SAEs – Day 0 to Day 30 post-vaccination

A total of 1286 subjects (Rotarix-627, placebo-659) reported at least 1 SAE from Day 0-30 post-vaccination. The RR was 0.90 (95% CI: 0.81-1.01). The following table summarizes SAE reporting by MedDRA SOC:

	HRV vaccine N = 36755				Placebo N = 34454				RR (HRV / Placebo)		
			95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo											
At least one symptom	627	1.71	1.58	1.84	659	1.91	1.77	2.06	0.90	0.81	1.01
Blood and lymphatic system disorders	8	0.02	0.01	0.04	7	0.02	0.01	0.04	1.09	0.34	3.55
Cardiac disorders	3	0.01	0.00	0.02	4	0.01	0.00	0.03	0.75	0.11	4.42
Congenital, familial and genetic disorders	7	0.02	0.01	0.04	6	0.02	0.01	0.04	1.16	0.33	4.19
Eye disorders	3	0.01	0.00	0.02	1	0.00	0.00	0.02	2.58	0.20	137.7
Gastrointestinal disorders	36	0.10	0.07	0.14	50	0.15	0.11	0.19	0.68	0.43	1.07
General disorders and administration site conditions	13	0.04	0.02	0.06	17	0.05	0.03	0.08	0.71	0.32	1.56
Hepatobiliary disorders	0	0.00	0.00	0.01	1	0.00	0.00	0.02	0.00	0.00	38.85
Immune system disorders	1	0.00	0.00	0.02	2	0.01	0.00	0.02	0.50	0.01	9.57
Infections and infestations	493	1.34	1.23	1.46	531	1.54	1.41	1.68	0.88	0.78	1.00
Injury, poisoning and procedural complications	15	0.04	0.02	0.07	21	0.06	0.04	0.09	0.68	0.33	1.40
Investigations	1	0.00	0.00	0.02	0	0.00	0.00	0.01	infinity	0.01	infinity
Metabolism and nutrition disorder	12	0.03	0.02	0.06	25	0.07	0.05	0.11	0.47	0.21	0.97
Musculoskeletal and connective tissue disorders	3	0.01	0.00	0.02	1	0.00	0.00	0.02	2.99	0.24	156.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0.01	0.00	0.03	3	0.01	0.00	0.03	1.66	0.32	10.69
Nervous system disorders	17	0.05	0.03	0.07	24	0.07	0.04	0.10	0.65	0.33	1.27
Psychiatric disorders	2	0.01	0.00	0.02	0	0.00	0.00	0.01	infinity	0.13	infinity
Renal and urinary disorders	1	0.00	0.00	0.02	0	0.00	0.00	0.01	infinity	0.03	infinity
Reproductive system and breast disorders	1	0.00	0.00	0.02	2	0.01	0.00	0.02	0.31	0.01	6.23
Respiratory, thoracic and mediastinal disorders	60	0.16	0.12	0.21	48	0.14	0.10	0.18	1.25	0.84	1.86
Skin and subcutaneous tissue disorders	5	0.01	0.00	0.03	2	0.01	0.00	0.02	2.29	0.37	24.24
Social circumstances	1	0.00	0.00	0.02	0	0.00	0.00	0.01	infinity	0.03	infinity
Vascular disorders	1	0.00	0.00	0.02	3	0.01	0.00	0.03	0.23	0.00	3.16

(Source: Summary of Clinical Safety, pg 62-71)

Among the SOCs, a significant difference between groups in SAE rates (i.e. rates of subjects who reported at least one PT in the specified SOC) was observed only for the SOC *Metabolism and nutrition disorders* (Rotarix-0.03%, placebo-0.07%; RR=0.47, 95% CI: 0.21-0.97).

No SAE PT was reported in ≥ 1% of Rotarix subjects. Significant differences in SAE rates between groups were observed for the following PTs:

SOC *Gastrointestinal disorders*
PT *Diarrhoea* (Rotarix-0.02%, placebo-0.07%; RR=0.35, 95% CI: 0.14-0.78)

SOC *Infections and infestations*
PT *Gastroenteritis* (Rotarix-0.20%, placebo-0.32%; RR=0.62, 95% CI: 0.45-0.84)

SOC *Metabolism and nutrition disorders*
PT *Dehydration* (Rotarix-0.02%, placebo-0.06%; RR=0.43, 95% CI: 0.17-0.97)

Rates of SAEs under the PT *Pneumonia* (Rotarix-0.33%, placebo-0.35%) and PT *Convulsions* (Rotarix-0.02%, placebo-0.02%) were similar or the same between groups. No SAEs under the PT *Kawasaki's disease* were reported in either group.

Rates of SAEs under the PT *Intussusception* (SOC *Gastrointestinal disorders*) were the same in both groups (Rotarix-9 cases, 0.024%; placebo-7 cases, 0.020%). SAEs under the PT *Hematochezia* were not reported in either group. In Rota-023, considered the core study on IS risk, definite (adjudicated) IS was reported in 6 Rotarix recipients and 7 placebo recipients from Day 0-30 post-vaccination. Details of all IS analyses for Rota-023 were reviewed in section 8.1.1.
Reviewer Note: In addition to the 6 definite cases of IS in the Rotarix group from Rota-023, the 3 other IS cases in the Rotarix group included in the Core ISS analysis for PT *Intussusception* were:
Rota-023: definite IS, onset on Day 29 post-Dose 1 (diagnosis on Day 31 post-Dose 1)
Rota-023: probable IS, onset on Day 22 post-Dose 2
Rota-036: IS, onset 8 days post-Dose 2

SAEs – entire study period
A total of 4519 subjects (Rotarix-2219, placebo-2300) reported at least 1 SAE during the entire study period. The rate was significantly less in the Rotarix group compared to the placebo group (RR=0.89, 95% CI: 0.84-0.94). The following table summarizes SAE reporting by MedDRA SOC:

	HRV vaccine N = 36755				Placebo N = 34454				RR (HRV / Placebo)		
			95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo											
At least one symptom	2219	6.04	5.80	6.29	2300	6.68	6.41	6.94	0.89	0.84	0.94
Blood and lymphatic system disorders	33	0.09	0.06	0.13	33	0.10	0.07	0.13	0.88	0.52	1.47
Cardiac disorders	7	0.02	0.01	0.04	10	0.03	0.01	0.05	0.61	0.19	1.80
Congenital, familial and genetic disorders	17	0.05	0.03	0.07	14	0.04	0.02	0.07	1.09	0.50	2.40
Ear and labyrinth disorders	0	0.00	0.00	0.01	1	0.00	0.00	0.02	0.00	0.00	38.85
Eye disorders	4	0.01	0.00	0.03	2	0.01	0.00	0.02	1.80	0.25	20.13
Gastrointestinal disorders	110	0.30	0.25	0.36	142	0.41	0.35	0.49	0.73	0.56	0.94
General disorders and administration site conditions	41	0.11	0.08	0.15	32	0.09	0.06	0.13	1.19	0.73	1.96
Hepatobiliary disorders	1	0.00	0.00	0.02	2	0.01	0.00	0.02	0.50	0.01	9.57
Immune system disorders	3	0.01	0.00	0.02	6	0.02	0.01	0.04	0.46	0.07	2.17
Infections and infestations	1737	4.73	4.51	4.95	1900	5.51	5.28	5.76	0.84	0.79	0.90
Injury, poisoning and procedural complications	150	0.41	0.35	0.48	131	0.38	0.32	0.45	1.05	0.83	1.34
Investigations	3	0.01	0.00	0.02	2	0.01	0.00	0.02	0.98	0.10	12.73
Metabolism and nutrition disorders	63	0.17	0.13	0.22	0.98	0.28	0.23	0.35	0.62	0.44	0.86
Musculoskeletal and connective tissue disorders	5	0.01	0.00	0.03	4	0.01	0.00	0.03	1.25	0.27	6.28

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	0.02	0.01	0.04	9	0.03	0.01	0.05	0.85	0.28	2.50
Nervous system disorders	110	0.30	0.25	0.36	93	0.27	0.22	0.33	1.08	0.81	1.45
Psychiatric disorders	8	0.02	0.01	0.04	1	0.00	0.00	0.02	6.61	0.87	295.9
Renal and urinary disorders	6	0.02	0.01	0.04	3	0.01	0.00	0.03	1.86	0.40	11.59
Reproductive system and breast disorders	5	0.01	0.00	0.03	7	0.02	0.01	0.04	0.48	0.12	1.78
Respiratory, thoracic and mediastinal disorders	207	0.56	0.49	0.65	183	0.53	0.46	0.61	1.09	0.89	1.33
Skin and subcutaneous tissue disorders	33	0.09	0.06	0.13	26	0.08	0.05	0.11	1.20	0.69	2.09
Social circumstances	2	0.01	0.00	0.02	0	0.00	0.00	0.01	infinity	0.19	infinity
Surgical and medical procedures	1	0.00	0.00	0.02	1	0.00	0.00	0.02	1.00	0.01	78.20
Vascular disorders	4	0.01	0.00	0.03	7	0.02	0.01	0.04	0.51	0.11	2.03

(Source: Summary of Clinical Safety, pg 164-188)

Significant differences in rates between groups were observed for the following SOCs:

SOC *Gastrointestinal disorders* (Rotarix-0.30%, placebo-0.35%; RR=0.73, 95% CI: 0.56-0.94)
SOC *Infections and infestations* (Rotarix-4.73%, placebo-5.51%; RR=0.84, 95% CI: 0.79-0.90)
SOC *Metabolism and nutrition disorders* (Rotarix-0.17%, placebo-0.28%; RR=0.62, 95% CI: 0.44-0.86)

Only the PTs *Gastroenteritis* and *Pneumonia* were reported in ≥ 1% of Rotarix subjects (1.3% and 1.2 %, respectively). Significant differences in SAE rates between groups were observed for the following PTs:

SOC *Gastrointestinal disorders*
PT *Diarrhoea* (Rotarix-0.07%, placebo-0.10%; RR=0.51, 95% CI: 0.30-0.85)
PT *Ileus* (Rotarix-0.00%, placebo-0.02%; RR=0.00, 95% CI: 0.00-0.85)

SOC *Infections and infestations*
PT *Gastroenteritis* (Rotarix-1.25%, placebo-2.07%; RR=0.61, 95% CI: 0.55-0.69)
PT *Gastroenteritis rotavirus* (Rotarix-0.02%, placebo-0.11%; RR=0.10, 95% CI: 0.03-0.24)

SOC *Metabolism and nutrition disorders*
PT *Dehydration* (Rotarix-0.15%, placebo-0.25%; RR=0.62, 95% CI: 0.43-0.89)

In addition, rates of SAEs under PT *Foreign body trauma* were significantly higher in the Rotarix group compared to the placebo group (Rotarix-11, 0.03%, placebo-1, 0.00%; RR-9.11, 95% CI: 1.31-394.8). All cases involved swallowing a foreign body between 48-483 days post-dose, and were assessed as not related to vaccination.

Rates of SAEs under the PT *Intussusception* were similar in both groups (Rotarix-16 cases, 0.04%; placebo-22 cases, 0.06%). SAEs under the PT *Hematochezia* occurred in 1 subject in each group.

Rates of SAEs under the PT *Pneumonia* (Rotarix-1.23%, placebo-1.28%) and PT *Convulsions* (Rotarix-0.09%, placebo-0.06%) were similar or the same between groups.

Only 1 SAE under the PT *Kawasaki's disease* was reported (Rota-023, Rotarix group; see section 8.1.1.2.3).

Supplementary ISS analysis

SAEs – Day 0 to Day 30 post-vaccination
A total of 80 subjects (Rotarix-56, placebo-24) reported at least 1 SAE from Days 0-30 post-vaccination. Overall SAE rates were not significantly different between groups (RR=1.23, 95% CI: 0.75-2.08). Significant differences in SAE rates between groups were not observed for any SOC or PT. No SAE PT was reported in ≥ 1% of Rotarix subjects.

Only 1 SAE under the PT *Intussusception* was reported (Rotarix group). SAEs under the PTs *Hematochezia* or *Kawasaki's disease* were not reported in either group.

SAEs – entire study period

A total of 425 subjects (Rotarix-279, placebo-146) reported at least 1 SAE during the entire study period. Overall SAE rates were not significantly different between groups (RR=0.99, 95% CI: 0.81-1.22). Significant differences in SAE rates between groups were not observed for any SOC or PT. Only the PTs *Gastroenteritis* and *Pneumonia* were reported in ≥ 1% of Rotarix subjects (2.2% and 1.9 %, respectively).

SAEs under the PT *Intussusception* were reported in 2 (0.07%) Rotarix recipients and 1 (0.06%) placebo recipient. One SAE under the PTs *Hematochezia* was reported in each of the groups. Three SAEs under PT *Kawasaki's disease* were reported in the Rotarix group (see section **Kawasaki disease – BLA studies** below).

Individual studies - Rota-023

SAE analysis has already been reviewed in detail in section 8.1.1.

Individual studies – Rota-036

SAE analysis has already been reviewed in detail in section 8.1.2.

Individual studies – Rota-005

A total of 21 subjects reported an SAE during the study ($10^{5.6}$ $CCID_{50}$- 8, $10^{6.8}$ $CCID_{50}$-7, placebo-6). None of the SAEs were judged as related to vaccination. Of these, only 4 subjects reported an SAE from Day 0-30 post-vaccination as follows:

Bronchiolitis, *Dehydration* – 5 days post-Dose 2, $10^{5.6}$ $CCID_{50}$
Gastroesophageal reflux disease – 7 days post-Dose 1, $10^{6.8}$ $CCID_{50}$
Lymphadenitis – 8 days post-Dose 2, $10^{6.8}$ $CCID_{50}$
Febrile infection – 1 day post-Dose 1, placebo

There were no cases of intussusception.

The percentage of subjects reporting at least 1 SAE in the $10^{6.8}$ $CCID_{50}$ (3.3%) was lower than in Rota-023 (5.6%), Rota-036 (10.96%), and Rota-006 (11.93%).

Individual studies – Rota-033

A total of 17 subjects (Lot A-4, Lot B-8, Lot C-4, placebo-1) reported an SAE during the study period. All SAEs were judged as not related to vaccination. Only 5 subjects reported an SAE from Days 0-30 post-vaccination as follows:

Gastroenteritis – 20 days post-Dose 2, placebo
Gastroenteritis – 17 days post-Dose 2, Lot B
Dysentery, Gastroenteritis – 5 days post-Dose 1, Lot B
Bronchiolitis – 14 days post-Dose 1, Lot B
Bronchospasm, Pneumonia – 22 days post-Dose 2, Lot B

Individual studies – Rota-060

A total of 29 subjects (co-adm group-15 [6.0%], sep-admin group-14 [6.0%]) reported an SAE during the study period. Only one SAE was judged to be related to vaccination (see below). Ten SAEs were reported from Days 0-30 as follows:

RSV bronchiolitis – 28 days post-Dose 3 of routine vaccines, co-admin group
Pneumonia – 15 days post-Dose 2, co-admin group

Viral infection – 9 days post-Dose 1, co-admin group (vaccine-related)
Brain neoplasm malignant – 3 days post-Dose 1 of routine vaccine, sep-admin group
Croup infectious – 4 days post-Dose 2 of routine vaccine, sep-admin group
Pyelonephritis – 7 days post-Dose 2 of Rotarix, sep-admin group
Tympanic membrane perforation – 21 days post-Dose 1 of Rotarix, sep-admin group
Gastroenteritis viral – 5 days post-Dose 2 of Rotarix, sep-admin group
Pyloric stenosis – 1 day post-Dose 1 of routine vaccine, sep-admin group
Pneumonia – 16 days post-Dose 3 of routine vaccine, sep-admin group

One case of intussusception was reported (separately-administered group) 90 days post-Dose 3 of routine vaccination. Kawasaki's disease was not reported.

The percentage of subjects reporting at least 1 SAE in Rota-060 (6.1%) was comparable to Rota-023 (5.6%) and lower than Rota-036 (10.96%) and Rota-006 (11.93%).

Intussusception within Day 0 - 30 post-vaccination – all BLA studies
The reviewer calculated incidence of IS post-vaccination in different onset intervals using data from all BLA studies at all Rotarix potencies. Only data pertaining to the lyophilized formulation with buffer was used for the Rotarix group calculations. Date of illness onset was used instead of date of diagnosis, including IS cases for Rota-023.

Onset interval (days)	Rotarix IS	Rotarix N*	Incidence (per 10,000)	Placebo IS	Placebo N	Incidence (per 10,000)
1 to 7	3	40315	0.74	1	34739	0.29
8 to 14	1	40315	0.25	1	34739	0.29
15 to 21	3	40315	0.74	2	34739	0.58
22 to 30	3	40315	0.74	3	34739	0.86
1 to 14	4	40315	0.99	2	34739	0.58
1 to 21	7	40315	1.74	4	34739	1.15
1 to 30	10	40315	2.48	7	34739	2.02

*Included 484 subjects from Rota-060

Gastrointestinal hemorrhage (non-IS)
In a post-hoc Core ISS analysis, the applicant compared pooled rates of PTs categorized under MedDRA High Level Term (HLT) *Gastrointestinal hemorrhages* between Rotarix and placebo groups. When the PTs *Diarrhoea hemorrhagic*, *Gastritis hemorrhagic*, *Gastrointestinal hemorrhage*, *Hematochezia*, *Rectal hemorrhage*, and *Upper Gastrointestinal hemorrhage* were combined, 19 (0.05%) Rotarix compared to 9 (0.03%) placebo subjects reported at least one of these AEs (RR=1.22, 95% CI: 0.52-3.09). This imbalance was primarily driven by *Hematochezia* (Rotarix – 15, placebo – 7). Of the 28 cases, 6 (Rotarix – 4, placebo – 2) were SAEs, summarized below:

Diarrhoea haemorrhagic (Rota-023, Nicaragua): 6 month male, 20 days post-Dose 1
Upper gastrointestinal haemorrhage (Rota-023, Mexico): 10 month female, 20 days post-Dose 2
Gastritis haemorrhagic (Rota-023, Mexico): 6 month female, 7 days post-Dose 2
Haematochezia (Rota-036, Finland): 11 month female, 499 days post-Dose 2
Haematochezia (Rota-007, Singapore): 13 month male, 31 days post-Dose 2 (placebo)
Rectal haemorrhage (Rota-023, Argentina): 6 month male, 139 days post-Dose 2 (placebo)

24 of the 28 cases (Rotarix – 17, placebo – 7) occurred within 31 days post-vaccination. Only 3 of the 24 cases (Rotarix – 3, placebo – 0) during this interval were reported as SAEs.

Reviewer Note: The reviewer also looked at the same gastrointestinal hemorrhage-related PTs in the Supplementary ISS groups. When the PTs *Hematochezia*, *Melaena*, and *Rectal hemorrhage* were pooled, 5 Rotarix versus 1 placebo recipient reported at least 1 PT within 31 days post-vaccination. There were no GI hemorrhage-related PTs categorized as SAEs within 31 days post-

vaccination, and only 2 cases of *Hematochezia* (Rotarix – 1, placebo – 1) were reported at any time during the studies.

Kawasaki disease – BLA studies

Three BLA studies (Rota-006, Rota-007, Rota-023) reported a total of 4 cases of Kawasaki disease. All cases occurred in Rotarix recipients and were assessed as not related to vaccination. Cases are summarized in the table below.

Study	Country	Rotarix potency	Age at onset	Sex	Race	Dose # after which AE occurred	Time from last dose to onset
Rota-006	Brazil	$10^{5.6}$ $CCID_{50}$	13 months	M	Mixed	2	7 months
Rota-007	Singapore	$10^{5.6}$ $CCID_{50}$	8 months	M	Asian	2	3 months
Rota-007	Singapore	$10^{5.6}$ $CCID_{50}$	6 months	M	Asian	2	55 days
Rota-023	Mexico	$10^{6.5}$ $CCID_{50}$	2 years	F	Hispanic	2	19 months

Note: Table prepared by reviewer, based on data from Study Reports from Rota-006, Rota-007, and Rota-023

Unsolicited AEs – Day 0 to Day 30 post-vaccination

Core ISS analysis

Unsolicited AE, any intensity

A total of 2709 (53.3%) of Rotarix recipients and 1455 (50.1%) of placebo recipients reported at least one unsolicited AE of any intensity from Days 0-30 post-vaccination. The difference was not significant (RR=1.01, 95% CI: 0.94-1.08). The table below summarizes unsolicited AE reporting by MedDRA SOC. Significant differences between groups were not observed for any SOC.

	HRV vaccine N = 5082				Placebo N = 2902				RR (HRV / Placebo)		
			95% CI				95% CI			95% CI	
Primary System Organ Class	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo											
At least one symptom	2709	53.31	51.92	54.69	1455	50.14	48.30	51.97	1.01	0.94	1.08
Blood and lymphatic system disorders	4	0.08	0.02	0.20	1	0.03	0.00	0.19	1.74	0.17	87.53
Cardiac disorders	0	0.00	0.00	0.07	1	0.03	0.00	0.19	0.00	0.00	38.79
Congenital, familial and genetic disorders	5	0.10	0.03	0.23	3	0.10	0.02	0.30	1.21	0.23	7.93
Ear and labyrinth disorders	6	0.12	0.04	0.26	6	0.21	0.08	0.45	0.67	0.18	2.57
Eye disorders	132	2.60	2.18	3.07	69	2.38	1.85	3.00	0.98	0.73	1.34
Gastrointestinal disorders	515	10.13	9.32	11.00	250	8.61	7.62	9.70	1.12	0.96	1.31
General disorders and administration site conditions	1120	22.04	20.91	23.20	563	19.40	17.98	20.89	1.06	0.96	1.18
Immune system disorders	24	0.47	0.30	0.70	22	0.76	0.48	1.15	0.76	0.40	1.45
Infections and infestations	1576	31.01	29.74	32.30	848	29.22	27.57	30.91	0.99	0.91	1.08
Injury, poisoning and procedural complications	10	0.20	0.09	0.36	11	0.38	0.19	0.68	0.44	0.16	1.18
Investigations	4	0.08	0.02	0.20	1	0.03	0.00	0.19	2.04	0.20	100.6
Metabolism and nutrition disorders	44	0.87	0.63	1.16	32	1.10	0.76	1.55	0.88	0.54	1.44
Musculoskeletal and connective tissue disorders	6	0.12	0.04	0.26	0	0.00	0.00	0.13	infinity	0.60	infinity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.00	0.00	0.07	1	0.03	0.00	0.19	0.00	0.00	19.87
Nervous system disorders	49	0.96	0.71	1.27	33	1.14	0.78	1.59	0.76	0.48	1.23
Psychiatric disorders	265	5.21	4.62	5.86	143	4.93	4.17	5.78	0.94	0.77	1.17
Renal and urinary disorders	1	0.02	0.00	0.11	1	0.03	0.00	0.19	1.00	0.01	78.29

Reproductive system and breast disorders	3	0.06	0.01	0.17	1	0.03	0.00	0.19	1.52	0.11	85.89
Respiratory, thoracic and mediastinal disorders	363	7.14	6.45	7.89	201	6.93	6.03	7.91	0.96	0.80	1.16
Skin and subcutaneous tissue disorders	285	5.61	4.99	6.28	126	4.34	3.63	5.15	1.20	0.96	1.50
Social circumstances	1	0.02	0.00	0.11	2	0.07	0.01	0.25	0.25	0.00	4.89
Surgical and medical procedures	3	0.06	0.01	0.17	0	0.00	0.00	0.13	infinity	0.21	infinity
Vascular disorders	4	0.08	0.02	0.20	2	0.07	0.01	0.25	1.20	0.16	13.77

(Source: Summary of Clinical Safety, pg 90-103)

The following unsolicited AE PTs were reported in ≥ 1% of Rotarix subjects:

SOC *Eye disorders*: *Conjunctivitis* (2.3%)
SOC *Gastrointestinal disorders*: *Abdominal pain* (1.1%), *Constipation* (1.5%), *Flatulence* (2.2%), *Gastrointestinal disorder* (1.7%), *Teething* (1.3%), *Vomiting* (1.4%)
SOC *General disorders and administration site conditions*: *Injection site pain* (2.1%), *Irritability* (11.4%), *Pyrexia* (13.5%)
SOC *Infections and infestations*: *Bronchitis* (1.7%), *Influenza* (2.7%), *Nasopharyngitis* (5.4%), *Otitis media* (2.9%), *Pharyngitis* (1.8%), *Respiratory tract infection* (1.6%), *Rhinitis* (6.5%), *Upper respiratory tract infection* (6.4%), *Viral infection* (1.3%)
SOC *Psychiatric disorders*: *Crying* (4.4%)
SOC *Respiratory, thoracic and mediastinal disorders*: *Cough* (3.7%)
SOC *Skin and subcutaneous tissue disorders*: *Dermatitis* (1.2%), *Rash* (1.3%)

Significant differences between groups were observed for the following PTs:

SOC *General disorders and administration site conditions*
PT *Irritability* (Rotarix-11.37%, placebo-8.72%; RR=1.20, 95% CI: 1.04-1.40)

SOC *Gastrointestinal disorders*
PT *Flatulence* (Rotarix-2.20%, placebo-1.31%; RR=1.53, 95% CI: 1.05-2.27)

SOC *Respiratory, thoracic and mediastinal disorders*
PT *Rhinorrhoea* (Rotarix-0.89%, placebo-1.93%; RR=0.61, 95% CI: 0.40-0.93)

Rates of Grade 3 *Irritability* and Grade 3 *Flatulence* were similar between groups, indicating that most of the AEs in these two categories were of mild/moderate intensity.

Rates of AEs coded under the PT *Hematochezia* were similar between groups (Rotarix-0.28%, placebo-0.21%).

Unsolicited AE, grade 3 intensity
A total of 270 (5.31%) Rotarix recipients and 143 (4.93%) of placebo recipients reported at least one Grade 3 unsolicited AE from Days 0-30 post-vaccination. The difference was not significant (RR=1.01, 95% CI: 0.82-1.24). The table summarizes Grade 3 unsolicited AE reporting by MedDRA SOC. Significant differences between groups were not observed for any SOC.

	HRV vaccine N = 5082				**Placebo N = 2902**				**RR (HRV / Placebo)**		
			95% CI				**95% CI**			**95% CI**	
Primary System Organ Class	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo											
At least one symptom	270	5.31	4.71	5.97	143	4.93	4.17	5.78	1.01	0.82	1.24
Blood and lymphatic system disorders	0	0.00	0.00	0.07	1	0.03	0.00	0.19	0.00	0.00	20.15

Congenital, familial and genetic disorders	1	0.02	0.00	0.11	1	0.03	0.00	0.19	1.00	0.01	78.29
Ear and labyrinth disorders	2	0.04	0.00	0.14	0	0.00	0.00	0.13	infinity	0.10	infinity
Eye disorders	11	0.22	0.11	0.39	5	0.17	0.06	0.40	1.12	0.36	4.11
Gastrointestinal disorders	29	0.57	0.38	0.82	15	0.52	0.29	0.85	1.00	0.52	2.02
General disorders and administration site conditions	87	1.71	1.37	2.11	52	1.79	1.34	2.34	0.86	0.60	1.24
Immune system disorders	3	0.06	0.01	0.17	0	0.00	0.00	0.13	infinity	0.21	infinity
Infections and infestations	169	3.33	2.85	3.86	90	3.10	2.50	3.80	1.01	0.77	1.31
Injury, poisoning and procedural complications	1	0.02	0.00	0.11	0	0.00	0.00	0.13	infinity	0.01	infinity
Metabolism and nutrition disorders	5	0.10	0.03	0.23	3	0.10	0.02	0.30	0.85	0.17	5.47
Musculoskeletal and connective tissue disorders	3	0.06	0.01	0.17	0	0.00	0.00	0.13	infinity	0.21	infinity
Nervous system disorders	1	0.02	0.00	0.11	0	0.00	0.00	0.13	infinity	0.03	infinity
Psychiatric disorders	19	0.37	0.23	0.58	7	0.24	0.10	0.50	1.38	0.56	3.89
Reproductive system and breast disorders	0	0.00	0.00	0.07	1	0.03	0.00	0.19	0.00	0.00	19.87
Respiratory, thoracic and mediastinal disorders	30	0.59	0.40	0.84	22	0.76	0.48	1.15	0.71	0.40	1.30
Skin and subcutaneous tissue disorders	6	0.12	0.04	0.26	2	0.07	0.01	0.25	1.53	0.27	15.48
Surgical and medical procedures	1	0.02	0.00	0.11	0	0.00	0.00	0.13	infinity	0.01	infinity
Vascular disorders	0	0.00	0.00	0.07	2	0.07	0.01	0.25	0.00	0.00	5.30

(Source: Summary of Clinical Safety, pg 104-108)

In general, grade 3 unsolicited AEs were infrequent. The following Grade 3 unsolicited AE PTs were reported in ≥ 1% of Rotarix subjects:

SOC *General disorders and administration site conditions: Pyrexia* (1.3%)
SOC *Infections and infestations*: *Otitis media* (1.2%)

Significant differences were observed for the following PTs:

SOC *Infections and infestations*
PT *Bronchiolitis* (Rotarix-0.12%, placebo-0.45%; RR=0.28, 95% CI: 0.09-0.81)

SOC *Respiratory, thoracic and mediastinal disorders*
PT *Rhinorrhoea* (Rotarix-0.00%, placebo-0.24%; RR=0.00, 95% CI: 0.00-0.38)

There were no reports of grade 3 PT *Hematochezia* in either group.

Supplementary ISS analysis

Unsolicited AE, any intensity
A total of 1338 (43.5%) of Rotarix recipients and 667 (41.3%) of placebo recipients reported at least one unsolicited AE of any intensity from Days 0-30 post-vaccination. The difference was not significant (RR=1.03, 95% CI: 0.94-1.13). Significant differences between groups were not observed for any SOC.

The following unsolicited AE PTs were reported in ≥ 1% of Rotarix subjects:

SOC *Eye disorders*: *Conjunctivitis* (1.5%)
SOC *Gastrointestinal disorders*: *Abdominal pain* (1.7%), *Constipation* (1.5%), *Vomiting* (1.1%)
SOC *General disorders and administration site conditions*: *Irritability* (2.9%), *Pyrexia* (4.0%)
SOC *Infections and infestations*: *Acarodermatitis* (1.2%), *Bronchiolitis* (1.1%), *Bronchitis*

(1.9%), *Influenza* (6.5%), *Nasopharyngitis* (3.6%), *Oral candidiasis* (1.2%), *Otitis media* (1.3%), *Rhinitis* (2.0%), *Upper respiratory tract infection* (5.6%), *Viral infection* (3.8%)
SOC *Respiratory, thoracic and mediastinal disorders*: *Cough* (3.6%), *Rhinorrhoea* (1.7%)
SOC *Skin and subcutaneous tissue disorders*: *Rash* (1.4%)

Significant differences were observed for the following PTs:

SOC *Infections and infestations*
PT *Bronchitis* (Rotarix-1.85%, placebo-0.74%; RR=2.39, 95% CI: 1.27-4.90)

SOC *Respiratory, thoracic and mediastinal disorders*
PT *Rhinorrhoea* (Rotarix-1.69%, placebo-2.91%; RR=0.60, 95% CI: 0.40-0.91)

***Reviewer Note*:** The applicant stated that the imbalance in PT *Bronchitis* was only driven by an imbalance of bronchitis AEs in Rota-006. Based on the analysis dataset for Rota-006 (< $10^{6.0}$ $CCID_{50}$ groups), the reviewer obtained a total of 44 (3.9%) Rotarix recipients compared to 10 (1.8%) placebo recipients who reported non-SAE PT *Bronchitis* from Days 0 to 30 post-vaccination. Grade 3 bronchitis occurred in 1 Rotarix compared to 0 placebo recipients. SAE PT *Bronchitis* was reported in 4 Rotarix versus 0 placebo recipients during Days 0 to 30 post-vaccination. In the core ISS analysis, when PTs *Bronchitis* and *Bronchitis acute* were combined, 116 (2.3%) Rotarix recipients compared to 45 (1.6%) placebo subjects reported an AE during the same interval. Grade 3 bronchitis rates were comparable (0.16% versus 0.14%). In Rota-006, the rate of any PT *Bronchitis* in the Rotarix group receiving the licensure potency dosage was higher than in the placebo group (3.7% vs 1.8%); no Grade 3 or SAE PT *Bronchitis* was reported in this Rotarix group.

Despite a significantly higher rate of PT *Bronchitis* in the Rotarix group, significant differences in other lower respiratory-related PTs (*Bronchiolitis, Bronchopneumonia, Pneumonia, Lower respiratory tract infection*) were not observed. A significant difference in rate of PT *Bronchitis* between groups was also not seen in the Core ISS analysis.

Unsolicited AE, grade 3 intensity
A total of 70 (2.28%) of Rotarix recipients and 37 (2.29%) of placebo recipients reported at least one Grade 3 unsolicited AE from Days 0-30 post-vaccination. The difference was not significant (RR=0.97, 95% CI: 0.64-1.48). Grade 3 unsolicited AEs were less common overall; there were no Grade 3 AE PTs reported in ≥ 1% of Rotarix subjects. Significant differences were not observed for the any SOCs or PTs, including PT *Bronchitis*.

Individual studies –Rota-036
Analyses of unsolicited AEs were previously reviewed in section 8.1.2.

Individual studies – Rota-005

Unsolicited AE, any intensity
A total of 264 subjects ($10^{5.6}$ $CCID_{50}$-112 [52.8%], $10^{6.8}$ $CCID_{50}$-104 [49.8%], placebo-48 [44.4%]) reported at least one unsolicited AE of any intensity from Days 0-42 post-vaccination. Given the small numbers of cases in many PTs, rates were similar between groups by PT. AE WHO PTs reported in ≥ 1% and < 10% of Rotarix subjects were *Contact dermatitis* (both groups), *Injection site reaction* (both groups), *Fever* ($10^{6.8}$ group), *Injury* ($10^{6.8}$ group), *Heart disorder* ($10^{6.8}$ group), *Abdominal pain* (both groups), *Constipation* (both groups), *Diarrhea* ($10^{6.8}$ group), *Flatulence* (both groups), *Gastroesophageal reflux* (both groups), *Gastrointestinal disorder nos* (both groups), *Toothache* (both groups), *Vomiting* ($10^{6.8}$ group), *Nervousness* (both groups), *Somnolence* (both groups), *Viral infection* (both groups), *Moniliasis* (both groups), *Otitis media* ($10^{5.6}$ group), *Rhinitis*

($10^{6.8}$ group), *Sinusitis* ($10^{6.8}$ group), *Eczema* (both groups), *Rash* (both groups), *Erythematous* rash ($10^{6.8}$ group), *Seborrhea* ($10^{6.8}$ group), and *Conjunctivitis* (both groups).

AE PTs reported in ≥ 10% of Rotarix subjects were *Otitis media* ($10^{6.8}$ group), *Upper Respiratory tract infection* (both groups), *Asthma* (both groups), *Bronchitis* ($10^{5.6}$ group), *Cough* ($10^{6.8}$ group), *Pneumonia* (both groups), *Respiratory disorder* ($10^{5.6}$ group),

48 subjects ($10^{5.6}$ $CCID_{50}$-19 [9.0%], $10^{6.8}$ $CCID_{50}$-20 [9.6%], placebo-9 [8.3%]) reported at least one vaccine-related unsolicited AE during this interval. Rates were similar between groups by PT.

Unsolicited AE, grade 3
A total of 32 subjects ($10^{5.6}$ $CCID_{50}$-13[6.1%], $10^{6.8}$ $CCID_{50}$-11 [5.3%], placebo-8 [7.4%]) reported at a grade 3 AE from Days 0-42 post-vaccination. Rates were similar between groups by PT. No Grade 3 PTs were reported in ≥ 1% of Rotarix subjects.

Comparison with Rota-036 and Rota-006
The percentage of subjects who reported at least 1 unsolicited AE in the$10^{6.8}$ $CCID_{50}$ group (49.8%) was lower than that in the $10^{6.6}$ $CCID_{50}$ group in Rota-006 (60.7%) and the Rotarix group in Rota-036 (63.7%, Day 0-30 post-dose).

Individual studies – Rota-033

Unsolicited AE, any intensity
A total of 432 subjects (Lot A-119 [49.0%], Lot B-119 [49.4%], Lot C-126 [51.2%], placebo-68 [54.8%]) reported at least one unsolicited AE of any intensity from Days 0-32 post-vaccination. Given the small numbers of cases in many PTs, rates were similar between groups by PT. PTs reported in ≥ 1% and < 10% of Rotarix subjects were *Conjunctivitis* (Lot B, Lot C), *Abdominal pain* (all lots), *Constipation* (Lot A), *Pyrexia* (Lot A, Lot B), *Bronchitis* (all lots), *Acute bronchitis* (all lots), *Candidiasis* (Lot C), *Impetigo* (Lot A), *Influenza* (all lots), *Pharyngitis* (all lots), *Respiratory tract infection* (Lot B), *Tonsillitis* (Lot A, Lot C), *Tracheitis* (Lot B), *Upper respiratory tract infection* (all lots), *Bronchospasm* (all lots), *Cough* (Lot B), *Rhinitis* (Lot A, Lot C), *Dermatitis* (all lots), *Allergic dermatitis* (Lot A, Lot C), *Atopic dermatitis* (Lot C), and *Contact dermatitis* (Lot B). Only PT *Nasopharyngitis* (all lots) was reported in ≥ 10% of Rotarix subjects.

Four AEs were assessed as related to vaccination:

Grade 1 *Abdominal pain*- 12 days post-Dose 2, Lot A
Grade 1 *Dehydration*- 2 days post-Dose 2, Lot A
Grade 1 *Abdominal pain* – 23 days post-Dose 2, Lot C
Grade 1 *Nasopharyngitis* – 3 days post-Dose 1, placebo

Unsolicited AE, Grade 3 intensity
Only 2 subjects (Lot B-1, Lot C-1) reported a grade 3 unsolicited AE from Days 0-30 post-vaccination. Both were assessed as related to vaccination as follows:

Grade 3 *Influenza* – 12 days post-Dose 1, Lot B
Grade 3 *Influenza* – 18 days post-Dose 1, Lot C

Individual studies – Rota-060

Unsolicited AE, any intensity
A total of 57 subjects (co-adm group-27 [10.8%], sep-admin group-30 [12.8%]) reported at least one unsolicited AE during the study period. Given the small numbers of cases in many PTs, rates were similar between groups by PT. The only significant imbalance observed between groups was for PT *Gastrooesophageal reflux disease* (co-adm group-0, sep-admin group-5 [2.1%], p=0.021). Of these

5 subjects, 2 had onset on the day of Dose 2 of routine vaccines, 1 had onset on the day of Dose 2 of Rotarix, 1 had onset 15 days post-Dose 1 of Rotarix, and 1 had onset 9 days post-Dose 2 of Rotarix. All were Grade 1 in intensity and not assessed as causally due to vaccination. The applicant concluded that this imbalance was likely due to a chance observation.

Other AE MedDRA PTs reported in ≥ 1% and < 3% of Rotarix subjects were *Pyrexia* (sep-ad group), *Otitis Media* (both groups), *Upper respiratory tract infection* (co-ad group), *Viral infection* (co-ad group), and *Eczema* (sep-ad group).

Only one AE was assessed as related to vaccination:
Grade 2 *Pyrexia* – 1 day post-Dose 1 of routine vaccines, sep-ad group

Unsolicited AE, Grade 3 intensity
Only 4 subjects (co-ad group -3, sep-ad group -1) reported a grade 3 unsolicited AE during the study period. No grade 3 AE was related to vaccination. The 4 AE PTs were *Bronchiolitis*, *Otitis media*, *Pneumonia*, and *Viral infection*.

10.3.3 Dropouts

Core ISS analysis
The percentages of Rotarix and placebo subjects who dropped out due to a non-SAE or SAE were similar between groups (Rotarix-0.43%, placebo-0.39%). For each study, there were no significant differences in dropout rates between treatment groups by PT. The majority of AEs were judged as not related to vaccination. Vaccine-related AEs were previously reviewed for Rota-006, Rota-023, and Rota-036 (see sections 8.1.1, 8.1.2, and 8.1.4). Among the other studies in the Core ISS, there were no reported vaccine-related AEs leading to dropout.

Overall rates of dropout were similar between groups in each study, given the small numbers (note: Rota-007 had 3 dropouts in the Rotarix group only, Rota-033 had 4 dropouts in the Rotarix group only). The vast majority of subjects in each study dropped out because of the following: consent withdrawal (not due to an AE), migration from study area, or lost to follow-up.

Supplementary ISS analysis
The percentages of Rotarix and placebo subjects who dropped out due to a non-SAE or SAE were similar between groups (Rotarix-0.58%, placebo-0.62%). There were no significant differences dropout rates between treatment groups by PT. Most of the AEs were judged as not related to vaccination. Vaccine-related AEs were previously reviewed for Rota-004 and Rota-006 (see sections 8.1.3 and 8.1.4). Among the other studies in the Supplementary ISS, there were no vaccine-related AEs leading to dropout.

Overall dropout rates were similar between groups in each study. The vast majority of subjects in each study dropped out because of the following: consent withdrawal (not due to an AE), migration from study area, or lost to follow-up.

Rota-005
One subject ($10^{6.8}$ $CCID_{50}$ group) dropped out due to an SAE (*Gastroesophageal reflux*). Five subjects ($10^{5.6}$ $CCID_{50}$-2, $10^{6.8}$ $CCID_{50}$-2, placebo-1) dropped out due to a non-SAE (grade 3 *Lethargy*, *Fussiness/Vomiting*, grade 1 *Hepatomegaly*, grade 2 *Body rash*, and grade 3 *Diarrhea/Vomiting/Fever*). All AEs leading to dropout were judged as not related to vaccination, and are briefly described below.

Grade 2 *Gastroesophageal reflux* – 7 days post-Dose 1, $10^{6.8}$ $CCID_{50}$ group
Grade 1 *Hepatomegaly* – 45 days post-Dose 1, $10^{6.8}$ $CCID_{50}$ group
Grade 3 *Diarrhea/Vomiting/Fever* – 16 days post-Dose 1, $10^{6.8}$ $CCID_{50}$ group
Grade 3 *Lethargy* – 7 days post-Dose 1, $10^{5.6}$ $CCID_{50}$ group

Fussiness/Vomiting – during solicited period post-Dose 1, $10^{5.6}$ $CCID_{50}$ group
Grade 2 *Body rash* – 61 days post-Dose 1, placebo

Most of the subjects who dropped out did so because they withdrew consent (not due to an AE), migrated from the study area or were lost to follow-up ($10^{5.6}$ $CCID_{50}$-84%, $10^{6.8}$ $CCID_{50}$-87%, placebo-70%).

Rota-033
Three subjects (Lot A-1, Lot B-1, Lot C-1) dropped out due to vaccine-unrelated SAE deaths, which were described previously in section 10.3.1. One non-SAE (Grade 3 *Diarrhea* with vaccine strain isolated, post-Dose 1, vaccine-related) was reported post-Dose 1 following receipt of Lot A Rotarix.

Most of the subjects dropped out because they withdrew consent (not due to an AE), migrated from the study area or were lost to follow-up (Lot A-71%, Lot B-81%, Lot C-90, placebo-92%).

Rota-060
Only 1 subject (sep-admin group) dropped out due to an SAE (*Atypical rhabdoid tumor*, 3 days post-Dose 1 of routine vaccine, vaccine-unrelated). No dropouts due to non-SAEs were reported. Most of the subjects who dropped out did so because they withdrew consent (not due to an AE), migrated from the study area or were lost to follow-up.
***Reviewer note*:** In the Rota-060 Study Report, the applicant stated that 417 of the 484 total subjects completed the Active Phase of the study (i.e. up to Visit 6). However, in the Annex Report 1, which contained the final safety data, the applicant noted that 432 of the 484 subjects completed the extended safety follow-up phase (i.e. 11 months of age).

10.4 Other Safety Findings

10.4.1 AE Incidence Tables (Systemic Events)

Solicited general AEs – Day 0 to Day 7 post-vaccination

Core ISS analysis
A total of 3286 Rotarix recipients and 2015 placebo recipients had a completed solicited AE CRF/eCRF. Compliance was high (>98%) in each group for subjects who returned AE diary cards after each dose.

Solicited AEs, any intensity
The rates of each AE symptom, regardless of intensity, after each dose and after any dose are summarized in the table below. Rates of each AE after Dose 1, Dose 2, and any dose were similar between groups; all 95% CIs included 1.0. In both groups, fussiness/irritability was the most common AE, followed by cough/runny nose, fever, and loss of appetite. Symptoms reported in ≥ 10% of Rotarix subjects after any dose were fever, fussiness/irritability, loss of appetite, vomiting, and cough/runny nose. Diarrhea was reported in 6.82% of Rotarix subjects after any dose.

Solicited AEs, any intensity

Solicited symptom (any intensity)	**Dose**	**Group**	**N**	**n**	**%**	**95% CI**		**RR (HRV over Placebo)**		
									95% CI	
						LL	**UL**	**RR**	**LL**	**UL**
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo										
Fever	1	HRV	3284	835	25.43	23.94	26.95			
		Placebo	2013	660	32.79	30.74	34.89	0.97	0.87	1.08
	2	HRV	3201	883	27.59	26.04	29.17			
		Placebo	1973	663	33.60	31.52	35.74	0.93	0.84	1.03
	Overall	HRV	3286	1308	39.81	38.13	41.50			

	per subject	Placebo	2015	983	48.78	46.58	50.99	0.94	0.87	1.03
Fussiness/ irritability	1	HRV	3284	1699	51.74	50.01	53.46			
		Placebo	2013	1041	51.71	49.50	53.92	0.99	0.91	1.07
	2	HRV	3201	1338	41.80	40.08	43.53			
		Placebo	1973	833	42.22	40.03	44.43	1.00	0.91	1.09
	Overall per subject	HRV	3286	2045	62.23	60.55	63.90			
		Placebo	2015	1241	61.59	59.42	63.72	1.00	0.93	1.08
Loss of appetite	1	HRV	3284	807	24.57	23.11	26.08			
		Placebo	2013	496	24.64	22.77	26.58	1.02	0.90	1.14
	2	HRV	3201	662	20.68	19.29	22.13			
		Placebo	1973	421	21.34	19.55	23.21	1.01	0.89	1.15
	Overall per subject	HRV	3286	1142	34.75	33.12	36.41			
		Placebo	2015	710	35.24	33.15	37.37	1.00	0.91	1.11
Vomiting	1	HRV	3284	420	12.79	11.67	13.98			
		Placebo	2013	217	10.78	9.46	12.22	1.04	0.88	1.24
	2	HRV	3201	256	8.00	7.08	8.99			
		Placebo	1973	154	7.81	6.66	9.08	0.86	0.69	1.06
	Overall per subject	HRV	3286	578	17.59	16.30	18.94			
		Placebo	2015	318	15.78	14.22	17.45	0.97	0.84	1.12
Diarrhea	1	HRV	3284	139	4.23	3.57	4.98			
		Placebo	2013	63	3.13	2.41	3.99	1.31	0.95	1.82
	2	HRV	3201	99	3.09	2.52	3.75			
		Placebo	1973	58	2.94	2.24	3.78	0.95	0.67	1.37
	Overall per subject	HRV	3286	224	6.82	5.98	7.73			
		Placebo	2015	115	5.71	4.73	6.81	1.12	0.88	1.43
Cough/runny nose	1	HRV	2583	717	27.76	26.04	29.53			
		Placebo	1897	572	30.15	28.09	32.27	0.97	0.86	1.08
	2	HRV	2522	794	31.48	29.67	33.34			
		Placebo	1863	624	33.49	31.35	35.69	0.97	0.87	1.09
	Overall per subject	HRV	2584	1143	44.23	42.31	46.17			
		Placebo	1899	897	47.24	44.97	49.51	0.96	0.88	1.05

Per dose:
N = number of vaccinated subjects with solicited symptom documented in the CRF/eCRF
n/% = number/percentage of subjects reporting at least once the symptom
Overall per subject:
N = number of vaccinated subjects with solicited symptom documented in the CRF/eCRF for Dose 1 or Dose 2
n/% = number/percentage of subjects reporting at least once the symptom after Dose 1 or Dose 2
95% CI, LL, UL= Exact 95% Confidence Interval, Lower Limit, Upper Limit
RR = Relative Risk adjusted for study effect
Potential imbalances were noted based on 95% CI for the relative risk across studies excluding 1
(Source: Summary of Clinical Safety, pg 41)

Among individual studies, the following symptoms with a 95% CI (of the RR) that excluded 1.0 were observed:

Rota-005: any vomiting post-Dose 2 (RR=0.43, 95% CI: 0.19-0.99)
Rota-036: any vomiting post-Dose 2 (RR=0.62, 95% CI: 0.43-0.91)

Solicited AEs, Grade 3 intensity

The rates of Grade 3 individual AE symptoms are summarized below. Overall, Grade 3 symptoms were less frequent, and rates were similar between groups after each dose and after any dose. The exception was cough/runny nose after any dose, which was slightly but statistically significantly

higher in the Rotarix group (RR=1.41, 95% CI: 1.01-1.99). However, rates of cough/runny nose after each dose were not significantly different between groups. Grade 3 symptoms reported in ≥ 1% and <10% of Rotarix subjects after any dose were fever, fussiness/irritability, vomiting, diarrhea, and cough/runny nose.

Solicited AEs, grade 3 intensity

Solicited symptom (grade 3)	Dose	Group	N	n	%	95% CI		RR (HRV over Placebo)		
						LL	UL	RR	95% CI LL	95% CI UL
HRV vaccine (at least 10_6.0 CCID50 per dose) versus placebo										
Fever	1	HRV	3284	11	0.33	0.17	0.60			
		Placebo	2013	10	0.50	0.24	0.91	0.95	0.36	2.54
	2	HRV	3201	21	0.66	0.41	1.00			
		Placebo	1973	14	0.71	0.39	1.19	1.03	0.48	2.25
	Overall per subject	HRV	3286	31	0.94	0.64	1.34			
		Placebo	2015	23	1.14	0.72	1.71	0.99	0.55	1.82
Fussiness/ irritability	1	HRV	3284	136	4.14	3.49	4.88			
		Placebo	2013	122	6.06	5.06	7.19	0.83	0.64	1.07
	2	HRV	3201	108	3.37	2.78	4.06			
		Placebo	1973	62	3.14	2.42	4.01	1.26	0.91	1.77
	Overall per subject	HRV	3286	207	6.30	5.49	7.18			
		Placebo	2015	164	8.14	6.98	9.42	0.90	0.72	1.12
Loss of Appetite	1	HRV	3284	15	0.46	0.26	0.75			
		Placebo	2013	9	0.45	0.20	0.85	1.17	0.47	3.12
	2	HRV	3201	18	0.56	0.33	0.89			
		Placebo	1973	15	0.76	0.43	1.25	0.72	0.33	1.59
	Overall per subject	HRV	3286	32	0.97	0.67	1.37			
		Placebo	2015	23	1.14	0.72	1.71	0.89	0.49	1.63
Vomiting	1	HRV	3284	68	2.07	1.61	2.62			
		Placebo	2013	29	1.44	0.97	2.06	1.17	0.72	1.92
	2	HRV	3201	51	1.59	1.19	2.09			
		Placebo	1973	29	1.47	0.99	2.10	0.92	0.55	1.54
	Overall per subject	HRV	3286	113	3.44	2.84	4.12			
		Placebo	2015	54	2.68	2.02	3.48	1.05	0.74	1.51
Diarrhea	1	HRV	3284	21	0.64	0.40	0.98			
		Placebo	2013	14	0.70	0.38	1.16	0.89	0.41	1.96
	2	HRV	3201	18	0.56	0.33	0.89			
		Placebo	1973	17	0.86	0.50	1.38	0.68	0.32	1.44
	Overall per subject	HRV	3286	39	1.19	0.85	1.62			
		Placebo	2015	30	1.49	1.01	2.12	0.79	0.47	1.35
Cough/runny nose	1	HRV	2583	49	1.90	1.41	2.50			
		Placebo	1897	28	1.48	0.98	2.13	1.62	0.99	2.68
	2	HRV	2522	56	2.22	1.68	2.87			
		Placebo	1863	37	1.99	1.40	2.73	1.41	0.91	2.20
	Overall per subject	HRV	2584	92	3.56	2.88	4.35			
		Placebo	1899	60	3.16	2.42	4.05	1.41	1.01*	1.99*

(Source: Summary of Clinical Safety, pg 42)

For individual studies, the following symptoms with a RR 95% CI that excluded 1.0 were observed:

Rota-005: grade 3 loss of appetite post-Dose 1 (RR=0.00, 95% CI: 0.00-0.98)
Rota-039: grade 3 vomiting post-Dose 2 (RR=0.10, 95% CI: 0.01-0.70) and post-any dose (RR=0.22, 95% CI: 0.06-0.88)

Supplementary ISS analysis
A total of 3028 Rotarix recipients and 1588 placebo recipients had a completed solicited AE CRF/eCRF. Compliance was high (>98%) among subjects in each group who returned AE diary cards after each dose.

Solicited AEs, any intensity
The rates for each AE symptom of any intensity after Dose 1, Dose 2, and any dose were similar between groups when subjects from all studies were pooled, with all 95% CIs of RRs including 1.0. Among individual studies, the following symptoms with a 95% CI that excluded 1.0 were observed:

Rota-004: any loss of appetite post-Dose 2 (RR=1.67; 95% CI: 1.02-2.81) and post-any dose (RR=1.51; 95% CI: 1.07-2.17)
Rota-007: any fussiness/irritability post-Dose 1 (RR=1.23; 95% CI: 1.06-1.43)

Solicited AEs, grade 3 intensity
The rates for each AE symptom of grade 3 intensity after each dose and after any dose were similar between groups when subjects from all studies were pooled, with all 95% CIs including 1.0. Grade 3 AEs were less common overall. Among individual studies, no RR estimates with 95% CIs that excluded 1.0 were observed.

Individual studies – Rota-005 (Phase II, US and Canada)

Grade 2 or 3 fever, vomiting, or diarrhea – Day 0 to 14
The percentage of subjects who reported Grade 2/3 fever, vomiting, or diarrhea during the 15-day post-vaccination period was similar between groups after each dose. There was no statistically significant difference in percentages between either Rotarix versus placebo.

Solicited AEs – Day 0 to 14
For each solicited symptom (cough/runny nose, diarrhea, irritability, loss of appetite, fever, vomiting), the rates of subjects who reported a symptom of any intensity, a grade 2 or 3 symptom, a grade 3 symptom, or a vaccine-related symptom were similar between groups after any dose. Irritability was the most common symptom, followed by cough/runny nose and loss of appetite. Grade 3 events were less common. For each symptom, statistically significant differences in rates were not seen between each Rotarix group versus placebo and between Rotarix groups. The exception was vomiting, which occurred less frequently in the $10^{6.8}$ $CCID_{50}$ group (16.3%) compared to placebo (25%) (p=0.072, significance level of alpha=0.1).

Symptoms that were reported in ≥ 10% of Rotarix subjects in both groups after any dose were fever, fussiness/irritability, loss of appetite, vomiting, and cough/runny nose. Diarrhea was reported in 11.0% of Rotarix subjects in the $10^{6.8}$ group and 8.5% in the $10^{5.6}$ group. Grade 3 symptoms reported in ≥ 1% and <10% of Rotarix subjects were cough/runny nose (both groups), diarrhea ($10^{5.6}$ group), loss of appetite ($10^{6.8}$ group), fever ($10^{5.6}$ group), and vomiting (both groups). Only Grade 3 irritability was reported in ≥ 10% of Rotarix subjects (both groups).

Individual studies – Rota-033 (Phase III, lot-to-lot consistency, Latin America)

Solicited AEs – Day 0 to 7

For each solicited symptom (diarrhea, irritability, loss of appetite, fever, vomiting), the rates of subjects who reported any symptom of any intensity, a grade 3 symptom, or a vaccine-related symptom were similar between groups after any dose. Irritability was the most common symptom, followed by loss of appetite and fever. Grade 3 events were uncommon. For each symptom at each subcategory (any, grade 3, vaccine-related), statistically significant differences in rates were not seen between Lot A versus Lot B, Lot A versus Lot C, or Lot B versus Lot C.

Symptoms that were reported in ≥ 10% of Rotarix subjects in all lots after Dose 1 were irritability, loss of appetite, vomiting, and fever. Diarrhea was reported in 5.8% of subjects from Lot A, 5.4% of subjects from Lot B, and 6.1% of subjects from Lot C. Grade 3 symptoms reported in ≥ 1% and <10% of Rotarix subjects were irritability (Lots A, B), diarrhea (Lots A, B), and vomiting (all lots).

Symptoms that were reported in ≥ 10% of Rotarix subjects in all lots after Dose 2 were irritability, loss of appetite, vomiting, and fever. Diarrhea was reported in 6.8% of subjects from Lot A, 5.4% of subjects from Lot B, and 3.3% of subjects from Lot C. Grade 3 symptoms reported in ≥ 1% and <10% of Rotarix subjects were irritability (all lots) and vomiting (all lots).

Individual studies – Rota-036 (pivotal Phase III, Europe)

Reactogenicity findings were reported in detail in section 8.1.2. There were no significant safety signals from Day 0 to Day 7 post-vaccination.

Comparison across studies in the Core ISS

Solicited AEs – Day 0 to 7

Rates of cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-7 after any Rotarix dose (≥ $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-005	Rota-006	Rota-007	Rota-033	Rota-036	Rota-039	Rota-048
Cough/runny nose	43.3%	73.9%	25.4%	NC	40.3%	40.8%	43.0%
Diarrhea	10.0%	10.4%	3.3%	10.5%	4.2%	3.5%	7.0%
Fever	30.9%	74.1%	40.6%	28.4%	34.1%	33.3%	5.0%
Irritability	76.6%	81.6%	39.6%	60.3%	62.4%	67.2%	74.0%
Loss of appetite	45.8%	41.1%	30.6%	32.3%	34.1%	33.9%	28.0%
Vomiting	13.4%	22.0%	7.8%	23.9%	14.4%	31.0%	25.0%

NC = not collected

Note: Table prepared by reviewer from data in Summary of Clinical Safety, pgs 131-143)

Grade 3 Solicited AEs – Day 0 to 7

Rates of Grade 3 cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-7 after any Rotarix dose (≥ $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-005	Rota-006	Rota-007	Rota-033	Rota-036	Rota-039	Rota-048
Cough/runny nose	0.5%	12.5%	0.6%	NC	1.8%	0.0%	1.0%
Diarrhea	0.5%	2.0%	0.8%	1.6%	1.0%	0.6%	1.0%
Fever	0.5%	3.0%	0.6%	0.7%	0.2%	1.2%	0.0%
Irritability	11.9%	16.1%	2.2%	3.9%	4.4%	2.9%	7.0%
Loss of appetite	1.0%	1.8%	0.5%	1.0%	1.0%	0.6%	0.0%
Vomiting	1.0%	5.2%	1.1%	6.8%	2.0%	1.7%	6.0%

NC = not collected

Note: Table prepared by reviewer from data in Summary of Clinical Safety, pgs 131-143

Solicited AEs – Day 0 to 14

Rates of cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-14 after any Rotarix dose (≥ $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-005	Rota-006	Rota-007	Rota-039	Rota-048
Cough/runny nose	51.7%	78.3%	31.7%	50.0%	55.5%
Diarrhea	11.0%	14.3%	4.7%	5.7%	9.0%
Fever	31.1%	75.2%	42.1%	37.4%	7.0%
Irritability	75.1%	81.7%	41.7%	73.0%	79.9%
Loss of appetite	50.2%	44.6%	33.5%	41.4%	30.0%
Vomiting	16.3%	24.6%	8.7%	35.1%	28.0%

Note: Table prepared by reviewer from data in study reports of Rota-005, Rota-006, Rota-007, Rota-039, and Rota-048

Grade 3 Solicited AEs – Day 0 to 14

Rates of Grade 3 cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-14 after any Rotarix dose (≥ $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-005	Rota-006	Rota-007	Rota-039	Rota-048
Cough/runny nose	1.0%	17.0%	0.8%	1.1%	2.0%
Diarrhea	0.5%	4.3%	1.2%	1.7%	3.0%
Fever	0.5%	3.9%	1.1%	1.7%	0.0%
Irritability	12.9%	17.6%	2.8%	3.4%	10.0%
Loss of appetite	1.0%	2.8%	0.8%	0.6%	0.0%
Vomiting	1.9%	7.2%	1.5%	1.7%	8.0%

Note: Table prepared by reviewer from data in study reports of Rota-005, Rota-006, Rota-007, Rota-039, and Rota-048

Comparison across studies in the Supplementary ISS

Solicited AEs – Day 0 to 7

Rates of cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-7 after any Rotarix dose (< $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-004	Rota-005	Rota-006	Rota-007	Rota-014
Cough/runny nose	NC	45.2%	72.4%	28.9%	47.7%
Diarrhea	9.1%	6.2%	8.5%	2.4%	11.2%
Fever	26.4%	32.4%	76.4%	43.1%	15.7%
Irritability	71.7%	76.7%	79.5%	44.1%	46.7%
Loss of appetite	34.0%	49.1%	40.9%	33.2%	31.0%
Vomiting	9.8%	16.2%	21.8%	6.6%	20.9%

NC = not collected

Note: Table prepared by reviewer from data in Summary of Clinical Safety, pgs 145-157

Grade 3 Solicited AEs – Day 0 to 7

Rates of Grade 3 cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-7 after any Rotarix dose (< $10^{6.0}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-004	Rota-005	Rota-006	Rota-007	Rota-014
Cough/runny nose	NC	0.5%	12.3%	0.7%	5.2%
Diarrhea	1.1%	0.0%	1.8%	0.5%	1.4%
Fever	0.0%	1.4%	2.9%	0.6%	1.1%
Irritability	6.0%	11.9%	16.7%	1.7%	7.3%
Loss of appetite	0.4%	0.5%	2.0%	0.4%	2.8%
Vomiting	4.2%	1.9%	5.1%	0.8%	5.9%

NC = not collected

Note: Table prepared by reviewer from data in Summary of Clinical Safety, pgs 145-157

Solicited AEs – Day 0 to 14

Rates of cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-14 after any Rotarix dose ($10^{5.6}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-004*	Rota-005	Rota-006	Rota-007	Rota-014	Rota-014(+OPV)	Rota-014(+IPV)
Cough/runny nose	NC	51.4%	77.8%	35.6%	54.5%	56.1%	53.0
Diarrhea	11.3%	8.5%	11.3%	3.4%	15.2%	13.5%	16.8%
Fever	32.1%	33.5%	78.1%	45.5%	21.5%	19.6%	23.5%
Irritability	77.7%	79.2%	80.7%	47.2%	51.2%	50.0%	52.3%
Loss of appetite	38.9%	52.8%	45.6%	35.8%	37.7%	37.2%	38.3%
Vomiting	12.8%	21.2%	27.4%	8.3%	27.6%	29.7%	25.5%

* = $10^{5.3}$ $CCID_{50}$ per dose; NC = not collected

Note: Table prepared by reviewer from data in study reports of Rota-004, Rota-005, Rota-006, Rota-007, Rota-014

Grade 3 Solicited AEs – Day 0 to 14

Rates of Grade 3 cough/runny nose, diarrhea, fever, irritability, loss of appetite, and vomiting from Day 0-14 after any Rotarix dose ($10^{5.6}$ $CCID_{50}$ per dose) are compared across studies below.

Symptom (any intensity)	Rota-004*	Rota-005	Rota-006	Rota-007	Rota-014	Rota-014(+OPV)	Rota-014(+IPV)
Cough/runny nose	NC	1.9%	16.9%	1.2%	6.7%	6.1%	7.4%
Diarrhea	1.9%	1.4%	4.3%	0.9%	2.4%	2.7%	2.0%
Fever	0.4%	1.4%	3.7%	1.7%	2.0%	0.7%	3.4%
Irritability	8.3%	15.1%	18.0%	2.3%	9.1%	8.8%	9.4%
Loss of appetite	0.4%	0.5%	3.9%	0.9%	5.1%	4.1%	6.0%
Vomiting	4.5%	2.4%	8.1%	1.7%	9.4%	11.5%	7.4%

* = $10^{5.3}$ $CCID_{50}$ per dose; NC = not collected

Note: Table prepared by reviewer from data in study reports of Rota-004, Rota-005, Rota-006, Rota-007, Rota-014

10.4.2 Laboratory Findings, Concomitant Medications

Genetic stability of RV vaccine strain

Sequencing analyses of the entire genome of the vaccine virus RIX4414 from 18 clinical stool samples (from 5 subjects with diarrhea, 6 subjects who may have acquired vaccine virus via non-vaccination transmission, and 7 asymptomatic subjects who were part of planned stool testing) indicated that VP4, VP7 and NSP4 were nearly always the only variable proteins. There was no clear association between amino acid substitutions in these proteins and either duration of virus shedding or GE. In Rota-039, no mutations in the VP4, VP87, and NSP4 genes were seen in vaccine RV antigen from 2 GE stool samples of Rotarix recipients. Sequencing analyses of vaccine RV antigen from the 6 non-vaccinated subjects indicated that a second replication cycle did not increase the mutation rate, and the new mutations were not associated with a virulent phenotype.

Concomitant medications post-vaccination

The percentages of subjects in each group that received any medication, antipyretic, prophylactic antipyretic, and antibiotic during the post-vaccination period were calculated in each study except Rota-023. The post-vaccination period was defined as either Days 0-7 (Rota-033, Rota-036), Days 0-14 (Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, Rota-039, Rota-048), or any time during the active phase (Day 0 to Month 5) of the study (Rota-060).

Overall, the percentages of subjects in each of the 4 categories were similar between groups. Frequencies in each category varied across studies, and correlations between type of co-

administered routine vaccine (DTwP-containing vaccines, DTaP-containing vaccines) and frequencies of medication use were not observed.

10.4.3 Product-Demographic Interactions

Age, gender

Age at Dose 1 and gender distribution were similar across all studies. The only exceptions were in Rota-007 and Rota-036, where the median age at Dose 1 was higher than in other studies (13 weeks and 12 weeks, respectively).

Study demographics of subjects from the ISS studies are summarized in the tables below.

Core ISS

Study	Total number of subjects	Mean/ Median age Dose 1 Rotarix (in weeks)	Mean/ Median age Dose 2 Rotarix (in weeks)	Female:Male ratio	Race (%)				
					White/Caucasian	Black	Hispanic	Oriental	Other
005	317	8.8/9.0	17.8/18.0	151:166	73.8	6.6	11.7	0.6	7.3
006	1137	8.5/8.0	18.1/18.0	543:594	25.1	2.9	0.0	0.1	71.9
007	1306	13.3/13.0	18.0/18.0	638:668	0.1	0.0	0.0	93.0	7.0
023	63225	8.1/7.0	15.8/15.0	30976:32249	10.9	1.0	81.3	0.0	6.8
033	854	8.5/8.0	17.2/17.0	415:439	0.0	2.0	98.0	0.0	0.0
036	3994	11.5/12.0	19.6/20.0	1887:2107	98.3	0.3	0.0	0.0	1.4
039	226	8.8/9.0	16.6/17.0	114:112	0.0	0.0	0.0	0.0	100
048	150	9.1/9.0	14.1/14.0	82:68	99.3	0.0	0.0	0.0	0.7
Total	71209	8.4/8.0	16.1/16.0	34806:36403	16.2	1.0	73.4	1.7	7.8

Supplementary ISS

Study	Total number of subjects	Mean/ Median age Dose 1 (in weeks)	Mean/ Median age Dose 2 (in weeks)	Female:Male ratio	Race (%)				
					White/Caucasian	Black	Hispanic	Oriental	Other
004	405	8.3/8.0	16.2/16.0	191:214	99.0	0.0	0.0	0.2	0.7
005	320	8.5/8.0	17.5/17.0	172:148	76.9	5.6	11.9	0.6	5.0
006	1706	8.4/8.0	18.0/18.0	815:891	23.4	3.1	0.0	0.1	73.4
007	1811	13.3/13.0	17.9/18.0	914:897	0.1	0.0	0.0	93.3	6.6
014	447	8.1/7.0	12.6/12.0	224:223	15.2	82.6	0.0	0.0	2.2
Total	4689	10.3/10.0	17.3/17.0	2316:2373	23.8	9.4	0.8	36.1	29.9

Rota-060

Study	Total # of subjects	Mean/ Median age Dose 1 Rotarix (in weeks)	Mean/ Median age Dose 2 Rotarix (in weeks)	Female:Male ratio	Race (%)				
					White/Caucasian (European)	African American	Asian	Other	American Hispanic/Latino
060	484	Co-ad: 8.7/9.0 Sep-ad: 12.8/13.0	Co-ad: 17.5/17.0 Sep-ad: 21.5/21.0	228:256	75.6	12.6	1.2	8.1	14.7

*Ethnicity was categorized separately from race

Overall, no consistent and noticeable trends in frequencies of deaths, SAEs, unsolicited AEs, or solicited AES, according to age at Dose 1 or gender, were observed across studies.

Ethnicity/race
The vast majority of subjects in each study were categorized into one of the major ethnic/racial group as follows:

Asian/Oriental: Rota-007, Rota-038
Black: Rota-014
White/Caucasian: Rota-004, Rota-005, Rota-036, Rota-048, Rota-060
Hispanic: Rota-023, Rota-033
Other/Mixed: Rota-006

From the data on solicited events presented in the sections **Comparison across studies in the Core ISS** and **Comparison across studies in the Supplementary ISS**, consistently higher rates of fever, diarrhea, cough/runny nose and irritability were seen in Rota-006, a study in which the majority of subjects were of mixed ancestry. However, rates of these 4 symptoms were similar across study groups. In each country (Brazil, Mexico, Venezuela), rates of these symptoms were similar between treatment groups, except for diarrhea which occurred less in the $10^{5.6}$ $CCID_{50}$ group in Mexico. When stratified by race (Mixed, White, Black), rates were also similar between treatment groups, except for diarrhea which occurred less in the $10^{6.6}$ $CCID_{50}$ group in the Black subjects compared to Black placebo subjects. Rates of cough, diarrhea, and fever were the highest in Brazil across treatment groups, while rates of irritability were the lowest in Venezuela. Across treatment groups, rates of diarrhea and irritability were the lowest in White subjects, while rates of fever were the lowest in Black subjects.

In Rota-023, a proportionally higher number of deaths, pneumonia deaths, non-fatal pneumonia SAEs, and overall SAEs during Dose 1 to Visit 3 occurred in Brazil and in subjects of mixed ancestry. In Rota-033, a proportionally higher number of subjects who reported at least one solicited and unsolicited AEs after any dose was reported in Peru. However, in both studies, proportions of subjects in these ethnic/geographical subsets in each of these clinical AE categories were similar between Rotarix and placebo groups. Across studies, consistent and noticeable trends were not observed in frequencies of deaths, SAEs, or non-SAEs according to ethnicity/race.

Pre-term infants
Rota-023, Rota-033, and Rota-039 did not have any gestational age and/or birth weight exclusion criteria, while Rota-006 and Rota-036 included subjects with a birth weight > 2000 grams. The other studies (Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, and Rota-048) only enrolled subjects who were born at ≥ 36 weeks gestation.

To identify any safety issues in pre-term infants, the applicant conducted a post-hoc analysis for Rota-023 by first identifying infants with a gestational age of ≤ 36 weeks reported in the “pre-existing medication conditions” section of the CRF. Precise gestational ages that were not recorded in the CRF were confirmed by the investigator.

A total of 254 pre-term infants were identified (Rotarix-134, placebo-120). The median gestational age in each group was 35.0 weeks (range: 29-36 weeks for Rotarix, 28-36 weeks for placebo). All infants were vaccinated according to their chronological age, and were followed for safety from Dose 1 to Visit 3. Thirteen pre-term infants (Rotarix-7, 5.2%; placebo-6, 5.0%) reported at least one SAE; the differences in overall rates and rates by individual PT between groups were not statistically significant. Only the SAE PT *Bronchiolitis* was reported in ≥ 1% of Rotarix subjects (3 subjects, 2.2%). No fatalities or IS cases were reported in either group.

Fifty-two subjects (Rotarix-29, placebo-23) were part of the Year 1 efficacy subset and followed up to 1 year of age. The median gestational age in each group was 35.0 weeks (range: 33-36 weeks

for Rotarix, 29-36 weeks for placebo). A total of 10 pre-term infants (Rotarix-5, placebo-5) reported at least one SAE from after Visit 3 until Visit 4 (i.e. 1 year of age). Overall SAE rates and rates by SAE PT were not significantly different between groups. PTs reported in the Rotarix group were *Bronchiolitis* (1 subject), *Bronchitis* (1 subject), *Diarrhea infectious* (1 subject), *Gastroenteritis* (2 subjects), and *Pneumonia* (1 subject).

Of note, none of the pre-term infants in the Rotarix group had blood tests for immunogenicity. Severe RV GE occurred in one infant in each group (Rotarix – G2P[4], placebo- G1 type).
***Reviewer Note*:** The applicant did not state whether pre-term infants were actually enrolled in Rota-033 and Rota-039.

10.4.4 Product-Disease Interactions

All vaccinated subjects were healthy at enrollment. However, in Rota-014, inclusion of HIV-positive infants was discovered retrospectively from investigations of fatal cases. During Part 1 of the study, 6 of 7 subjects who died were HIV positive. Among the 7 deaths, 3 (1.7%) were Rotarix recipients and 4 (4.4%) were placebo recipients. All fatalities were judged as not related to vaccination, and most of the deaths were due to HIV-related opportunistic infections. Subsequent to this investigation, maternal HIV status was ascertained in order to enroll only subjects whose mothers tested HIV negative for Part 2 of the study.

The applicant also performed HIV testing on blood samples collected from the remaining 265 subjects in Part 1. Of the 172 subjects who provided consent, 5 subjects tested HIV positive (Rotarix-2, placebo-3). No SAEs were reported in these 5 subjects and all unsolicited AEs were mild or moderate in intensity. None of these subjects demonstrated anti-RV IgA seroconversion post-Dose 2.

Based on limited data provided above, the applicant concluded that Rotarix administration did not raise any safety concerns in HIV-positive subjects.

10.4.5 Product-Product Interactions

Concomitant administration of routine pediatric vaccines

Concomitant administration of routine pediatric vaccines with Rotarix or placebo was allowed in all studies except Rota-004 and Rota-048. Rota-006 and Rota-036 have been reviewed in detail in sections 8.1.2 and 8.1.4, and were part of the Core and/or Supplementary ISS analyses. Other studies have also been reviewed in this safety overview section, as part of the Core and Supplementary ISS analyses and also individually (Rota-005, Rota-033).

The proportion of TVC subjects in each study who were co-administered routine vaccines with Dose 1 and Dose 2 of Rotarix or placebo is summarized as follows:

Rota-005: >94% of US subjects and >93% of Canadian subjects in each group received routine vaccines (US: Infanrix, OmniHIB or ActHIB [or Comvax], Prevnar, IPOL; Canada: Pentacel) with Dose 1 and Dose 2
Rota-006: > 98% of subjects in each group received DTPw-HB+Hib vaccine with Dose 1 and Dose 2; OPV administered 2 weeks apart from Rotarix or placebo
Rota-007: >98% of subjects in each group received DTPa-IPV/HiB with Dose 1 and Dose 2; no subjects received HBV together with Dose 1 of Rotarix or placebo, while only 5 subjects received HBV with Dose 2

Rota-014: not specifically noted in the study report; subjects were to have received either DTPa/Hib + OPV or DTPa-IPV/Hib with each study dose
Rota-023: only 6% of subjects received routine vaccinations with Dose 1 (DTPw- 3.34-3.4%, Hib – 3.0%, HBV- 5.1-5.3%); 3% of subjects received routine vaccinations with Dose 2 (DTPw- 2.9-3.0%, Hib – 2.4%, HBV – 1.8-1.9%); OPV administered 2 weeks apart from Rotarix or placebo)
Rota-036: 98.5-100% of subjects in each group received DTPa-HBV-IPV/Hib, Prevenar, and Meningitec with Dose 1; 99.7-100% of placebo received routine vaccinations with Dose 2
Rota-039: ≥ 95% of subjects in each group received Infanrix IPV Hib with Dose 1 and Dose 2
Rota-060: All subjects (N=249) in the Co-Ad group received Pediarix, Prevnar, and ActiHIB with Rotarix (232/249 subjects received both doses of Rotarix)

Safety – Adverse Events

As mentioned previously in this safety overview section, rates of AEs (deaths, SAEs, non-SAEs, concomitant medications) were similar between groups in each study. Safety data indicated that there appeared to be no clear correlation between co-administration of routine vaccines with Rotarix and increased frequencies of AEs. The only exception appeared to the frequency of fever of any intensity from Days 0-7, which among the Core ISS Analysis studies, was lower after each dose and after any dose in Rotarix recipients from Rota-048 (in which no co-administration of routine vaccines were allowed) than among Rotarix subjects in each of the other studies. However, because rates were similar between Rotarix and placebo groups in each study that allowed co-administration of routine vaccines, the higher rates of fever in the these studies compared to Rota-048 was likely attributable to the co-administered routine vaccines. Furthermore, rates of Grade 3 fever were much less frequent across all studies. In the Supplementary ISS Analysis, rates of any fever from Days 0- 7 post-vaccination in subjects from Rota-004 (co-administration not allowed) were generally lower than those in other studies except Rota-014. Again, rates Grade 3 fever were lower across all studies.

Immune response to concomitant vaccine antigens

Immunogenicity of co-administered vaccinations was evaluated in all or a subset of subjects from Rota-005, Rota-006, Rota-007, Rota-014, Rota-036, and Rota-060.

<u>Rota-006 and Rota-036</u>

The immunogenicity of co-administered vaccine antigens in Rota-006 and Rota-036 were reviewed in sections 8.1.4 and 8.1.2. In both studies, there were no significant differences between treatment groups in seroprotection rates, seropositivity rates, or GMC/GMTs to any of the vaccine antigens that did not favor any of the Rotarix groups. Although there appeared to be no impact of Rotarix at any potency on the immune responses to co-administered antigens at selected post-Dose 2 of Rotarix (post-Dose 3 of routine vaccines) time points, clinical limits for non-inferiority for each of the routine antigens were not pre-defined.

For Rota-036, the applicant also performed a post-hoc immunogenicity analysis of the Spain subset to demonstrate non-inferiority of Rotarix compared to placebo for each co-administered routine vaccine antigen. The Spain subset was chosen due the same routine vaccines (DTaP-HepB-IPV) given at the same schedule (2, 4, and 6 months). For the difference in seroprotection rates between groups (i.e. placebo minus Rotarix) for each antigen, non-inferiority was met if the UL of the 95% CI of the rate difference was < 10%. Based on this definition, Rotarix was inferior to placebo for seroprotection against anti-poliovirus type 2 (UL=10.81%) (see table below).

Study	Placebo					HRV vaccine					Difference % (Placebo-HRV)		
				95% CI					95% CI			95% CI	
Antigen: parameter	N	n	%	LL	UL	N	n	%	LL	UL	%	LL	UL
Anti-diphtheria: % ≥0.1 IU/mL													
Rota-036 Spain	90	90	**100.0**	96.0	100.0	191	191	**100.0**	98.1	100.0	**0.00**	-4.09	1.97
Anti-tetanus: % ≥0.1 IU/mL													
Rota-036 Spain	90	89	**98.9**	94.0	100.0	191	189	**99.0**	96.3	99.9	**-0.06**	-5.04	2.81
Anti-HBs: % ≥10 mIU/mL													
Rota-036 Spain	89	84	**94.4**	87.4	98.2	186	178	**95.7**	91.7	98.1	**-1.32**	-8.52	3.80
Anti-PRP: % ≥1.0 µg/mL													
Rota-036 Spain	90	35	**38.9**	28.8	49.7	190	87	**45.8**	38.6	53.2	**-6.90**	-18.82	5.57
Anti-polio type 1: % ≥1:8													
Rota-036 Spain	54	51	**94.4**	84.6	98.8	119	117	**98.3**	94.1	99.8	**-3.87**	-13.56	1.52
Anti-polio type 2: % ≥1:8													
Rota-036 Spain	54	45	**83.3**	70.7	92.1	116	97	**83.6**	75.6	89.8	**-0.29**	-13.68	10.81
Anti-polio type 3: % ≥1:8													
Rota-036 Spain	50	49	**98.0**	89.4	99.9	117	114	**97.4**	92.7	99.5	**0.56**	-8.09	5.66

Adapted from Summary of Clinical Efficacy, pg 120

***Reviewer Note*:** Based on FDA non-inferiority criteria for anti-polio response (UL of the 95% CI of the rate difference ≤ 5%), Rotarix was also inferior to placebo for seroprotection against anti-poliovirus type 3 (UL = 5.66%).
***Reviewer Note*:** Figures in the table above are different that those in the Rota-036 Study Report.

For the ratio of GMCs between groups (i.e. placebo/Rotarix) for pertussis and pneumococcal antigens, non-inferiority was met if the upper limit of the 95% CI of the GMC ratio was <1.5 for the pertussis antigens. Based on these criteria, Rotarix was not inferior to placebo for GMCs against any of the antigens (see table below).

Study	Placebo				HRV vaccine				GMC (Placebo/HRV)		
Antigen: parameter	N	GMC	LL	UL	N	GMC	LL	UL	Ratio	LL	UL
Anti-PT GMC (EL.U/mL)											
Rota-036 Spain	90	**28.5**	25.0	32.4	190	**27.0**	24.1	30.2	**1.06**	0.88	1.27
Anti-FHA GMC (EL.U/mL)											
Rota-036 Spain	90	**97.0**	82.4	114.3	191	**95.2**	85.3	106.3	**1.02**	0.84	1.24
Anti-PRN GMC (EL.U/mL)											
Rota-036 Spain	90	**52.4**	41.4	66.2	191	**49.0**	41.8	57.4	**1.07**	0.81	1.41

Adapted from Summary of Clinical Efficacy, pg 121

***Reviewer Note*:** Figures in the table above are different that those in the Rota-036 Study Report.

<u>Rota-005</u>
Routine vaccine immunogenicity was evaluated as a secondary study objective and measured at Visit 2 (2 months post-study Dose1), Visit 3 (2 months post-study Dose 2), and Visit 4 (6-8 months post-routine Dose 3). Seroprotection or seropopositivity for each antigen was defined as follows:

Anti-pneumococcal (7 serotypes): ≥ 0.05 µg/mL (≥ 2.0 µg/mL also measured)
Anti-PRP: ≥ 0.15 µg/mL, ≥ 1.0 µg/mL
Anti-diphtheria: ≥ 0.1 IU/mL

Anti-tetanus: ≥ 0.1 IU/mL
Anti-PRN: ≥ 5 EL.U/mL
Anti-FHA: ≥ 5 EL.U/mL
Anti-PT: ≥ 5 EL.U/mL
Anti-polio (1, 2, 3): ≥ 8 ED_{50}

Clinical limits for non-inferiority of Rotarix compared to placebo for each of the routine antigens were not pre-defined for these studies in the original protocol.

In the ATP immunogenicity cohort, >95% of US subjects received 2 doses of routine vaccines between Visit 1 and Visit 3. Among US subjects with available anti-D, anti-T, anti-PT, anti-FHA, anti-PRN and anti-pneumococcal antibody results at Visit 4, >91% of subjects in each group ($10^{5.6}CCID_{50}$, $10^{6.8}CCID_{50}$, placebo) received 3 doses of DTPa and Prevnar between Visit 1 (i.e. Dose 1) and before Visit 4. For subjects with available anti-PRP results at Visit 4, 86-89% of subjects in each group received 3 doses of Hib vaccine between Visit 1 and before Visit 4. For subjects with available anti-polio results at Visit 4, 52-54% of subjects in each group received 3 doses of Hib vaccine between Visit 1 and before Visit 4.

In the ATP immunogenicity cohort, >93% of Canadian subjects received 2 doses of routine vaccines between Visit 1 and Visit 3. Among Canadian subjects with available routine vaccine serology results at Visit 4, >83% of subjects in each group received 3 doses of Pentacel between Visit 1 and before Visit 4.

Immunogenicity analyses included only subjects who received at least 2 doses of routine vaccine antigens between Visit 1 and before Visit 4. For each routine antigen, seroprotection/seropositivity rates and GMCs/GMTs at Visit 4 were similar between either of the Rotarix ($10^{5.6}CCID_{50}$ and $10^{6.8}CCID_{50}$) and placebo groups in the ATP immunogenicity cohort. Immunogenicity at Visit 3 was also similar between groups.

The applicant also performed a post-hoc analysis of the US subset to demonstrate non-inferiority of Rotarix ($10^{6.8}CCID_{50}$ potency) compared to placebo for each co-administered routine vaccine antigen. For the difference in seroprotection rates between groups (i.e. placebo minus Rotarix) for each antigen, non-inferiority was met if the upper limit of the 95% CI of the rate difference was < 10%. Based on this definition, Rotarix was not inferior to placebo for seroprotection against any of the antigens (see table below).

Study	**Placebo**					**HRV vaccine**					**Difference % (Placebo-HRV)**		
				95% CI					**95% CI**			**95% CI**	
Antigen: parameter	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Anti-diphtheria: % ≥0.1 IU/mL													
Rota-005 US	50	39	**78.0**	64.0	88.5	105	89	**84.8**	76.4	91.0	**-6.76**	-21.32	5.61
Anti-tetanus: % ≥0.1 IU/mL													
Rota-005 US	51	50	**98.0**	89.6	100.0	107	107	**100.0**	96.6	100.0	**-1.96**	-10.30	1.55
Anti-HBs: % ≥10 mIU/mL													
Rota-005 US	-	-	**-**	-	-	-	-	**-**	-	-	**-**	-	-
Anti-PRP: % ≥1.0 µg/mL													
Rota-005 US	51	22	**43.1**	29.3	57.8	109	69	**63.3**	53.5	72.3	**-20.17**	-35.71	-3.65
Anti-polio type 1: % ≥1:8													
Rota-005 US	49	48	**98.0**	89.1	99.9	108	108	**100.0**	96.6	100.0	**-2.04**	-10.69	1.44
Anti-polio type 2: % ≥1:8													
Rota-005 US	49	49	**100.0**	92.7	100.0	108	106	**98.1**	93.5	99.8	**1.85**	-5.46	6.50

Anti-polio type 3: % ≥1:8													
Rota-005 US	49	47	**95.9**	86.0	99.5	108	106	**98.1**	93.5	99.8	**-2.04**	-10.69	1.44

Note: analysis was not performed for anti-HBs because hepatitis B vaccine was not a protocol-specified vaccine and therefore used permissively in Rota-005.

Adapted from Summary of Clinical Efficacy, pg 120

***Reviewer Note*:** Based on FDA-suggested non-inferiority criteria for anti-polio response (UL of the 95% CI of the rate difference ≤ 5%), Rotarix was inferior to placebo for seroprotection against anti-polio type 2 (UL = 6.50%).

For the ratio of GMCs between groups (i.e. placebo/Rotarix) for pertussis and pneumococcal antigens, non-inferiority was met if the upper limit of the 95% CI of the GMC ratio was < 2.0 for the pneumococcal antigens and <1.5 for the pertussis antigens. Based on these criteria, Rotarix was inferior to placebo for GMC against PT (UL=1.65), PRN (UL=1.62), and *S. pneumoniae* type 14 (UL=2.06) (see table below).

Study	**Placebo**				**HRV vaccine**				**GMC (Placebo/HRV)**		
Antigen: parameter	**N**	**GMC**	**LL**	**UL**	**N**	**GMC**	**LL**	**UL**	**Ratio**	**LL**	**UL**
Anti-PT GMC (EL.U/mL)											
Rota-005 US	49	**21.8**	17.2	27.8	105	**18.2**	15.1	22.0	**1.20**	0.87	1.65
Anti-FHA GMC (EL.U/mL)											
Rota-005 US	50	**35.8**	29.6	43.3	108	**32.8**	28.8	37.5	**1.09**	0.87	1.38
Anti-PRN GMC (EL.U/mL)											
Rota-005 US	51	**25.3**	18.1	35.5	108	**23.3**	18.6	29.2	**1.09**	0.73	1.62
S. pneumoniae type 4 GMC (µg/mL)											
Rota-005 US	49	**1.018**	0.817	1.269	104	**0.979**	0.807	1.187	**1.04**	0.74	1.46
S. pneumoniae type 6B GMC (µg/mL)											
Rota-005 US	47	**0.141**	0.098	0.204	102	**0.120**	0.093	0.154	**1.18**	0.76	1.84
S. pneumoniae type 9V GMC (µg/mL)											
Rota-005 US	52	**1.085**	0.840	1.401	102	**1.111**	0.926	1.334	**0.98**	0.71	1.34
S. pneumoniae type 14 GMC (µg/mL)											
Rota-005 US	52	**2.638**	1.930	3.605	104	**1.881**	1.508	2.345	**1.40**	0.96	2.06
S. pneumoniae type 18C GMC (µg/mL)											
Rota-005 US	51	**0.977**	0.727	1.314	103	**1.028**	0.835	1.266	**0.95**	0.66	1.37
S. pneumoniae type 19F GMC (µg/mL)											
Rota-005 US	50	**0.900**	0.675	1.201	102	**0.840**	0.686	1.028	**1.07**	0.75	1.52
S. pneumoniae type 23F GMC (µg/mL)											
Rota-005 US	48	**0.318**	0.223	0.452	101	**0.328**	0.257	0.419	**0.97**	0.63	1.49

Adapted from Summary of Clinical Efficacy, pg 121-122

***Reviewer Note*:** Based on FDA-suggested non-inferiority criteria for GMT ratios for *S. pneumoniae* antigens (UL of the 95% CI of the GMT ratio ≤ 1.5), Rotarix was also inferior to placebo for GMC against *S. pneumoniae* type 6B (UL=1.84) and type 19F (UL=1.52).

<u>Rota-007</u>

Routine vaccine immunogenicity was evaluated as a secondary objective and measured at Visit 4 (2 months post-study Dose 2, 1 month post-routine Dose 3). Seroprotection or seropopositivity for each antigen was defined as follows:

Anti-PRP: ≥ 0.15 µg/mL, ≥ 1.0 µg/mL
Anti-diphtheria: ≥ 0.1 IU/mL

Anti-tetanus:	≥ 0.1 IU/mL
Anti-PRN:	≥ 5 EL.U/mL
Anti-FHA:	≥ 5 EL.U/mL
Anti-PT:	≥ 5 EL.U/mL
Anti-polio (1, 2, 3):	≥ 8 ED_{50}
Anti-HBs:	≥ 10 mIU/ml

Clinical limits for non-inferiority of Rotarix compared to placebo for each routine antigen were not pre-defined for these studies in the original protocol.

Among subjects in the ATP immunogenicity cohort with available routine vaccine serology results at Visit 4, >96% of subjects in each of the groups ($10^{5.3}$ $CCID_{50}$, $10^{5.6}$ $CCID_{50}$, $10^{6.6}$ $CCID_{50}$, placebo) received DTPa-IPV/Hib concomitantly with both doses of Rotarix or placebo and received 3 doses of DTPa-IPV/Hib between Visit 1 and before Visit 4. Also, among these same subjects, >91% in each group received one dose of HBV between Visit 1 and before Visit 4.

Immunogenicity analyses included only subjects who received at least 2 doses of routine vaccine antigens between Visit 1 and before Visit 4. For each routine antigen, seroprotection/seropositivity rates and GMCs/GMTs at Visit 4 were similar between any of the 3 Rotarix groups and placebo. Statistical analyses of the rate differences and between placebo and each Rotarix group demonstrated that there were no significant differences between the groups in seroprotection or seropositivity rates for each antigen (95% CIs for each of the rate differences included 1.0). Similarly, GMC or GMT ratios showed that there were no significant differences between groups in GMCs or GMTs for each antigen (95% CIs for each of the ratios included 0).
***Reviewer Note*:** Although the applicant did not define clinical limits for non-inferiority, based on FDA criteria, Rotarix did not demonstrate inferiority to placebo for seroprotection/seropositivity rates or GMCs/GMTs against any of the routine vaccine antigens.

Rota-014
The primary study objective was to demonstrate that co-administration of Rotarix with OPV does not decrease anti-polio immune response one month post-Dose 3 of polio vaccine. Immunogenicity against polioviruses types 1, 2, and 3 were measured at 1 month post-Dose 3 of polio vaccination in 3 groups: Rotarix ($10^{5.6}CCID_{50}$) + OPV, Rotarix ($10^{5.6}CCID_{50}$) + IPV, and placebo + OPV. The study was comprised of 2 parts, Part 1 and Part 2, with the 3 groups represented in each part.

Seroprotection was defined as anti-polio 1, 2, and 3 antibodies each ≥ 8 ED_{50}. Seroprotection rates and GMTs were calculated for each group in Part 1, Part 2, and Parts 1 and 2 combined. The study objective was met if the upper limit of the 95% CI for the difference in the seroprotection rate of the pooled group (Rotarix-IPV and placebo-OPV, Parts 1 and 2) minus the Rotarix-OPV group was ≤ 10% for each polio serotype.

Although the ATP immunogenicity cohort was used for the primary analyses, only about 50% of the cohort subjects were included in the analyses due to insufficient amount of serum. Also, subjects included in the analysis may have already received a dose of OPV prior to enrollment because OPV vaccination at birth was allowed in subjects according to the EPI.

Seroprotection rates against poliovirus types 1, 2, and 3 were 100% in all groups except the HRV-OPV and placebo-OPV groups, both of which had seroprotection rates of 98.0 and 98.4%, respectively, against polio type 3. The upper limits of the 95% CI for the rate difference between the pooled group and Rotarix-OPV group were <10% against each of the poliovirus types (type 1= 6.9%; type 2= 6.9%; type 3= 9.7%), thus demonstrating non-inferiority based on study criteria.

Reviewer Note: Based on FDA-suggested criteria for non-inferiority (UL 95% CI difference ≤ 5%), Rotarix did not demonstrate non-inferiority for seroprotection against any of the polio types. However, because the applicant did not define clinical limits for non-inferiority, the study was likely not adequately powered to demonstrate non-inferiority using FDA-suggested criteria. In addition, the polio vaccination schedule for this study (2, 3, and 4 months) is different than the US schedule (2, 4, and 6 months).

The placebo-OPV/Rotarix-OPV and Rotarix-IPV/Rotarix-OPV GMT ratios also indicated that there were no statistically significant differences in GMTs between the groups for all polio types, since 95% CIs of the ratios included 1.0. The only exception was the Rotarix-IPV/Rotarix-OPV polio type 3 GMT ratio (2.8), the 95% CI of which did not include 1.0 (1.8-4.6).

Rota-060

The primary objective of the US study was to demonstrate that co-administration of Rotarix ($10^{6.5}CCID_{50}$) with Pediarix (DTaP-IPV-Hep B), Prevnar, and ActHIB does not impair the immune responses to each of these routine vaccine antigens at one month post-Dose 3 of routine vaccinations (approximately 7 months of age). Healthy subjects 6-12 weeks of age were randomly assigned to one of the following treatment groups:

- 2 doses of Rotarix co-administered with routine vaccines (co-ad group)
- 2 doses of Rotarix administered 1 month apart from routine vaccines (sep-ad group)

Subjects previously vaccinated against diphtheria, tetanus, pertussis, poliovirus, Hib, or *S. pneumoniae*, or those with histories of these diseases (plus hepatitis B), were excluded from the study. Subjects who received only one dose of Hep B vaccine at least 30 days prior to enrolment were included in the study.

GMC or GMT was measured for all antigens. Seroprotection or seropositivity for each antigen was defined as follows:

Anti-PRP:	≥ 1.0 µg/mL
Anti-HBs:	≥ 10 mIU/ml
Anti-polio (serotypes 1, 2, 3):	≥ 1:8
Anti-diphtheria:	≥ 0.1 IU/mL
Anti-tetanus:	≥ 0.1 IU/mL
Anti-PRN:	≥ 5 EL.U/mL
Anti-FHA:	≥ 5 EL.U/mL
Anti-PT:	≥ 5 EL.U/mL
Anti-*S. pneumoniae*: (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F)	≥ 0.05 µg/mL (≥ 2.0 µg/mL also measured)

Demonstration of non-inferiority of the co-ad group in terms of immune response to routine vaccine antigens required meeting all of the following criteria:

- Lower limit (LL) of the 95% CI on the difference in anti-PRP seroprotection rates (co-ad group minus sep-ad group) ≥ -10%
- LL of the 95% CI on the difference in anti-HBs seroprotection rates (co-ad group minus sep-ad group) ≥ -10%
- LL of the 95% CI on the difference in anti-poliovirus seroprotection rates (co-ad group minus sep-ad group) for serotypes 1, 2, and 3 ≥ -10%

- LL of the 95% CI on the difference in anti-diphtheria seroprotection rates (co-ad group minus sep-ad group) ≥ -10%
- LL of the 95% CI on the difference in anti-tetanus seroprotection rates (co-ad group minus sep-ad group) ≥ -10%
- LL of the 95% CI on the anti-pertussis GMC ratios (co-ad group divided by sep-ad group) for PT, FHA, and PRN ≥ 0.67
- LL of the 95% CI on the anti-*S. pneumoniae* GMC ratios (co-ad group divided by sep-ad group) for each of the seven serotypes ≥ 0.5

***Reviewer Note*:** These criteria are consistent with FDA-suggested non-inferiority criteria post-Dose 3 at 7 months of age except for anti-polio (FDA-suggested: LL of 95% CI≥ -5%) and anti-*S. pneumoniae* non-inferiority (FDA-suggested: LL of 95% CI ≥ 2/3).

Based on a sample size of 200 in each group, alpha=0.025, reference rate estimates for seroprotection endpoints or standard deviation estimates for GMC endpoints for each antigen, and limits of non-inferiority for each antigen mentioned above, the study had 90% power overall to meet the primary objective. Except for anti-PRP (92% power) and anti-PRN (99% power) endpoints, all the other endpoints each had 100% power to meet the non-inferiority criterion for that endpoint.

A total of 317 subjects (co-ad group-180, sep-ad group-137) were included in the ATP immunogenicity cohort. Demographic characteristics were similar between the groups. The percentage of subjects who received a dose of Hep B vaccine before Visit 1 was similar (co-ad group-87.8%, sep-ad group-89.1%).

For each of the routine antigens, seroprotection/seropositivity rates and GMCs/GMTs at Visit 4 were similar between groups in the ATP immunogenicity cohort (as well as in the TVC). Furthermore, the LL of the 95% CI on the difference in seroprotection rates and on the GMC ratios for each antigen were higher than the pre-defined non-inferiority criteria stated above (see two tables below). Therefore, the study was able to meet its primary objective and demonstrate that co-administration of Rotarix with routine vaccines did not impair the immune responses to these routine vaccine antigens.

Difference in seroprotection rates (ATP immunogenicity cohort)

							Difference in seroprotection rates			
									95% CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-PRP	Co-Ad	180	89.4	Sep-Ad	137	88.3	**Co-Ad – Sep-Ad**	1.12	-5.81*	8.60
Anti-HBsAg	Co-Ad	169	100	Sep-Ad	126	100	**Co-Ad – Sep-Ad**	0.00	-2.22*	2.96
Anti-Poliovirus 1	Co-Ad	128	100	Sep-Ad	91	100	**Co-Ad – Sep-Ad**	0.00	-2.91*	4.05
Anti-Poliovirus 2	Co-Ad	139	100	Sep-Ad	95	97.9	**Co-Ad – Sep-Ad**	2.11	-0.62*	7.35
Anti-Poliovirus 3	Co-Ad	146	100	Sep-Ad	105	100	**Co-Ad – Sep-Ad**	0.00	-2.56*	3.53
Anti-Diphtheria	Co-Ad	178	100	Sep-Ad	136	100	**Co-Ad – Sep-Ad**	0.00	-2.11*	2.75
Anti-Tetanus	Co-Ad	178	100	Sep-Ad	136	100	**Co-Ad – Sep-Ad**	0.00	-2.11*	2.75

N = number of subjects with available results
% = percentage of subjects who are seroprotected one month after Dose 3 of childhood routine vaccination (Visit 6)
95%CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit
*Lower limits of the 95% CI ≥-10% (the pre-specified clinical limit for non-inferiority)
(Source: Study Report Body Rota-060, pg 73)

GMC ratios (ATP immunogenicity cohort)

							GMC ratio			
									95 % CI	
Antibody	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**

Anti -PT	Co-Ad	179	58.9	Sep-Ad	137	60.9	**Co-Ad / Sep-Ad**	0.97	0.85*	1.10
Anti -FHA	Co-Ad	179	270.9	Sep-Ad	137	265.0	**Co-Ad / Sep-Ad**	1.02	0.89*	1.17
Anti -PRN	Co-Ad	179	105.7	Sep-Ad	137	118.6	**Co-Ad / Sep-Ad**	0.89	0.72*	1.10
Anti-PN 4	Co-Ad	178	1.96	Sep-Ad	136	2.19	**Co-Ad / Sep-Ad**	0.90	0.75**	1.07
Anti-PN 6B	Co-Ad	179	1.42	Sep-Ad	135	1.42	**Co-Ad / Sep-Ad**	1.00	0.75**	1.33
Anti-PN 9V	Co-Ad	179	2.60	Sep-Ad	136	2.65	**Co-Ad / Sep-Ad**	0.98	0.81**	1.19
Anti-PN 14	Co-Ad	180	4.84	Sep-Ad	136	5.35	**Co-Ad / Sep-Ad**	0.90	0.75**	1.09
Anti-PN 18C	Co-Ad	180	2.44	Sep-Ad	136	2.97	**Co-Ad / Sep-Ad**	0.82	0.68**	1.00
Anti-PN 19F	Co-Ad	180	1.99	Sep-Ad	137	1.92	**Co-Ad / Sep-Ad**	1.03	0.87**	1.23
Anti-PN 23F	Co-Ad	178	2.15	Sep-Ad	136	2.55	**Co-Ad / Sep-Ad**	0.84	0.67**	1.06

N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups);
*lower limit of the 95% CI ≥0.67 (the pre-specified clinical limit for non-inferiority)
**lower limit of the 95% CI ≥0.5 (the pre-specified clinical limit for non-inferiority)
(Source: Study Report Body Rota-060, pg 74)

***Reviewer Note*:** The applicant was still able to demonstrate non-inferiority of anti-polio and anti-*S. pneumoniae* responses using FDA-suggested criteria.

Non-BLA studies
In Rota-045 (see section 10.4.13), the applicant stated that no interference of immune responses to poliovirus serotypes 1, 2, and 3 was observed when OPV was co-administered with Rotarix. However, no data were provided (summary update of Rota-045 reported in the Periodic Safety Update Report).

Post-marketing report
There were no reports of drug interactions in the Periodic Safety Update Report (PSUR).

10.4.6 Immunogenicity (Therapeutic Proteins) (if relevant)

Not applicable to Rotarix.

10.4.7 Carcinogenicity

SAE Neoplasms

Core ISS analysis
Five Rotarix (0.01%) and 3 placebo recipients (0.01%) reported at least one SAE PT from Days 0-30 post-vaccination under the SOC *Neoplasms benign, malignant and unspecified*. The difference between groups was not significantly different (RR=1.66; 95% CI: 0.32-10.69). The following PTs, all judged not to be related to vaccination, were reported in the Rotarix group (all from Rota-023):

Ependymoma (Argentina): 12 week male, symptom onset on the day of Dose 1
Intracranial hemangioma (Peru): 6 week male, symptom onset 16 days post-Dose 1,
Leukemia (Nicaragua): 7 week male, symptom onset 16 days post-Dose 1
Neuroblastoma (Mexico): 14 week male, 8 days post-Dose 2
Testicular neoplasm (Venezuela): 14 week male, days post-Dose 2

Eight Rotarix (0.02%) and 9 placebo recipients (0.03%) reported at least one SAE PT regardless of time-to-onset under the SOC *Neoplasms benign, malignant and unspecified*. The difference between groups was not statistically significant (RR=0.85; 95% CI: 0.28-2.50). Besides the 5 PTs

listed above that occurred from Days 0-30, 3 other PTs, all occurring post-Dose 2 and judged not to be related to vaccination, were reported in the Rotarix group:

Chronic myeloid leukemia (Rota-007, Singapore): 16 month male, 365 days
Myelodysplastic syndrome (Rota-023, Argentina): 21 month female, 546 days
Primitive neuroectodermal tumor (Rota-036, Finland): 20 month male, 451 days

Supplementary ISS analysis
Only one SAE PT was reported during the course of the studies under the SOC *Neoplasms benign, malignant and unspecified*:

Hemangioma (Rota-007, Singapore): 8 month female, 143 days post-Dose 2, vaccine-unrelated

Non-SAE neoplasms

Core ISS analysis
Only one non-SAE PT was reported during the course of the studies under the SOC *Neoplasms benign, malignant and unspecified*:

Hemangioma (Rota-005, US): 13 week female, 33 days post-Dose 1 (also 41 days post-Dose 2), not related to vaccination

Supplementary ISS analysis
Only one non-SAE PT was reported during the course of the studies under the SOC *Neoplasms benign, malignant and unspecified*:

Neoplasm, unspecified head tumor (Rota-006, Brazil): 14 week female, 27 days post-Dose 1, not related to vaccination

Rota-060
Only one non-SAE PT was reported during the course of the studies under the SOC *Neoplasms benign, malignant and unspecified*:

Brain neoplasm malignant: 8 week female, 3 days post-Dose 1 of routine vaccine, not related to vaccination.

10.4.8 Withdrawal Phenomena/Abuse Potential

There were no reports of withdrawal phenomena or abuse potential in the BLA studies or PSUR.

10.4.9 Human Reproduction and Pregnancy Data

There were no reports of Rotarix administration during pregnancy or lactation in the BLA studies or the PSUR.

10.4.10 Assessment of Effect on Growth

Height and weight

Height (cm) and weight (kg) measurements were recorded at each study visit in Rota-005, Rota-006, Rota-007, and Rota-014. In each study, height and weight increases between visits were similar between Rotarix and placebo groups.

10.4.11 Overdosage Exposure

Overdosage was not reported in any of the BLA studies. In addition, no reports of Rotarix overdosage were reported in the PSUR.

10.4.12 Person-to-Person Transmission, Shedding

RV antigen shedding post-vaccination

RV shedding in stools was evaluated at predetermined time points in Rota-005, Rota-006 (subset), Rota-007 (subset; planned total of 200 subjects), Rota-014 (subset; planned subset of 150 subjects), Rota-033 (subset; planned total of 50 subjects), Rota-039, and Rota-048. RV shedding in Rota-006 was in section 8.1.4. RV shedding was measured as part of vaccine-take evaluation in Rota-005 (co-primary endpoint), Rota-007 (secondary immunogenicity endpoint), Rota-014 (secondary endpoint), Rota-033 (secondary endpoint), Rota-039 (primary endpoint), and Rota-048 (primary endpoint). In addition, assessment of RV shedding was a secondary endpoint in Rota-014, Rota-033, and Rota-039.

In all studies, stool sample collections were conducted primarily on Day 7 after each dose and tested using an ELISA assay at the laboratory of Dr. R. Ward (Children's Hospital Medical Centre, Cincinnati, US). Stool collection time points for individual studies were as follows:

Rota-005: pre-Dose 1, pre-Dose 2 (60 days post-Dose 1), Day 7 post-dose
Rota-006: pre-Dose 1, pre-Dose 2 (60 days post-Dose 1), Day 7 post-dose
Rota-007: pre-Dose 1, pre-Dose 2 (30 days post-Dose 1), Day 7 and Day 15 post-dose
Rota-014: pre-Dose 1, pre-Dose 2 (30 days post-Dose 1), Day 7 post-dose
Rota-033: pre-Dose 1, Days 3/7/10/15/30/45/60 post-dose
Rota-039: pre-Dose 1, pre-Dose 2 (60 days post-Dose 1), Day 7 and Day 15 post-dose
Rota-048: pre-Dose 1, pre-Dose 2 (30 days post-Dose 1), Day 7 and Day 15 post-dose

Any RV antigen detected in non-diarrheal stool samples was assumed to be vaccine strain. In Rota-005, RV detected in stools during the RV season was further analyzed by RT-PCR for G type, and by sequence analysis to distinguish G1 vaccine type RV from G1 wild-type RV.

Any RV antigen detected in diarrheal stool samples was also analyzed by RT-PCR to determine G type at the laboratory of ---------- (Finland) or GSK's laboratory. Any G1 RV detected was further evaluated by gene sequencing at GSK's laboratory in Belgium (Rota-005, Rota-006, Rota-007, Rota-014) or Delft Diagnostic Laboratory in the Netherlands (Rota-033, Rota-039, Rota-048) to distinguish wild-type from vaccine strain.

Post-Dose 1 RV shedding – Rotarix groups
In each study, the percentages of subjects who shed vaccine RV strain on Day 7 post-Dose 1 were:

Rota-005: 47.5% ($10^{5.6}$ group), 54.6% ($10^{6.8}$ group)

Rota-006: 36.2% ($10^{5.3}$ group), 35.2% ($10^{5.6}$ group), 44.1% ($10^{6.6}$ group)
Rota-007: 78.8% ($10^{5.3}$ group), 76.2% ($10^{5.6}$ group), 80.0% ($10^{6.6}$ group)
Rota-014: 11.4% ($10^{5.6}$ group + OPV), 17.5% ($10^{5.6}$ group + IPV)
Rota-033: 50.0% ($10^{6.5}$ group – pooled lots)
Rota-039: 55.6% ($10^{6.5}$ group)
Rota-048: 58.5% ($10^{6.5}$ group)

In studies with shedding data at Day 15, the percentages of subjects who shed RV ranged from 19.2% (Rota-033) to 64.1% (Rota-007,$10^{6.6}$ group). At Day 30, the percentages ranged from 0% (Rota-014 – both groups, Rota-033) to 24.3% (Rota-007,$10^{6.6}$ group). At Day 60, between 0% (Rota-006, $10^{5.3}$ and $10^{5.6}$ groups) and 1.1% (Rota-006, $10^{6.6}$ group) of subjects shed RV.

In each study, which had at least 2 time points, peak RV shedding occurred at Day 7 in all groups.

Higher shedding rates at Days 7, 15, and 30 in all Rotarix groups from Rota-007 compared to other studies may be related to either a population effect (Singapore, mostly Asian) or older age at Dose 1 (mean age=13.3 weeks) where maternal antibodies may have already declined.

Reviewer Note: Acceptable ranges of post-dose collection days for the Day 7 post-Dose 1 time point varied from study to study (Rota-005: Days 1-31; Rota-006 & Rota-048: Days 6-10; Rota-007: Days 7-10; Rota-014 & Rota-033: Days 6-8; Rota-039: Days 5-9). In Rota-005, the reviewer obtained 50% (75/150) and 54% (75/139) shedding rates for the $10^{5.6}$ and $10^{6.8}$ groups, respectively, from Days 6-8 post-Dose 1. In addition, 25.0% (1/4) of subjects in the $10^{5.6}$ group and 66.7% 1 (2/3) of subjects in the $10^{6.8}$ group shed RV from Days 11-15.

Post-Dose 2 RV shedding – Rotarix groups
For each study, the percentages of subjects who shed vaccine RV strain on Day 7 post-Dose 2 are given below. The percentage of shedders in each group is lower than on Day 7 post-Dose 1, with the exception of the $10^{5.6}$ group in Rota-014.

Rota-005: 15.6% ($10^{5.6}$ group – Day 10), 15.3% ($10^{6.8}$ group)
Rota-006: 11.5% ($10^{5.3}$ group), 21.3% ($10^{5.6}$ group), 16.5% ($10^{6.6}$ group)
Rota-007: 28.6% ($10^{5.3}$ group), 18.9% ($10^{5.6}$ group), 18.4% ($10^{6.6}$ group)
Rota-014: 13.9% ($10^{5.6}$ group + OPV), 7.7% ($10^{5.6}$ group + IPV)
Rota-033: 4.2% ($10^{6.5}$ group – pooled lots)
Rota-039: 10.1% ($10^{6.5}$ group)
Rota-048: 12.9% ($10^{6.5}$ group)

In studies with shedding data at Day 15, the percentages of subjects who shed RV ranged from 0% (Rota-033) to 16.2% (Rota-007,$10^{6.6}$ group). Shedding data at Days, 30, 45, and 60, available only for Rota-033, demonstrated 0% shedding at these time points.

In each study, which had at least 2 time points, peak RV shedding occurred at Day 7 in all groups.

Reviewer Note: In Rota-005, the acceptable range of collection days for the Day 7 post-Dose 2 time point was 1 to 25 days. From Days 6-8 post-Dose 2, shedding rates were 16.5% (20/121) and 15.3% (17/111) for the $10^{5.6}$ and $10^{6.8}$ groups, respectively. Shedding rates from Days 11-15 post-Dose 2 were 25.0% (2/8) in the $10^{5.6}$ group and 0% (0/4) in the $10^{6.8}$ group. One subject in the $10^{6.8}$ group shed RV on Day 25

RV shedding and GE symptoms
Previous reviews of solicited AEs post-vaccination have shown that rates of diarrhea and vomiting were similar between Rotarix groups and placebo, including rates of diarrhea and vomiting from

Rota-007. This indicates that RV shedding is not associated with an increase in GE symptoms in Rotarix recipients compared to placebo recipients.

Live RV shedding post-vaccination

Rota-039 and Rota-048
In Rota-039 and Rota-048, live RV detection was performed at GSK's laboratory on available RV antigen-positive stool specimens collected at Day 7 post-Dose 1. A titration assay using --------- cells as substrate was performed. The percentage of live virus in all stool samples collected at Day 7 in each study were then extrapolated by multiplying the percentage of subjects with live RV detected in RV-positive samples by the percentage of subjects with RV-positive samples.

In Rota-039, 46% (6/13) of subjects with available RV-positive samples had live RV detected in the same stools. The overall estimated percentage of subjects with live RV in stool samples collected on Day 7 post-Dose 1 was 25.6% (90/162 x 0.462). Similarly, in Rota-048, 45% (15/33) of subjects with available RV-positive samples had live RV detected in those samples. The overall estimated percentage of subjects with live RV on Day 7 post-Dose 1 samples was 26.5% (49/84 x 0.455).

Rota-006, Rota-007, Rota-014, and Rota-033
Live virus detection using the same methods was also performed on 96 retained frozen stool samples (Day 7 post-Dose 1) from these 4 studies that were RV antigen-positive by ELISA. In parallel, 51 wild-type RV antigen-positive frozen stool samples from GE episodes in Rota-006, Rota-007, and Rota-033 were tested for live virus.

Live RV was detected in 14.6% (14/96) of RV-positive samples. In comparison, live RV was detected in 68.6% (35/51) of wild-type RV-positive samples from GE episodes, demonstrating higher shedding after wild-type RV GE than after Rotarix vaccination.

RV antigen shedding – non-vaccinated subjects

Of the 421 placebo recipients in Rota-005, Rota-006, Rota-007, Rota-014, Rota-039, and Rota-048 who had stool analysis results, 7 (Rota-005- 2, Rota-006-1, Rota-007- 3, Rota-039- 1) had stool samples that tested positive for vaccine RV antigen. None of the 7 subjects were symptomatic with a GE-like illness near the time of stool collection, and all were healthy. Four of the 7 seroconverted post-Dose 2. Two of the subjects had a twin brother or sister enrolled in the Rotarix group ($10^{6.8}$ group) in the same study at the same time, therefore possibly leading to transmission due to close contact. For the other 5 subjects, reasons for vaccine RV infection are not clear, although errors in stool sample labeling could not be ruled out.

RV shedding - Non-BLA studies

Rota-045 (see section 10.4.13)
This Phase II, randomized, double-blind, placebo-controlled study evaluated the immunogenicity, reactogenicity and safety of 2 doses of Rotarix ($10^{6.5}$ $CCID_{50}$) in healthy infants (Bangladesh) when co-administered with OPV versus given alone. Shedding was lower in the Rotarix + OPV group (17.6%) compared to the Rotarix without OPV group (31.0%).

10.4.13 Post-marketing Exposure

Rotarix, at a potency of ≥ $10^{6.0}$ $CCID_{50}$ per dose, is licensed in the following 100 countries:

Angola, Argentina, Aruba, Australia, Austria, Bahrain, Bangladesh, Belgium, Benin, Bolivia, Brazil, Bulgaria, Burkina Faso, Cameroon, Chile, Colombia, Congo, Costa Rica, Curacao, Cyprus, Czech Republic, Democratic Republic of Congo, Denmark, Dominican Republic, Ecuador, Egypt, El

Salvador, Estonia, Finland, France, Gabon, Germany, Greece, Guatemala, Guinea, Honduras, Hong Kong, Hungary, Iceland, Ireland, Italy, Ivory Coast, Jamaica, Jordan, Kazakhstan, Kenya, Kuwait, Latvia, Lithuania, Luxembourg, Macau, Madagascar, Malawi, Malaysia, Mali, Malta, Mauritania, Mauritius, Mexico, Morocco, Mozambique, Myanmar, Namibia, Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, RCA, Romania, Saudi Arabia, Senegal, Singapore, Slovakia, Slovenia, South Africa, Spain, Sri Lanka, Suriname, Sweden, Switzerland, Taiwan, Thailand, Togo, Trinidad and Tobago, Turkey, UK, UAE, Venezuela, Vietnam, Yemen

As of July 2007, ---------- doses of Rotarix have been distributed since July 2004, with an estimated maximum of ---------- individuals receiving 2 doses.

The applicant submitted a 3rd Periodic Safety Update Report (PSUR) with the BLA that covered the period from July 12, 2006 to January 1, 2007, during which --------- doses of Rotarix were distributed. A 4th PSUR was later submitted that covered the period from January 12, 2007 to July 11, 2007, during which --------- Rotarix doses were distributed. The following reports of safety events were considered for inclusion in this report:

- All serious and non-serious reports from spontaneous notifications, including published reports, but excluding all non-healthcare professional reports and all non-serious reports received solely from regulatory authorities
- Unblinded serious attributable reports arising from clinical studies (phase I-IV), post-marketing surveillance studies or compassionate use studies, named-patient use or received as solicited reports following use of Rotarix

SAEs and non-SAEs – July 12, 2006 to January 11, 2007

196 SAE and non-SAE case reports were reported during this interval (serious-70, non-serious-126) from 26 countries. The majority of reports were from France (22.96%), Belgium (11.22%), Brazil (7.65%), Mexico (7.14%), South Africa (5.61%), Germany (5.10%), and Argentina (5.10%).

SAEs and non-SAEs – January 12, 2007 to July 11, 2007

A total of 289 SAE and non-SAEs were reported during this interval (serious-133, non-serious-156).

Blood in stools – *July 12, 2006 to January 11, 2007*
24 cases were reported from 3 MedDRA PTs (*Haemorrhagic diarrhea*- 4*, Gastrointestinal haemorrhage*- 6*, Haematochezia*- 14), of which 10 were reported together with IS. The following characteristics were described for the 14 remaining reports:

- Male: female ratio = 7:4 (3 unknown)
- Median age = 2 months (range: 2-18 months)
- Median time to onset = 1 day (range: 1-17 days)
- Post-Dose 1 = 8; Post-dose 2=1 (5 unknown)
- Serious cases = 7
- Outcome resolved = 6; outcome improved= 2; outcome unresolved= 3 (3 unknown)
- Alternative cause reported = 4 cases (cow milk tolerance, Salmonellosis, possible association with a food component, infectious gastroenteritis)

Blood in stools – *January 12, 2007 to July 11, 2007*
48 cases of "blood in stools" were reported; 47 were from 3 MedDRA PTs (*Haemorrhagic diarrhea*- 3*, Gastrointestinal haemorrhage*- 4*, Haematochezia*- 40). 29 of the cases were reported together with IS. The following characteristics were described for the 19 remaining reports:

- Male: female ratio = 10:7 (2 unknown)
- Median age = 3 months (range: 1.5-5 months)
- Median time to onset = 2 day (range: 0-30 days)
- Post-Dose 1 = 14; Post-dose 2= 3 (5 unknown)
- Serious cases = 10
- Outcome resolved = 11; outcome improved= 1; outcome unresolved= 4 (3 unknown)
- Alternative cause reported = 2 cases (cow's milk tolerance, allergic colitis)

Intussusception – *July 12, 2006 to January 11, 2007*
24 IS cases were reported during the interval from the following countries: Brazil (7), Mexico (3), Belgium (3), France (2), Venezuela (2), Argentina (2), Austria (1), Chile (1), Colombia (1), South-Africa (1), and Thailand (1). 18 of these cases had sufficient information to be classified as definite IS according to the Brighton case definition. The following demographic and clinical characteristics of the 24 cases were described:

- Male: female ratio = 13:8 (3 unknown)
- Median age = 4 months (range: 2-7 months)
- Median time to onset = 6 days (range: 0-56 days)
- Post-Dose 1 = 10; Post-dose 2 =9 (5 unknown)
- Successful reduction by enema or surgery = 17; spontaneously resolved = 1 (subject diagnosed with "suspected' IS based on ultrasound) (6 unknown)
- Intestinal resection = 2 (one case had stool test positive for adenovirus)
- Outcome resolved = 18; outcome improved= 1; outcome unresolved= 1; fatal outcome = 2 (both from Brazil) (2 unknown)
- Reoccurrence of IS = none

19 of the 24 IS cases occurred <31 days post-vaccination; 10 (52%) occurred after Dose 1, 5 (26%) occurred after Dose 2, and 4 (21%) occurred after an unspecified dose number.

Intussusception – *January 12, 2007 to July 11, 2007*
97 IS cases were reported during the interval; most were from Brazil (41), Mexico (14), Panama (14), and Argentina (6). 54 of these cases were considered confirmed IS according to the Brighton case definition. The following demographic and clinical characteristics were described:

- Male: female ratio = 24:31 (42 unknown)
- Median age = 5 months (range: 2-13 months)(41 unknown)
- Median time to onset = 26 days (range: 0-243 days)(43 unknown)
- Post-Dose 1 = 25; Post-dose 2 = 17 (55 unknown)
- Successful reduction by enema or surgery = 53; spontaneously resolved = 3
- Intestinal resection = 6
- Outcome resolved = 55; outcome improved= 1; fatal outcome = 2 (39 unknown)
- Reoccurrence of IS = none

Other AEs of interest – *July 12, 2006 to January 11, 2007*
The following 4 AEs were reported in 4 different subjects:

(Non-febrile) convulsion (Chile): 5 month male, onset < 1 month post-Dose 1, causality not assessed
Apnea (Austria): 2 month male, onset 2 days post- Rotarix dose (dose number not specified) and on the same day of Infanrix Hexa and Prevnar doses, causality to vaccination not noted
Leukocytoclastic vasculitis (France): 2 month male, onset 26 days post-Dose 1 of Rotarix and routine vaccinations (Infanrix quinta, Prevnar), unlikely related to vaccination
Thrombocytopenic purpura (Colombia): 2 month female, onset 1 day post-Dose 1 of Rotarix and Infanrix Hexa, causality to vaccination not noted

Other AEs of interest – *January 12, 2007 to July 11, 2007*
The following 4 AEs were reported in 4 different subjects:

Crying, Hypotonia, Convulsion, Apnea, Loss of consciousness, Convulsion (Spain): 4 month male, onset 48 hours post- Rotarix dose (dose number not specified), event resolved same day
Congestive cardiomyopathy (Austria): 6 week female, 2 days post-Rotarix, etiology unknown, unlikely related to vaccination, condition improved
Pneumonia (Mexico): 5 month male, 47 days post-Rotarix/pneumococcal vaccine
Pneumonia (Colombia): 6 month female, 3 months post-Dose 2 Rotarix, 2 months post-Prevnar, recovered
Convulsion (Belgium): 6 month male, 3 days post-Rotarix/Prevnar, concurrent GE, etiology unknown, event resolved
Convulsion (Finland): 3 month male, 4 days post-Rotarix/Pentavac, concurrent diarrhea, event resolved, etiology unknown
Convulsion (South Africa): 2 month female, 3 days post-Rotarix/Infanrix Hexa, event resolved, event recurred with next Infanrix Hexa, Dose 2 of Rotarix not administered
Thrombocytopenia (Spain): 4 month female, bloody stools 6 days post-Rotarix (diagnosed with IS), thrombocytopenia status-post platelet transfusion, EBV-positive by serology
Thrombocytopenic purpura (Brazil): 1 year old (gender unknown), onset day post-Rotarix unknown
Jaundice, transaminases increased (France): 2 month male, 2 days post-Rotarix (Dose 1), resolved

Secondary transmission – *July 12, 2006 to January 11, 2007*
Two cases of secondary transmission were reported. In the first case, a male infant (France, age unknown) experienced mild vomiting and moderate diarrhea 24-48 hours after Rotarix vaccination of his brother. His symptoms resolved within 1-3 days. The etiology of the GE episode was not determined. In the second case, a 4-month female (France) developed moderate diarrhea 2 days post-Dose 1 of Rotarix. The etiology of this GE episode was not determined. The subject reportedly contaminated other children in a nursery, but the etiology of GE episodes in these children was also not determined.

Secondary transmission – *January 12, 2007 to July 11, 2007*
One case of possible secondary transmission was reported in an elderly female (Germany, age unknown) who experienced vomiting and diarrhea while caring for a sick grandson who had been recently vaccinated with Rotarix. Two days post-vaccination, the 5-month old grandson developed suspected RV GE. The interval between exposure to grandson and illness onset in the elderly female was unknown. Stool tests for RV were not performed.

Fatal cases – *July 12, 2006 to January 11, 2007*
Two fatal cases, both IS, were reported from Brazil. The first case (age and sex not known) received an unspecified dose of Rotarix in August 2006, and developed IS after an unspecified period of time and was hospitalized. The cause of death was also not specified, and it was unknown

whether an autopsy was performed. The second case, a 2 month female, received an unspecified dose of Rotarix on September 26, 2006. She developed IS with onset 6 days post-vaccination, and died --- days after onset. It was unknown whether an autopsy was performed.
***Reviewer Note*:** The 3rd PSUR also contained follow-up information on 2 fatal cases that occurred during the 2nd PSUR. The first case was a 9-month-old subject from Mexico (sex unknown) who died following a RV infection following an unspecified time interval. However, it remains unclear whether the subject actually received Rotarix. The second case involved a 3-month-old male from Venezuela who developed ITP, with symptom onset 3 hours after Rotarix vaccination. The patient also had received OPV and DTPa-HBV vaccines concomitantly.

Fatal cases – *January 12, 2007 to July 11, 2007*
Three fatal cases were reported. Two of the cases (Brazil, >6 weeks of age, gender unknown) died after developing IS post-Dose 1 of Rotarix. Interval from vaccination to IS onset and death unspecified. The third case (Kenya, 4 month male) developed profuse watery diarrhea 8 hours post-Dose 1 of Rotarix. He subsequently developed circulatory collapse and respiratory failure one day later and died that same day. Stool sample was positive for adenovirus.

Maladministration – *July 12, 2006 to January 11, 2007*
66 cases of maladministration were reported (reporting frequency = 0.8/100,000 doses distributed). Of the total, 46 cases were administered Rotarix via the incorrect route (IM-42, SQ-3, unknown-1) and 20 cases received vaccine at an incorrect age or on an inappropriate schedule.

14 of the 46 cases of incorrect administration route were associated with AEs (non-SAE-14, SAE-1). The lone SAE was reported as allergic shock which occurred in a 2 month old Belgian subject 30 minutes after IM administration of Rotarix. The event resolved the same day. The applicant felt that the clinical description of the case was inconsistent with the diagnosis.

7 of the 20 cases of incorrect age/scheduling of Rotarix administration were associated with AEs (non-SAE-3, SAE-4). All SAEs were reported as gastroenteritis (incorrect age-2, incorrect schedule-2) and eventually resolved.

Maladministration – *January 12, 2007 to July 11, 2007*
94 cases of maladministration were reported; 61 cases were administered Rotarix via the incorrect route and 33 cases received vaccine inappropriately for other reasons (incorrect age, inappropriate schedule, inappropriately stored vaccine).

12 of the 61 cases of incorrect administration route were associated with AEs (non-SAE-10, SAE-2). The 2 SAEs were reported as RSV pneumonia and injection site reaction; both resolved.

5 of the 33 cases of other inappropriately administered Rotarix vaccinations were associated with AEs (non-SAE-3, SAE-2). One of the SAEs was a case of IS 5 days post-Dose 1 of Rotarix at half of the recommended dose. The second SAE was a 19-month female who, after receiving Rotarix at an older age than recommended, developed GE and dehydration.

Most frequent reported AEs – from launch of Rotarix to July 11, 2007

The 10 most frequently reported AEs (SAEs and non-SAEs) are listed in the table below.

System Organ Class	Preferred Term	Number of Events	Reported Frequency per 100,000 doses distributed
Gastrointestinal disorders	Diarrhoea	252	2.05
Gastrointestinal disorders	Vomiting	174	1.41
Gastrointestinal disorders	Intussusception	133	1.08

General disorders and administration site conditions	Pyrexia	124	1.00
Injury, poisoning and procedural complications	Incorrect route of drug administration	116	0.94
Gastrointestinal disorders	Haematochezia	60	0.49
Metabolism and nutrition disorders	Anorexia	51	0.41
Infections and infestations	Gastroenteritis rotavirus	46	0.37
Psychiatric disorders	Crying	44	0.36
Gastrointestinal disorders	Abdominal pain	43	0.35

(Source: 4th PSUR, pg 42)

Blood in stools (PTs *Haemorrhagic diarrhea, Gastrointestinal haemorrhage, Haematochezia*)
57 cases of blood in stools (excluding those associated with IS) have been reported during this interval (0.46/100,000 doses distributed). 63% of the reports were from developing countries.

Intussusception
140 spontaneous reports of IS were made during this interval, 61 of which occurred within 30 days of Rotarix vaccination. The majority of the 61 cases were reported from Mexico (15), Brazil (10), Belgium (6) and Venezuela (6). 58 of the 61 cases had sufficient information to be classified as definite IS according to the Brighton case definition.

Based on statistical analyses described in the PSUR which used the background incidence of IS in children <1 year of age and a figure of 12.3 million distributed doses of Rotarix, the applicant calculated a total of 556 cases of IS that would have been expected to occur within 30 days post-vaccination during this period of observation. The observed-to-expected IS case ratios for infants 2-3 months, 3-4 months, 4-5 months, and 5-6 months of age were 8:66, 13:41, 15:312, and 15:137, respectively.

Analysis of the 61 IS cases by time to onset post-vaccination did not reveal any clustering of cases after Dose 1, Dose 2, or unspecified dose number.

Kawasaki disease
No cases of Kawasaki disease have been reported.

Non-BLA studies

The following 2 non-BLA studies were completed during the period of the 3rd PSUR, neither of which identified any new safety issues:

Rota-041
This Phase IIIB, double-blind, randomized, placebo-controlled, multi-center study evaluated the immunogenicity, safety and reactogenicity of 2 doses of Rotarix in healthy 6-12 week old infants at Dose 1. No fatal SAEs or were reported. Eleven SAEs (Rotarix-9, placebo-2) were reported, with only one SAE, idiopathic thrombocytopenic purpura (Rotarix group; 3.5 month female; onset 33 days post-Dose 1) assessed as causally related to vaccination. No IS cases or study discontinuations due to AEs/SAEs were reported.

Rota-045
This Phase II, randomized, double-blind, placebo-controlled study evaluated the immunogenicity, reactogenicity and safety of 2 doses of Rotarix in healthy infants (Bangladesh) when co-administered with OPV versus given alone. No vaccine-related SAEs were reported. Reactogenicity profiles were similar between Rotarix and placebo groups, and between Rotarix groups.

Results of the following 3 non-BLA studies were summarized in the 4th PSUR, none of which identified any new safety issues:

Rota-044
This Phase IIIB, double-blind, randomized, placebo-controlled, multi-center study evaluated the immunogenicity and safety of 2 doses of Rotarix in India in healthy 8 week old infants at Dose 1. No fatal SAEs or were reported. Five subjects (Rotarix-3, placebo-2) reported non-fatal SAEs, none of which were judged to be causally related to vaccination. No IS cases were reported.

Rota-051
This Phase II, randomized, double-blind, placebo-controlled study evaluated the immunogenicity, reactogenicity and safety of 2 doses of Rotarix in healthy infants in Vietnam. Reactogenicity profiles were similar between treatment arms, and clinically meaningful differences in unsolicited AEs and SAEs between groups were not observed.

Rota-061
This Phase III, randomized study evaluated the immunogenicity, safety, and reactogenicity of 3 lots of lyophilized Rotarix and a liquid Rotarix formulation when given as 2 doses in healthy infants. The 3 lots were similar in reactogenicity and unsolicited AE reporting. No fatal events or IS cases were reported between Dose 1 and Visit 3.

Other non-BLA studies
In addition, a list of SAEs from other non-BLA studies (Rota-003, Rota-013, Rota-----, Rota----, Rota-020, Rota-021, Rota-041, Rota-044, Rota-045) was submitted with the BLA. Besides the case of vaccine-related ITP mentioned previously in Rota-041, 2 other vaccine-related SAEs in Rotarix recipients were noted as follows:

Syncope vasovagal (Rota-021): 1.5 month male, onset on the day post-Dose 2, also received DTPw-HBV-Hib
Intussusception (Rota-021): 6 month female, onset 15 days post-Dose 3, also received DTPw-HBV-Hib

In addition, the following SAEs (all judged as unrelated to vaccination) associated with fatal outcomes were reported in Rotarix recipients:

Cardiopulmonary failure/Pneumonia/Renal failure (Rota-045): 3 month male, 16 days post-Dose 1
Bronchopneumonia (Rota-013): 7 month female, 124 days post-Dose 3
Bronchopneumonia/Gastroenteritis (Rota-013): 6 month female, 77 days post-Dose 3
Bronchopneumonia/Gastroenteritis (Rota-013): 5 month male, 46 days post-Dose 3
Cardiogenic shock/Congestive cardiomyopathy/Gastroenteritis (Rota-021): 5 month female, 24 days post-Dose 2, also received DTPw-HBV-Hib

The following cases of non-fatal pneumonia SAEs (PT *Pneumonia*, *Bronchopneumonia, Pneumonia viral*) were reported:
Rota-041: male, 28 days post-Dose 1 (Placebo)
Rota-044: male, 2 days post-Dose 2 (Rotarix)
Rota-013: male, 152 days post-Dose 3 (Rotarix)
Rota-013: male, 21 days post-Dose 2 (Rotarix)
Rota-013: male, 146 days post-Dose 3 (Rotarix)
Rota-013: male, 39 days post-Dose 2 (Rotarix)
Rota-013: male, 13 days post-Dose 1 (Rotarix)

Rota-013: male, 106 days post-Dose 3 (Rotarix)
Rota-013: male, 15 days post-Dose 2 (Rotarix)
Rota-013: female, 152 days post-Dose 3 (Placebo)
Rota-013: female, 13 days post-Dose 3 (Rotarix)
Rota-013: male, 113 days post-Dose 3 (Rotarix)
Rota-013: female, 39 days post-Dose 3 (Rotarix)
Rota----: female, 19 days post-Dose 1 (Rotarix)
Rota----: female, 14 days post-Dose 2 (Rotarix, OPV)
Rota-020: male, 36 days post-Dose 1 (Placebo, Infanrix-hexa)
Rota-020: female, 47 days post-Dose 1 (Rotarix, Infanrix-hexa)
Rota-020: female, 61 days post-Dose 1 (Rotarix, Infanrix-hexa)
Rota-021: male, 48 days post-Dose 1 (Rotarix, DTPw-HBV-Hib)

The following cases of convulsion SAEs (PT *Convulsion, Partial seizures*) were reported:
Rota-041: female, 58 days post-Dose 1 (Rotarix)
Rota-041: female, 34 days post-Dose 2 (Rotarix)
Rota-021: female, 67 days post-Dose 1 (Placebo, DTPw-HBV-Hib)

The following cases of bronchitis SAEs (PT *Bronchitis*) were reported:
Rota-013: male, 180 days post-Dose 3 (Rotarix)

Kawasaki disease (KD)
One case of KD was reported in a completed non-BLA study (Rota-061, lot consistency) in which all 1200 subjects were vaccinated with Rotarix. This case is summarized below.

Study	Country	Age at onset	Sex	Dose # after which AE occurred	Time from last dose to onset
Rota-061	Finland	3 months	M	1	12 days

Data obtained from Analysis of Kawasaki Reports Following Rotarix, pgs 11 & 20

Among ongoing trials (as of *Analysis of Kawasaki Reports Following Rotarix* dated June 18, 2007), 22 cases of KD have been reported from 3 trials being conducted in Asia: Rota-028 (Singapore), Rota-029 (Hong Kong), and Rota-030 (Taiwan). Of these 22 cases, 13 occurred in Rotarix recipients and 9 occurred in placebo recipients; the relative risk was 1.4 (95% CI: 0.6-3.4). Eleven of the 22 cases (Rotarix-8, placebo-3) met the criteria for KD, 9 cases (Rotarix-4, placebo-5) met the criteria for incomplete (atypical) KD, and 2 cases (Rotarix-1, placebo-1) had insufficient information to be categorized in either category. A summary of cases by study is presented below.

Study	Total KD reports		KD meeting criteria		Incomplete KD meeting criteria		Insufficient info to meet criteria	
	Rotarix	Placebo	Rotarix	Placebo	Rotarix	Placebo	Rotarix	Placebo
Rota-028	8	4	5	1	3	2	0	1
Rota-029	2	2	2	1	0	1	0	0
Rota-030	3	3	1	1	1	2	1	0
Total	13	9	8	3	4	5	1	1

Data obtained from Analysis of Kawasaki Reports Following Rotarix, pgs 21-23

***Reviewer Note*:** The reviewer summarized the total number of KD reports by category for both BLA and non-BLA studies. Results are summarized below.

Study	Total KD reports		KD meeting criteria		Incomplete KD meeting criteria		Insufficient info to meet criteria	
	Rotarix	Placebo	Rotarix	Placebo	Rotarix	Placebo	Rotarix	Placebo
Rota-028	8	4	5	1	3	2	0	1
Rota-029	2	2	2	1	0	1	0	0

Rota-030	3	3	1	1	1	2	1	0
Rota-006	1	0	0	0	1	0	0	0
Rota-007	2	0	1	0	0	0	1	0
Rota-023	1	0	0	0	0	0	1	0
Rota-061	1	0	1	0	0	0	0	0
Total	18	9	10	3	5	5	3	1

Data obtained from Analysis of Kawasaki Reports Following Rotarix, pgs 20-23

***Reviewer Note*:** The reviewer also totaled the number of KD reports with onset within 30 days of vaccination. Results are summarized below.

Within 30 days of vaccination

Study	**Total KD reports**		**KD meeting criteria**		**Incomplete KD meeting criteria**		**Insufficient info to meet criteria**	
	Rotarix	**Placebo**	**Rotarix**	**Placebo**	**Rotarix**	**Placebo**	**Rotarix**	**Placebo**
Rota-028	0	0	0	0	0	0	0	0
Rota-029	0	0	0	0	0	0	0	0
Rota-030	1	1	0	1	1	0	0	0
Rota-006	0	0	0	0	0	0	0	0
Rota-007	0	0	0	0	0	0	0	0
Rota-023	0	0	0	0	0	0	0	0
Rota-061	1	0	1	0	0	0	0	0
Total	2	1	1	1	1	0	0	0

Data obtained from Analysis of Kawasaki Reports Following Rotarix, pgs 20-23

Analysis of the time to onset of the 20 cases that met the KD or incomplete KD criteria did not reveal temporal clustering among either Rotarix subjects or all subjects. Only 2 cases had onset within the first month post-vaccination (Rotarix case – 3 days post-Dose 1, placebo case – 14 days post-Dose 2).

Analysis of the time to onset of all 27 reported cases from BLA (Rota-006, Rota-007, Rota-023) and non-BLA studies (Rota-028, Rota-029, Rota-030, Rota-061) similarly did not indicate temporal clustering among Rotarix subjects or all subjects. Only 3 cases had onset within the first month post-vaccination (Rotarix cases – 3 days post-Dose 1, 12 days post-Dose 1; placebo case – 14 days post-Dose 2).

Analyses of observed versus expected incidence of KD reports, based on published estimates of background incidence of KD under 5 years of age in each study region (Latin American, Europe, North America, South East Asia) demonstrated that overall, the number of observed and expected reports were similar (18 and 18.09, respectively) in Rotarix recipients (see table below). Among placebo recipients, the observed-to-expected ratio was 9 to 16.02; the lower number of observed reports was driven by results from Rota-028 (4 observed versus 8.45 expected).

	HRV				**Placebo**			
Region/study	**Subjects enrolled**	**Exposure time ***	**Observed (meeting full KD definition)**	**Expected**	**Subjects enrolled**	**Exposure time ***	**Observed (meeting full KD definition)**	**Expected**
Latin America								
006	1618	1778	1 (0)	0.09	537	578	0	0.03
023	30638	19945	1 (0)	1.00	30527	19666	0	0.98
024	4392	4392	0	0.22	2195	2195	0	0.11
Total			**2 (0)**	**1.31**			**0**	**1.12**
Asia								

007	1811	2223	2 (1)	2.22	653	802	0	0.80
028	3271	8450	8 (5)	8.45	3271	8450	4 (1)	8.45
029	1512	3908	2 (2)	3.91	1512	3908	2 (1)	3.91
030	570	1475	3 (1)	1.48	570	1475	3 (1)	1.48
039	398	133	0	0.13	52	18	0	0.02
Total			**15 (9)**	**16.19**			**9 (3)**	**14.66**
Europe								
061	1200	600	1 (1)	0.06	0	0	0	0
023	1035	259	0	0.03	1025	256	0	0.03
036	2646	3969	0	0.40	1348	2022	0	0.20
Total			**1 (1)**	**0.49**			**0**	**0.23**
North America								
005	421	351	0	0.05	108	90	0	0.01
060	484	363	0	0.05	0	0	0	0
Total			**0**	**0.10**			**0**	**0.01**
Overall total			**18 (10)**	**18.09**			**9 (3)**	**16.02**

*expressed in person-years
Source: Analysis of Kawasaki Reports Following Rotarix, pg 16

Ongoing targeted safety studies

The following 3 targeted safety studies are ongoing, with no results available at the time of the submitted PSUR:

Rota-022: Phase II, double-blind, randomized, placebo-controlled study to assess the safety, reactogenicity and immunogenicity of 3 doses of Rotarix ---------- in HIV-infected infants ----------weeks of age in South Africa.
Rota-052: Phase IIIb, randomized, double-blind, placebo-controlled study to explore the existence of horizontal transmission of the Rotarix vaccine strain between twins within a family.
Rota-054: Phase IIIb, double-blind, randomized, placebo-controlled, multi-country, multi-center study, to assess the safety, reactogenicity and immunogenicity of 2 doses of Rotarix when administered to medically stable pre-term (< 37 weeks) infants on a 0, 1- or 0, 2-month schedule.

10.5 Safety Conclusions

The available pooled safety data indicate that Rotarix, when administered at a potency of $10^{6.5}$ $CCID_{50}$ per dose and as a 2-dose series 1-2 months apart in healthy infants beginning 6-17 weeks of age, demonstrated similar frequencies of solicited AEs, unsolicited AEs, SAEs, and fatalities with those of placebo. The exceptions were gastroenteritis and diarrhea, which were reported significantly less as SAEs in Rotarix subjects compared to placebo subjects. Three different lots of Rotarix also had similar safety profiles. An increased risk of IS was not observed. Co-administration of Rotarix with routine pediatric vaccines did not impair the immune response to any of these vaccine antigens. Although data was limited, Rotarix appeared to be safe when administered to pre-term infants. Thus far, no significant post-marketing safety issues have been identified.

11 Additional Clinical Issues

11.1 Directions for Use

How Commercially Supplied
Rotarix will be supplied as a vial of lyophilized vaccine and a pre-filled oral applicator containing 1 ml of liquid $CaCO_3$ buffer. The applicator contains a plunger stopper and a transfer adapter for reconstitution.

Reconstitution
In all studies, Rotarix was prepared by reconstituting the lyophilized active ingredient (RIX4414 strain + excipients) with 1.0 ml of GSK's $CaCO_3$ buffer contained in a pre-filled syringe. After injecting the buffer into the vial containing the lyophilized vaccine, the vial was shaken well to resuspend the vaccine. The entire volume of resuspended product was then withdrawn into the same syringe, the needle (or transfer device) of the syringe was discarded, and the product was administered promptly as a single oral dose.

Reconstitution of the commercial lyophilized vaccine will follow the same procedures, using an oral applicator filled with buffer and a transfer adapter instead of a syringe and needle. The reconstituted vaccine should appear milky white in appearance. It should be inspected visually for particulate matter and/or discoloration, and not be administered if either of these conditions exists.

Administration
Rotarix is to be administered orally. The infant should be seated in a reclining position, and the entire content of the oral applicator containing the reconstituted vaccine should be administered on the inside of the cheek. Rotarix is not to be administered by injection.

Storage and Handling before Reconstitution
Both the lyophilized Rotarix and buffer should be stored and transported at 36° to 46° F (+2° to +8° C). Stability data demonstrated no loss of vaccine potency when the lyophilized vaccine and buffer were stored at this temperature range for at least -- months. If the vaccine is frozen, it should be discarded. The vaccine should be stored in its original package to protect from light.

Storage and Handling after Reconstitution
Rotarix should be administered promptly or stored at 36° to 46° F (+2° to +8° C) for up to 24 hours. Stability data demonstrated no loss of potency 24 hours after reconstitution when the vaccine was stored at this temperature range. Unused reconstituted vaccine should be discarded if not used within 24 hours.

11.2 Dose Regimens and Administration

Level of Confidence for the Dose/Regimen
Nine of the 11 BLA studies evaluated the safety and immunogenicity, with 3 studies evaluating the efficacy, of 2 doses of Rotarix at the proposed licensure potency of ≥ $10^{6.0}$ $CCID_{50}$ per dose. Eight of the 9 studies enrolled and vaccinated subjects who were at least 6 weeks of age at Dose 1, the proposed starting age for licensure. All studies required at least 4 weeks between doses, the minimum proposed dosing interval for licensure. The quality of data was acceptable and consistent for all trials, reflecting the randomized, double-blind, placebo-controlled design and conduct in each study.

Dose-toxicity and Dose-response Relationships
As described in section 8.1.4, Rota-006 evaluated 2 doses of Rotarix administered 2 months apart at 3 different dose potencies ($10^{5.3}$ $CCID_{50}$, $10^{5.6}$ $CCID_{50}$, and $10^{6.6}$ $CCID_{50}$). Rota-007 also evaluated 2 doses of Rotarix administered 1 month apart at the same range of potencies as in Rota-006. In both studies, overall, frequencies of solicited, unsolicited, and SAEs after each dose were similar between treatment groups. Although post-Dose 1 RV shedding rates were highest in the $10^{6.6}$ $CCID_{50}$ group in both studies, post-Dose 2 shedding for this group was lower than the $10^{5.6}$ $CCID_{50}$ group in Rota-006 and lower than both the $10^{5.3}$ $CCID_{50}$ and $10^{5.6}$ $CCID_{50}$ groups in Rota-007.

In Rota-006, Year 1 VE against any RV GE was higher for the $10^{6.6}$ $CCID_{50}$ group than the other lower potencies. A dose-response was observed for Year 1 VE against severe RV GE, with the highest VE observed in the $10^{6.6}$ $CCID_{50}$ group. Seroconversion rates and GMC were also the highest in the $10^{6.6}$ $CCID_{50}$ group, while a dose-response was seen for vaccine take rates.

In Rota-007, seroconversion rates and GMCs were the highest in the $10^{5.6}$ $CCID_{50}$ group, although estimates for both parameters were similar between the $10^{5.6}$ $CCID_{50}$ group and $10^{6.6}$ $CCID_{50}$ groups.

Both studies indicated that a dose-response for toxicity was not observed, while the highest potency ($10^{6.6}$ $CCID_{50}$) provided the most optimal combination of efficacy and immunogenicity.

The length of the dosing interval (1 versus 2 months) did not affect vaccine efficacy. In both pivotal Phase III studies (Rota-023 and Rota-036), 1 or 2 month intervals were allowed, resulting in higher VE against any RV GE, and equivalent or higher VE against severe RV GE, than in Rota-006 ($10^{6.6}$ $CCID_{50}$ group, 2-month interval).

Dosing interval also did not significantly affect immunogenicity. Although seroconversion rates, GMC, and vaccine take rates were higher in Rota-007 (1-month dose interval) than in Rota-006 (2-month dose interval), the differences may have been explained by an older study cohort in Rota-007 (11-17 weeks at Dose 1) compared to Rota-006 (6 to 12 weeks at Dose 1) and/or ethnic differences in these 2 studies (Asian versus Hispanic). However, when comparing Rota-007 with Rota-039, another study utilizing a 2-month dose interval in subjects 6-12 weeks of age from Thailand, seroconversion rates were similar between studies while GMC was higher in Rota-039 than in Rota-007. These results suggest that older age at Dose 1 and dosing interval did not significantly affect RV immunogenicity, and that ethnicity may influence RV immune response. Higher seroconversion rates and GMCs in Rota-036 (Europe, 1- or 2-month dose intervals) than in Rota-023 (Latin America, 1- or 2-month dose intervals) also indicate the RV immunogenicity may be influenced by ethnicity and/or socioeconomic factors.

Breastfeeding did not adversely impact RV immunogenicity in either study, nor did it impact efficacy in another study (Rota-036; see section 9.1.4).

Dose Modification for Special Populations
Dose modification was not evaluated for any special pediatric population, including infants born pre-term (< 36 weeks gestation) and immunocompromised infants. Studies that allowed inclusion of pre-term infants administered Rotarix at the proposed licensure potency of ≥ $10^{6.0}$ $CCID_{50}$ per dose.

Unresolved Dosing/Administration Issues
No other dosing or administration issues related to this product have been identified.

11.3 Special Populations

Eight of the 9 BLA studies that evaluated Rotarix at the proposed licensure potency of ≥ $10^{6.0}$ $CCID_{50}$ per dose enrolled and vaccinated infants who were at least 6 weeks of age at Dose 1; only Rota-007 required a minimum age of 8 weeks. The maximum age at Dose 1 varied between 12 weeks to 17 weeks. Of the remaining 2 BLA studies, age ranges at Dose 1 were 6-12 weeks, 5-10 weeks, and 8-17 weeks.

Gender distribution did not vary significantly across studies, and noticeable differences in the percentages of females versus males were not observed in each study.

As mentioned previously, all studies were randomized, double-blind, placebo-controlled trials. Study conduct and procedures, such as main inclusion and exclusion criteria, efficacy endpoint definitions, case ascertainment, stool testing, immunogenicity testing and endpoint definitions, and safety monitoring were similar across studies.

Rotarix was not formally evaluated in any special populations, including pre-term infants and infants with immunodeficiencies or other chronic conditions.

Rotarix was not evaluated in pregnant or lactating females.

11.4 Pediatrics

Rotarix is indicated for infants beginning 6 weeks of age. No other pediatric issues related to this product have been identified.

12 Conclusions – Overall

Rotarix, administered at a potency of $10^{6.5}$ $CCID_{50}$ and as a 2-dose series to healthy infants 6 to 24 weeks of age, was effective in preventing RV GE of any grade of severity and in preventing severe RV GE caused by naturally-occurring RV strains during the first year of life. Although not evaluated in the US, VE was observed across heterogeneous geographical populations. Protection against any and severe RV GE was also demonstrated against circulating G1 and certain non-G1 types that are similar in distribution in the US. Co-administration of Rotarix with other routine vaccines in the U.S. infant immunization schedule did not cause interference of the immune response to each of these routine antigens. Rotarix did not increase the post-vaccination risk of intussusception. However, a statistically significant increase in pneumonia-related deaths and convulsion-related SAEs were observed in Rotarix recipients compared to controls in Rota-023 during the post-vaccination period, although the number of pneumonia-related deaths occurring within 31 days post-vaccination were smaller.

13 Recommendations

13.1 Approval, Non-approval, Conditions

The reviewer recommends that Rotarix be approved for use in infants 6 to 24 weeks of age.

13.2 Recommendation on Postmarketing Actions

In Module 1.16 (Risk Management Plans), the applicant submitted a pharmacovigilance plan that is focused on safety aspects of interest as well, information that is missing, or information requiring additional surveillance. The plan consists of post-marketing surveillance for intussusception, pneumonia-related mortality, and changes in RV strain distribution, as well as demonstration of post-marketing vaccine effectiveness and genetic stability of vaccine virus. In addition, evaluation of Rotarix vaccine virus transmission in infant twins and Rotarix safety/immunogenicity in preterm and immunocompromised infants will be conducted through ongoing or future studies.

Intussusception

Active IS surveillance – Germany and the United Kingdom
The applicant states that it will provide support for active surveillance activities in Germany and the United Kingdom. Each country will utilize a pediatric surveillance unit for IS surveillance: the Erhebungseinheit for Seltene Paediatrische Erkrankungen in Deutschland (ESPED) in Germany and the British Paediatric Surveillance Unit (BPSU) in the UK. ESPED conducts national-level active surveillance on rare pediatric diseases from approximately 390 pediatric departments in Germany. ESPED IS surveillance, co-funded with Sanofi Pasteur MSD, has been ongoing since January 2006 and will continue through at least the end of 2008. BPSU includes 2,500 pediatricians and covers 12.8 million children below 16 years of age. IS surveillance will be initiated by the third quarter of 2007. For both units, IS cases will be reported to the applicant every six months and shared with regulatory authorities. GSK plans to commit to this active IS surveillance project for 2 years, then discuss with authorities to determine whether activities need to be continued.

Through ESPED and BPSU, the applicant plans to provide reliable baseline IS data before introduction of the vaccine to then be able to detect a significant increase in IS rate after introduction of routine Rotarix vaccination. In the table below, the applicant provided power calculations to be able to detect additional IS cases at various levels of vaccine coverage based on the RotaShield attributable risk (1 case per 10,000 vaccinees), expected live birth estimates for each country, and baseline IS rate from the Swiss Pediatric Surveillance Unit Report (3.9 per 10,000 children).

Vaccine Coverage:			5%		25%		50%		100%	
Country	Live Births	Baseline IS Cases*	Addn IS**	(Power)	Addn IS**	(Power)	Addn IS**	(Power)	Addn IS**	(Power)
D°	719 250	280	3	(27)	17	(67)	35	(89)	71	(99)
D°+UK	1 315 372	512	6	(38)	32	(87)	65	(99)	131	(100)

* Baseline intussusception rate (3.9 per 10,000 children) based on Swiss Pediatric Surveillance Unit Report[54]
** Attack rate for additional intussusception cases based on RotaShield AR = 1 case per 10,000 vaccinees[55]
°D: Germany; UK: United Kingdom
Source: Risk Management Plans, pg 43

Active and passive post-marketing IS surveillance (PASS protocol) – Mexico
In order to assess the temporal association between Rotarix vaccination and the occurrence of definite IS at different time periods post-vaccination (Days 0-15, Days 0-30), and to estimate the incidence of IS, active hospital surveillance (daily review of log books/clinical files) and passive IS surveillance (database review) will be conducted in Mexico, where universal mass vaccination has recently begun. The targeted surveillance population will be all children younger than one year of age. IS surveillance will be conducted through the Instituto Mexicano del la Seguridad Social (IMSS) network, which covers a population of over 40 million with a birth cohort of 575,000, and consists of 224 IMSS health facilities with pediatric care and a comprehensive electronic data warehouse that can readily link together hospitalization, outpatient, vaccination, and mortality data. This Passive and Active Surveillance Systems (PASS) Protocol has been endorsed by a panel of international experts, including 3 North American scientists, and was sent to the FDA and EMEA for comments. A copy of the PASS protocol was also submitted with the BLA.
Reviewer Note: According to the CBER reviewer of the PASS protocol, the protocol submitted with the BLA (dated April 2007) did not take into account comments previously made by CBER.

To assess the temporal association between Rotarix vaccination and IS, a self-controlled case series analysis will be performed after 660 IS cases have been enrolled; the enrollment period is anticipated to be 3 years. An interim analysis will also be performed after 360 IS cases are recruited.

Post-marketing IS surveillance – US
The applicant states that an additional post-marketing observation study in the US is not necessary due to the robustness of surveillance activities in Europe and Mexico. The applicant proposed to closely monitor all IS reports, and perform the following analyses in together with FDA/CDC:

- Number of cases observed compared to expected
- Distribution of time to onset
- Distribution of age and dose

Cases of hematochezia will also be reviewed.

Reviewer Note: During a pre-BLA meeting with the applicant on July 17, 2006, CBER stated that a post-marketing study must be conducted in the U.S. of sufficient size to capture IS events and for overall safety, and should be equivalent in scale to that being conducted by Merck for Rotateq®. The applicant subsequently agreed to conduct a US post-licensure observational safety study, in which safety data will be collected prospectively in a cohort of infants vaccinated in routine pediatric health care settings. The study will have 80% power to detect a RR of IS ≥ 2.5% at a 5% significance level. Other measured outcomes will include the following: deaths from all causes, hospitalizations due to acute lower respiratory tract infections, convulsions, and Kawasaki disease.

Pneumonia-related mortality

Active and passive post-marketing pneumonia-related mortality surveillance – Mexico
In order to assess the temporal association between Rotarix vaccination and the occurrence of pneumonia-related post-neonatal infant mortality during Days 0-30 post-vaccination, as well as to estimate the incidence of post-neonatal lower respiratory tract infection (LRTI)-related deaths, active hospital surveillance and passive surveillance will be conducted under the PASS protocol mentioned previously. The targeted surveillance population will be all children between 29 days-1 year of age. The following ICD-10 codes will be used to define surveillance endpoints: pneumonia, bronchopneumonia, acute bronchitis, acute bronchiolitis, and suppurative and necrotic conditions of the lower respiratory tract. A copy of the PASS protocol was also submitted with this BLA.

To confirm that there is no increased risk of pneumonia-related deaths post-Rotarix vaccination, a self-controlled case series analysis will be performed after 200 pneumonia-related post-neonatal infant deaths have been included. The enrollment period is anticipated to be 2 years.

RV strain distribution

RV strain surveillance – Europe
To confirm that the introduction of Rotarix vaccination reduces the relative detection of RV strains for which the vaccine is effective, as well as to monitor for changes in strain distribution after vaccine introduction, the applicant will conduct RV strain surveillance in collaboration with the European Rotavirus Surveillance Network (ERSN). The ERSN, a laboratory surveillance system established to detect and characterize circulating RV strains (including vaccine strain and uncommon strains), involves the following European countries: Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Slovenia, Spain, Sweden, and the UK. The ERSN is co-funded by GSK and Sanofi Pasteur MSD, with GSK funding the first 2 years. The first ERSN steering committee, which includes GSK, was held in February 2007. The applicant will submit updates of ERSN findings with the PSUR every 6 months. A copy of the ERSN Protocol was submitted with this BLA.

Vaccine effectiveness

To confirm that Rotarix vaccination is highly effective against hospitalized RV GE and against other non-vaccine RV strains, the applicant will conduct a case-control study at a site(s) with vaccine coverage >30% in children <1 year of age. Site selection, including evaluation of ERSN participating sites, is currently ongoing at the time of this BLA submission.

Genetic stability of vaccine virus

To monitor for potential occurrence of post-marketing genetic drifts or shifts in the vaccine strain, targeted sequencing of a subset of G1P8 samples from non-vaccinated individuals. The study site selected will have >30% vaccine coverage in children <1 year of age, sufficient availability of vaccination history data, and good RV surveillance. ----------. The ----------RV sequencing for this study. The study will be conducted for –------ with reports being submitted annually after study initiation.

Vaccine virus transmission

Rota-052
To further evaluate horizontal transmission of vaccine virus from Rotarix recipients to Rotarix non-recipients, the applicant is conducting a Phase IIIb study (Rota-052) under US IND. This randomized, double-blinded, placebo-controlled study will recruit 100 pairs of twins, with one

subject within each pair administered 2 doses of Rotarix and the other subject administered 2 doses of placebo. The rate of transmission of Rotarix vaccine strain from the vaccinated twin to the unvaccinated twin will be estimated. The study was initiated in January 2007 and results are anticipated in early 2008. A copy of the Rota-052 protocol was submitted with this BLA.

Preterm infants

Rota-054
To further evaluate the safety and immunogenicity of Rotarix in preterm infants, the applicant will conduct a Phase IIIb study in Europe (Rota-054) of 2 doses of Rotarix in preterm infants. This randomized, double-blinded, placebo-controlled study will enroll 999 preterm infants (≤ 36 weeks gestation) from France, Poland, Portugal, and Spain. Of the total number of subjects, 80% will have been born between 31-36 weeks gestation and 20% will have been born between 27-30 weeks gestation. Subject recruitment was initiated in January 2007 and results are anticipated in 2008. A copy of the Rota-054 protocol was submitted with this BLA.

Immunocompromised infants

Rota-022
To further evaluate the safety and immunogenicity of Rotarix in immunocompromised infants, the applicant is conducting a Phase II study in South Africa (Rota-022) of ------ doses of Rotarix in HIV-infected infants. The target enrolment is --- children ----------. Subject recruitment was initiated in January 2007 and results are anticipated in 2008. The study is anticipated to be finalized in 2008. A copy of the Rota-022 protocol was submitted with this BLA.

Risk Minimization Action Plan (RiskMAP)

The applicant stated that a RiskMAP was not needed due to the lack of identified risks associated with Rotarix, with the need to be re-evaluated in the event of a safety signal arising from any ongoing clinical trials or post-licensure pharmacovigilance activities.
Reviewer Note: Pneumonia-related deaths were statistically significantly higher in the Rotarix group compared to placebo in Rota-023, both for the PT Pneumonia and pooled PTs for Pneumonia, Bronchopneumonia, and Pneumonia cytomegalovirus.

CBER Requirements and Recommendations on Postmarketing Actions
The clinical and post-marketing reviewers agreed on the following postmarketing requirements and recommendations.

1. A U.S. post-licensure study must be conducted. CBER suggests that the study be observational cohort in design and of sufficient size to detect an increased risk of intussusception of 2.5 or greater with 80% probability. Other outcomes of this study should include Kawasaki disease, pneumonia hospitalizations, and convulsions (within 60 days following vaccination).
2. Active surveillance studies in Germany and the United Kingdom should also include Kawasaki disease as an outcome.
3. The PASS Study in Mexico should also include Kawasaki disease and pneumonia hospitalizations as outcomes.

13.3 Labeling

Line-by-line modifications and comments of the draft package insert (PI) and patient package insert (PPI) were made by CBER and forwarded to the applicant during the review cycle. Please refer to the final PI and PPI. The PPI was not being required for a serious safety risk.

14 Comments and questions for the applicant

Rota-023

1. On page 118, Table 38 of the Rota-023 Visit 1-3 report, you calculated a p-value of 0.054 for the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus). However, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.
2. Please provide any detailed clinical information for Subject No. 38000 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Rota-004

1. In Study Rota-004, inclusion in the ATP efficacy cohort required that a subject had no RV other than vaccine strain in stool samples collected between the day of Dose 1 and 2 weeks post-Dose 2. Similarly, inclusion in the ATP immunogenicity cohort required that a subject had no RV other than vaccine strain in stool samples collected from Dose 1 until Visit 3. On page 12, Table 3 of the Rota-004 Annex Report 2, you identified one subject who experienced an RV GE episode between Dose 1 and 2 weeks post-Dose 2 due to G1 wild type strain. However, based on information provided in your study report and analysis datasets, this subject did not appear to be excluded from either the ATP efficacy or immunogenicity cohorts. Please clarify.

Rota-006

1. On page 128, Table 31 of your Rota-006 Year 1 study report, you indicate that 1 placebo recipient in the ATP immunogenicity cohort shed vaccine virus in stool collected between Day 6 to Day 10 post-Dose 2. However, on page 127, you state that “None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV.” Please clarify.
2. On page 100, Supplement 31 of your Annex report for Rota-006, the second subheading “From Dose 1 up to the end of first efficacy period” appears to be mislabeled and should be “From Dose 1 up to the end of second efficacy period.” Please clarify.
3. On page 129, Table 33 of your Rota-006 Year 1 study report, the denominator (N) used to calculate vaccine take after Dose 1 and after Dose 2 are described as “… or with vaccine virus in stools collected after Visit 1 to Visit 2” and “…or with vaccine virus in stools collected after Visit 2 to Visit 3,” respectively. This appears to be an error, as each N should include the number of subjects with available stool results during these visit intervals and not the number of subjects with vaccine virus detected in their stools. Similarly, on page 130, Table 34, you label N used to calculate vaccine take on combined Doses 1 and 2 as “… or who seroconverted at Visit 2, or with vaccine virus in stools collected after Visit 1 to Visit 3.” This denominator should instead include subjects with available antibody results at Visit 2 or available stool results collected after Visit 1 to Visit 3. In your vaccine take rate tables in other study reports, you label N in a similar manner. Please clarify.
4. Please provide any detailed clinical information for Subject No. 01650 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Rota-007

1. In Rota-007, please provide any detailed clinical information for Subject No. 02295 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Rota-060

1. On pages 55 and 56 of the initial Rota-060 Study Report, you report that 417 of the 484 total subjects completed the active phase of the study (i.e. up to Visit 6). However, on pages 30 and 31 of the Rota-060 Annex Report 1, which contained the final safety data, you report that 432 of the 484 subjects completed the extended safety follow-up phase. Please explain why more subjects completed the extended safety follow-up phase than the earlier active phase.
2. On page 21 of the Tabular Listing of All Clinical studies, you stated that subjects in Rota-060 were administered *Rotarix* at a potency of $10^{6.5}$ CCID $_{50}$ per dose. However, on page 3 and page 9 of your Rota-060 study report, you state that the vaccine composition was not less than $10^{6.0}$ $CCID_{50}$. Please clarify whether a potency of $10^{6.5}$ $CCID_{50}$ per dose was used in Rota-060.

Clinical Overview

1. On page 81 of the Clinical Overview, you state that the p-value of the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus) was not statistically significant (p = 0.054). However, as previously stated above in Comment 1 under the Rota-023 section, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.
2. On page 85, paragraph 3, you state that 6 cases of definite IS (1 – vaccine, 5-placebo) occurred within 31 days after Dose 1, and 7 cases (2 – vaccine, 5 – placebo) occurred within the same time period after Dose 2. These figures do not match with Table 27 on pg 84. Please clarify.

Efficacy Summary

1. On page 69 of the Summary of Clinical Efficacy report, you stats that the exclusion criterion "Previous confirmed occurrence of RV GE" was common to all studies except Rota-023. However, this criterion was not included in the protocol for Rota-036. Please clarify.
2. On page 57 of the Summary of Clinical Efficacy, you labeled Table 18 as "Anti-HRV IgA seroconversion rates and GMCs two months after dose 2 in study Rota-007 (ATP cohort for immunogenicity)." However, on page 107 of the Rota-007 Study Report, the same serocnversion rates and GMCs were listed on line PII(M2) which meant "one month after the second dose of HRV vaccine or placebo (Visit 3)." Please clarify.
3. On page 120, Table 59 of the Summary of Clinical Efficacy Report, in the Rota-036 Spain category, the numbers of subjects (N, n) for both treatment arms and seroprotection rates for the vaccine antigens were different than corresponding figures for these same antigens in the Spain subset in Tables 36, 38, 39, and 40 in the Rota-036 Year 1 study report. Similarly, on page 121, Table 60 of the Summary of Clinical Efficacy Report, Rota-036 Spain category, the numbers (N) of subjects and anti-PT, anti-FHA, and anti-PRN GMCs for both treatment groups were different than corresponding figures for the same antigens in Table 37 of the Rota-036 Year 1 study report. Please explain the reason(s) for these differences.

Safety Summary

1. On page 78 of the Summary of Clinical Safety Report under the first bullet "13 cases…," you state that among intussusception cases diagnosed from Day 0-Day 30, "5 cases in the placebo group were diagnosed within 31 days after Dose 1" and "2 cases in the HRV vaccine group…were diagnosed within 31 days after Dose 2." However, in Table 24 on page 76 of the same report, there were 2 cases of IS in the placebo group under the Day 0-30 post Dose 1

stratum and 5 cases of IS in the Rotarix group under the Day 0-30 post Dose 2 stratum. Please clarify.

Post-Marketing Report

1. On page 20, section 6.5.2 of the Periodic Safety Update Report, you state that one of the fatal cases was a 2-month-old female subject. However, on page 31 of your Risk Management Plan, you refer to this case as a 2-year-old female subject. Please clarify.

Risk Management Plan

1. On page 46 of your Risk Management Plan, you state that "An additional exploratory analysis showed no imbalance between treatment groups in terms of number of subjects hospitalized for pneumonia during the period from 31 days before through 31 days after each vaccine dose." However, as explained on pages 122-123 of the Rota-023 Visit 1-3 study report, analyses were conducted on pneumonia hospitalizations within 31 days and beyond 31 days after each dose. Please clarify.

Kawasaki Disease Report

1. In your Analysis of Kawasaki Reports Following Rotarix, you state that one placebo recipient in Rota-028 (Subject B0405862A) and one Rotarix recipient (Subject B0406754A) in Rota-030 lacked sufficient information to be classified either as Kawasaki disease or incomplete Kawasaki disease. Please provide any follow-up clinical information for these subjects regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.
2. On page 16, Table 4 of the Analysis of Kawasaki Reports Following Rotarix, you included 30,638 Rotarix subjects and 30,527 placebo subjects for Rota-023. However, in the Rota-023 Visit 1-3 study report, you state that 31,673 Rotarix and 31,552 placebo subjects were enrolled and vaccinated, and used these figures for your safety analyses. Please explain the numerical differences between reports. Also, for each study in the Table 4, please provide the actual numbers of subjects who received at least one dose of Rotarix and placebo, respectively. Please also provide the actual exposure time in person-years for each treatment arm in each study, if available.
3. Please provide information on race for each case of Kawasaki disease from Rota-028, Rota-29, Rota-30, and Rota -061 that you reported in your Analysis. In addition, please provide the names of any routine childhood vaccinations that were administered or co-administered, the last dose number of these vaccines prior to disease onset, and interval between the last dose and disease onset. For the cases from these studies that received Rotarix, please also provide the dose potency that was administered to each of these cases.

15. Appendix 1 – Table 1: Overview of study characteristics

Study # (Phase)	Countries	# sites	Start date End date	# planned/ # enrolled	# given Rotarix/ placebo	Dose potency ($CCID_{50}$)	Age at 1st dose/ mean (weeks)	Male: Female ratio	Ethnicity	Vaccine schedule (months)	Co-admin of routine infant vaccines	Feeding restrictions
Rota-004 (II)	Finland	6	8/21/00 6/26/02	405/ 405	270/135	$10^{5.3}$	6-12/ 8.3	214: 191	99% White	0, 2	No	1 hour pre-dose
Rota-005 (II)	US, Canada	41	12/13/00 8/02/02	500/ 529	421/108	$10^{5.6}$ $10^{6.8}$	6-12/ 8.7	260: 269	75% White	0, 2	Yes	None
Rota-006 (II)	Brazil, Mexico, Venezuela	3	5/25/01 11/08/03	2276/ 2276	1709/567	$10^{5.3}$ $10^{5.6}$ $10^{6.6}$	6-12/ 8.3	1197: 1079	73% Mixed; 24% White	0, 2 (subset: 0, 2, 4)	Yes, except OPV	None
Rota-007 (II)	Singapore	8	1/04/01 4/15/03	2640/ 2464	1811/653	$10^{5.3}$ $10^{5.6}$ $10^{6.6}$	11-17/ 13.3	1226: 1238	93% Oriental	0, 1	Yes	None
Rota-014 (II)	South Africa	6	11/22/01 10/25/03	450/ 450 (PI - 271; PII- 179)	297/150	$10^{5.6}$	5-10 (P I) 8-17 (P II)/ 6.2 (PI) 11.1 (PII)	225: 225	83% Black 15% White	0, 1	Yes, including OPV	None
Rota-023 (III)	Argentina, Brazil, Chile, Colombia, Dominican Republic, Finland*, Honduras, Mexico, Nicaragua, Panama, Peru**, Venezuela	177* (136†, 121‡)	8/05/03 10/20/05‡	60,000/ 63,225¶ (20,000/20,170†) (13,000/15,183‡)	31,673/ 31,552	$10^{6.5}$	6-12 (Chile: 6-13) / 8.2	32,255: 30,970	81% Hisp; 11% White	0, 1 *or* 0, 2	Yes, except OPV	None
Rota-033 (III)	Colombia, Mexico, Peru	7	8/08/03 1/29/04	854/ 854	730/124	$10^{6.5}$ $10^{6.5}$ $10^{6.5}$	6-12/ 8.5	439:415	98% Hisp	0, 2	Yes, except OPV	None
Rota-036 (III)	Czech Republic, Finland, France, Germany, Italy, Spain	87	9/08/04 8/10/06	3990/ 3994	2646/ 1348	$10^{6.5}$	6-14/ 11.5	2107: 1887	98% White	0, 1 *or* 0, 2	Yes	None
Rota-039 (III)	Thailand	2	3/27/05 12/30/05	450/ 450	398/52	$10^{6.5}$	6-12/ 8.7	235: 215	99% East/ South East Asian	0, 2	Yes	Yes (controlled)
Rota-048 (II)	Finland	5	8/16/05 11/10/05	250/ 250	200/50	$10^{6.5}$	6-12/ 9.1	119: 131	98% White	0, 1	No	None
Rota-060 (III)	US	44	6/13/2006 2/08/2007	480/ 484	459/0	$10^{6.5}$	6-12/ 8.7	256: 228	76% White 13% Black	0, 2	Yes (for 1 group)	None

*Participated in IS Safety study only; **Participated in IS and Year 1 Efficacy studies only; ¶IS Safety study; †Year 1 Efficacy subset; ‡Year 2 Efficacy subset
PI=Part 1; PII=Part II
(Note: Table prepared by reviewer; Source: summary reports for each study)

Appendix 1 - Table 2: Overview of safety data, Part 1

Study #	Treatment group/ # TVC subjects	GA & BW criteria	TVC Median Height (cm)/ Weight (kg)	# (%) TVC subjects completing Year 1	TVC Median follow-up duration (months), Year 1
Rota-004	$10^{5.3}$CCID$_{50}$/270 Placebo/ 135	≥ 36 weeks	58/5.5	372/405 (91.9)	5.6
Rota-005	$10^{5.6}$ CCID$_{50}$/ 212 $10^{6.8}$ CCID$_{50}$/ 209 Placebo/ 108	≥ 36 weeks	58/5.3	470/529 (88.8)	NA
Rota-006 (2-dose Subset)	$10^{5.3}$ CCID$_{50}$/ 538 $10^{5.6}$ CCID$_{50}$/ 540 $10^{6.6}$ CCID$_{50}$/ 540 Placebo/ 537	≥ 36 weeks >2000g	57/5.3	2004/2155 (93.0)	7.2¶
Rota-006 (3-dose Subset)	$10^{5.3}$ CCID$_{50}$/ 31 $10^{5.6}$ CCID$_{50}$/ 30 $10^{6.6}$ CCID$_{50}$/ 30 Placebo/ 30	≥ 36 weeks >2000g	57/5.5	121/121 (100)	NA
Rota-007	$10^{5.3}$ CCID$_{50}$/ 510 $10^{5.6}$ CCID$_{50}$/ 648 $10^{6.6}$ CCID$_{50}$/ 653 Placebo/ 653	≥ 36 weeks	60/6.2	2365/2464 (96.0) (up to Month 18 of age)	13.3¶ (up to Month 18 of age)
Rota-014	*Part 1:* $10^{5.6}$ CCID$_{50}$ (+ OPV)/ 91 $10^{5.6}$ CCID$_{50}$ (+ IPV)/ 90 Placebo (+ OPV)/ 90 *Part 2:* $10^{5.6}$ CCID$_{50}$ (+ OPV)/ 57 $10^{5.6}$ CCID$_{50}$ (+ IPV)/ 59 Placebo (+ OPV)/ 60	≥ 36 weeks	56/4.9	406/450 (90.2) (up to Month 5 of age)	NA
Rota-023	$10^{6.5}$ CCID$_{50}$/ 31,673 Placebo/ 31,552	No GA or BW criteria	Not measured	59,308/63,225 (93.8) (up to Month 4-6 of age) 17,882/20,169¶ (88.7)	3.3 (up to Month 4-6 of age) 10.5¶
Rota-033	$10^{6.5}$ CCID$_{50}$ (lot A)/ 243 $10^{6.5}$ CCID$_{50}$ (lot B)/ 241 $10^{6.5}$ CCID$_{50}$ (lot C)/ 246 Placebo/ 124	No GA or BW criteria	58/5.3	795/854 (93.1) (up to Month 6 of age)	NA
Rota-036	$10^{6.5}$ CCID$_{50}$/ 2646 Placebo/ 1348	>2000g	61.0/6.0	3944/3994 (98.7)	8.4
Rota-039	$10^{6.5}$ CCID$_{50}$ (buffer)/ 174 $10^{6.5}$ CCID$_{50}$ (no buffer)/ 174 $10^{6.5}$ CCID$_{50}$ (buffer, stored 7 days at 37°C)/ 50 Placebo (buffer)/ 26 Placebo (no buffer)/ 26	No GA or BW criteria	57/5.2	438/450 (97.3) (up to Month 6 of age)	NA
Rota-048	$10^{6.5}$ CCID$_{50}$ (liquid formulation)/ 100 $10^{6.5}$ CCID$_{50}$ (lyophilized formulation)/ 100 Placebo (liquid formulation) / 25 Placebo (lyophilized formulation) / 25	≥ 36 weeks	59/5.6	244/250 (97.6) (up to Month 4.5 of age)	NA
Rota-060	$10^{6.5}$ CCID$_{50}$ (co-administered routine vaccines)/ 249* $10^{6.5}$ CCID$_{50}$ (separately-administered routine vaccines)/ 235*	No GA or BW criteria	58/5.4	432/484 (89.3) (up to 11 months of age)	NA

TVC = Total vaccinated cohort (the number of subjects who received at 1 dose of Rotarix)
GA=gestational age; BW=birth weight; NA=not available in study report
¶TVC Efficacy Year 1; *TVC for Rota-060 includes subjects who received Rotarix, *Pediarix, Prevnar* or *ActHIB*. The number of subjects who received Rotarix in the separately – administered group was 210.
(Note: Table prepared by reviewer; Source: summary reports for each study)

15. Appendix 1 – Table 3: Overview of safety data, Part 2

Study #	ISS analysis group	Solicited general AEs	Solicited AE period (days)	Unsolicited AEs	Unsolicited AE period (days)	SAEs	Unsolicited AE & SAE coding	Weight & Height	Concomitant meds
Rota-004	Supplementary	Yes (except cough/runny nose)	15	Yes	43	Yes	WHO, MedDRA	First visit	Yes
Rota-005	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-006*	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-007	Core & Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-014	Supplementary	Yes	15	Yes	43	Yes	WHO, MedDRA	Each visit	Yes
Rota-023	Core	NC	NA	No§	NC	Yes	MedDRA	First visit	NT
Rota-033	Core	Yes (except cough/runny nose)	8	Yes	31	Yes	MedDRA	First visit	Yes
Rota-036	Core	Yes (subset) (also type of medical attention)	8	Yes	31 (also: type of medical attention)	Yes	MedDRA	First visit	Yes
Rota-039†	Core	Yes	15	Yes	31	Yes	MedDRA	First visit	Yes
Rota-048‡	Core	Yes	15	Yes	31	Yes	MedDRA	First visit	Yes
Rota-060	Not included	NC	NA	Yes¶	Throughout study	Yes	MedDRA	First visit	Yes

ISS = Integrated Safety Summary; NC=not tabulated; NA= not applicable
Core ISS analysis: at least $10^{6.0}CCID_{50}$ potency versus placebo
Supplementary ISS analysis: less than $10^{6.5}CCID_{50}$ potency versus placebo
*safety data after 3rd dose in subset of 121 infants not included in ISS
†safety data not included in ISS for the following study groups: Rotarix without buffer, Rotarix stored at 37°C
‡safety data not included in ISS for the following study group: Rotarix in liquid formulation
¶Specific AEs included new onset of chronic illness(es) that were not congenital anomalies and conditions prompting emergency room visits; also AEs leading to drop-out
§Only AEs leading to drop-out
(Note: Table prepared by reviewer; Source: summary reports for each study)

15. Appendix 1 - Table 4: Overview of efficacy studies, Part 1

Study #	Primary Objective	Start of efficacy follow-up	1st Efficacy Period (ATP analysis)	Treatment arm/ # ATP subjects	Randomization ratio	Mean duration of follow-up, 1st Efficacy Period (months)
Rota-004	VE of 2 Rotarix doses against any RV GE during 1st efficacy period	2 weeks post-Dose 2	2 weeks post-Dose 2 to end of 1st RV season	$10^{5.3}$/ 245 Placebo/ 123	2:1	6
Rota-006	*For each potency*: VE of 2 Rotarix doses against any RV GE during 1st efficacy period when co-administered with DTwP, HepB, Hib	Day of Dose 1	2 weeks post-Dose 2 to 12 months of age	$10^{5.3}$/ 468 $10^{5.6}$/ 460 $10^{6.6}$/ 464 Placebo/ 454	1:1:1:1	7
Rota-023	VE of 2 Rotarix doses against severe RV GE caused by circulating wild-type RV strains during 1st efficacy period	Day of Dose 1	2 weeks post-Dose 2 to 12 months of age	$10^{6.5}$/ 9009 Placebo/ 8858	1:1	8
Rota-036	VE of 2 Rotarix doses against any RV GE caused by circulating wild-type RV strains during 1st efficacy period	Day of Dose 1	2 weeks post-Dose 2 to end of 1st RV season	$10^{6.5}$/ 2572 Placebo/ 1302	2:1	6

(Note: Table prepared by reviewer; Source: summary reports for each study)

15. Appendix 1 – Table 5: Overview of efficacy studies, Part 2

Study #	GE case definition	Severe GE definition	GE diary card	RV detection	Case Ascertainment for GE
Rota-004	Diarrhea and/or vomiting	Vesikari scale (≥ 11 points)	Temperature, # vomiting episodes # abnormal loose stools, re-hydration treatment, medications	ELISA (Ward lab) RT-PCR, followed by --- ---------- or optional sequencing (----------)	Active (telephone contact every 2 weeks)
Rota-006	Diarrhea	Vesikari scale (≥ 11 points)	Temperature, # vomiting episodes # abnormal loose stools, re-hydration treatment, medications	ELISA (Ward lab) RT-PCR, followed by --- ---------- or optional sequencing (GSK lab, Belgium)	Active (weekly visits)
Rota-023	Diarrhea with or without vomiting	1°: clinical definition (hospitalization and/or re-hydration therapy) 2°: Vesikari scale (≥ 11 points)	Temperature, # vomiting episodes # abnormal loose stools, re-hydration treatment, medications	ELISA kit (GSK lab) RT-PCR, followed by Reverse Hybridization or optional sequencing (Delft lab, Netherlands)	Passive (Bi-weekly contact of medical facilities) Supplementary (contacting parent/guardian) Medical history at each clinic visit
Rota-036	Diarrhea with or without vomiting	1°:Vesikari scale (≥ 11 points) Exploratory: Clark scale (≥ 16 points)	Temperature, # vomiting episodes # abnormal loose stools, re-hydration treatment, medications + Medical attention	ELISA kit (GSK lab) RT-PCR, followed by Reverse Hybridization or optional sequencing (Delft lab, Netherlands)	Active (telephone contact weekly during RV season)

(Note: Table prepared by reviewer; Source: summary reports for each study)

15. Appendix 1 – Table 6: Overview of immunogenicity studies*, Part 1

Study #	Treatment arm/ # ATP immunogenicity subjects	Time of Blood sample post-Dose (months)			Serum Anti-RV IgA ELISA assay	RV shedding in stools	Vaccine take (combined Dose 1 & 2)	Immunogenicity of co-administered routine vaccines	Effects of breast feeding prior to vaccination
		Dose 1	Dose 2	Dose 3					
Rota-004	$10^{5.3}$/209 Placebo/ 112		1		Ward GSK (post-hoc)				
Rota-005	$10^{5.6}$/ 170 $10^{6.8}$/ 161 Placebo/ 79	2 (subset)	2		Ward	Yes	Yes	Yes	Yes (breast vs formula)
Rota-006	$10^{5.3}$/ 395 $10^{5.6}$/ 377 $10^{6.6}$/ 381 Placebo/ 373	2 (subset)	2 (subset)	2 (subset)	Ward GSK (post-hoc)	Yes (subset) Also live virus	Yes (subset)	Yes	Yes (breast vs formula; timing)
Rota-007	$10^{5.3}$/ 155 $10^{5.6}$/ 158 $10^{6.6}$/ 167 Placebo/ 160	1	1 and 2 (subset)		Ward	Yes (subset) Also live virus	Yes (subset)	Yes	Yes (breast vs formula)
Rota-014	*Part 1:* $10^{5.6}$ (+ OPV)/ 63 $10^{5.6}$ (+ IPV)/ 60 Placebo (+ OPV)/ 68 *Part 2:* $10^{5.6}$ (+ OPV)/ 43 $10^{5.6}$ (+ IPV)/ 47 Placebo (+ OPV)/ 46	1	1		Ward	Yes (subset) Also live virus	Yes (subset)	Yes	
Rota-023	$10^{6.5}$/ 393 Placebo/ 341		1 to 2 months (subset)		GSK				
Rota-033	$10^{6.5}$ (lot A)/ 154 $10^{6.5}$ (lot B)/ 167 $10^{6.5}$ (lot C)/ 173 Placebo/ 91	2 (subset)	2		Ward GSK (post-hoc)	Yes (subset) Also live virus	Yes (subset)		
Rota-036	$10^{6.5}$/ 794 Placebo/ 422		1 to 2 months (subset)		GSK			Yes	Yes (breast vs formula)
Rota-039	$10^{6.5}$ / 171 $10^{6.5}$ (non-buffer)/ 170 $10^{6.5}$ (37°C)/ 47 Placebo/ 25 Placebo (non-buffer)/ 26		2		GSK	Yes (subset) Also live virus	Yes (subset)		
Rota-048	$10^{6.5}$ (lyophilized)/ 96 $10^{6.5}$ (liquid)/ 95 Placebo (lyophilized)/ 22 Placebo (liquid)/ 24	1	1		GSK	Yes (subset) Also live virus	Yes (subset)		
Rota-060	$10^{6.5}$ $CCID_{50}$ (co-admin)/ 180 $10^{6.5}$ $CCID_{50}$ (separate)/ 137		2 to 3 months		GSK			Yes	

*Primary immunogenicity analyses based on ATP cohort for immunogenicity, except for antibody persistence results for Rota-004 and immunogenicity results for 3-dose subset for Rota-006 (both used TVC cohort); all subjects in each study had a pre-vaccination blood sample (subset in Rota-023 and Rota-036) except Rota-060
(Note: Table prepared by reviewer; Source: summary reports for each study)

15. Appendix 1 – Table 7: Overview of immunogenicity studies, Part 2

Study #	Immunogenicity of OPV and Rotarix when co-administered	Lot-to-lot consistency	Liquid vs. lyophilized formulation	Buffer vs no buffer, storage at 37°C	Maternally acquired pre-vaccination anti-RV IgG and neutralizing antibodies	Persistence of immunogenicity
Rota-004					Yes (subset)	Yes (end of 1st and 2nd efficacy periods)
Rota-005						Yes (end of 1st efficacy period)
Rota-006					Yes (subset)	Yes (end of 1st efficacy period)
Rota-007						
Rota-014	Yes				Yes (subset)	
Rota-023		(Yes)				
Rota-033		Yes				
Rota-036						
Rota-039				Yes (subset)		
Rota-048			Yes			
Rota-060						

(Note: Table prepared by reviewer; Source: summary reports for each study)

Applicant's responses to comments and questions in Section 14

Rota-023

1. On page 118, Table 38 of the Rota-023 Visit 1-3 report, you calculated a p-value of 0.054 for the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus). However, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.

Applicant's response: The applicant stated the following: "As indicated in response to Question 5, a slight difference in a p-value is possible between GSK's and CBER's statistical computation. This may be related to the statistical method used for the computation. The method used in study Rota-023 uses the same method as that proposed for the ISS and was shared with CBER during pre-BLA discussions on the ISS analysis plan. The p-value is associated to the null hypothesis that the relative risk equals one, and is ----------. The p-value is also in line with that provided by the ---------- as shown below. A possible explanation would be that the CBER Statistician is using one-sided p-value. If this is the case, 2.5% should be considered for statistical significance."

2. Please provide any detailed clinical information for Subject No. 38000 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Applicant's response: Clinical information was provided. The applicant also stated the following: "The information available in this report does not allow a full assessment as to whether the criteria of Kawasaki disease are met; only fever of unknown severity and duration and skin spots were reported. The mother refused to give more information to the investigator. The clinical picture does not suggest a case of Kawasaki disease. Moreover, considering that Kawasaki disease is suspected to have a possible infectious etiology, a time to onset of 19 months after second vaccination dose would not suggest a causal relationship. No etiological investigations were reported to explain the increased transaminases and bilirubin. It is unknown how the suspected Kawasaki disease was treated. No cardiac investigations are reported. The case was not reviewed by an expert consultant at this time."

Rota-004

1. In Study Rota-004, inclusion in the ATP efficacy cohort required that a subject had no RV other than vaccine strain in stool samples collected between the day of Dose 1 and 2 weeks post-Dose 2. Similarly, inclusion in the ATP immunogenicity cohort required that a subject had no RV other than vaccine strain in stool samples collected from Dose 1 until Visit 3. On page 12, Table 3 of the Rota-004 Annex Report 2, you identified one subject who experienced an RV GE episode between Dose 1 and 2 weeks post-Dose 2 due to G1 wild type strain. However, based on information provided in your study report and analysis datasets, this subject did not appear to be excluded from either the ATP efficacy or immunogenicity cohorts. Please clarify.

Applicant's response: The applicant stated the following: "Sequencing results were not available at the time of study analysis and therefore it was not possible to confirm if the RV G1 type present in the stool sample was RV wild type or vaccine strain. Before unblinding, the decision was made

to proceed with the analysis and study report while keeping the subjects in the ATP cohort for efficacy and immunogenicity. This decision was taken considering that, as per randomization, a comparable incidence of the RV wild type would have been expected for the HRV and the placebo groups and any impact would have been in disfavour of vaccine efficacy. Based on unblinding and subsequent sequencing, it was observed that all GE episodes were in the vaccine group and included one wild type G1 episode. The *a posteriori* analysis excluding the wild type subject gives a vaccine efficacy of 72.9% for any RV GE (95% CI = [26.8%, 90.8%]) instead of 73.0% (95% CI=[27.1%, 90.9%].)"

Rota-006

1. On page 128, Table 31 of your Rota-006 Year 1 study report, you indicate that 1 placebo recipient in the ATP immunogenicity cohort shed vaccine virus in stool collected between Day 6 to Day 10 post-Dose 2. However, on page 127, you state that "None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV." Please clarify.

Applicant's response: The applicant stated the following: "Sequencing was done post-priori for RV shed by the placebo recipients only. The sentence on page 127 of the report is correct as it reports the result of the sequencing done *post priori* for the placebo receipient who shed RV. Table 31 was not updated as sequencing was done only for the placebo recipients."

2. On page 100, Supplement 31 of your Annex report for Rota-006, the second subheading "From Dose 1 up to the end of first efficacy period" appears to be mislabeled and should be "From Dose 1 up to the end of second efficacy period." Please clarify.

Applicant's response: The applicant stated the following: "This is an error and should be 'From Dose 1 up to the end of second efficacy period.'"

3. On page 129, Table 33 of your Rota-006 Year 1 study report, the denominator (N) used to calculate vaccine take after Dose 1 and after Dose 2 are described as "… or with vaccine virus in stools collected after Visit 1 to Visit 2" and "…or with vaccine virus in stools collected after Visit 2 to Visit 3," respectively. This appears to be an error, as each N should include the number of subjects with available stool results during these visit intervals and not the number of subjects with vaccine virus detected in their stools. Similarly, on page 130, Table 34, you label N used to calculate vaccine take on combined Doses 1 and 2 as "… or who seroconverted at Visit 2, or with vaccine virus in stools collected after Visit 1 to Visit 3." This denominator should instead include subjects with available antibody results at Visit 2 or available stool results collected after Visit 1 to Visit 3. In your vaccine take rate tables in other study reports, you label N in a similar manner. Please clarify.

Applicant's response: For vaccine take after dose 1, the applicant stated the following: "Subjects without antibody result at visit 2 and with antigen negative stool samples were excluded from the denominator. Considering that immunogenicity is more sensitive than shedding for capturing vaccine take, including subjects without immunogenicity results and with antigen negative stool samples for the vaccine take analysis would lead to an underestimation of the real vaccine take. For this reason, these subjects were excluded from the analysis. The same rule was applied for vaccine take after Dose 2."

4. Please provide any detailed clinical information for Subject No. 01650 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Applicant's response: Clinical information was provided. The applicant also stated the following: "Conservatively, this case meets the criteria for a diagnosis of incomplete Kawasaki disease: fever (for an unknown duration), edema on hands and lower limbs, and conjunctival redness. Moreover, considering that Kawasaki disease is suspected to have a possible infectious etiology, a time to onset of 7 months after second vaccination dose would not suggest a causal relationship. It is unknown how the suspected Kawasaki disease was treated. No cardiac investigations are reported. The case was not reviewed by an expert consultant at this time."

Rota-007

1. In Rota-007, please provide any detailed clinical information for Subject No. 02295 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Applicant's response: Clinical information was provided. The applicant also stated the following: "No details are reported that allow a full assessment upon which the reported diagnosis of Kawasaki disease is based. No cardiac investigations are reported on this event that occurred 55 days after the 2nd dose of the rotavirus vaccine and 21 days after the 3rd dose of Infanrix-IPV/Hib and Engerix B. The case was not reviewed by an expert consultant at this time."

Rota-060

1. On pages 55 and 56 of the initial Rota-060 Study Report, you report that 417 of the 484 total subjects completed the active phase of the study (i.e. up to Visit 6). However, on pages 30 and 31 of the Rota-060 Annex Report 1, which contained the final safety data, you report that 432 of the 484 subjects completed the extended safety follow-up phase. Please explain why more subjects completed the extended safety follow-up phase than the earlier active phase.

Applicant's response: The applicant stated the following: "The reason why more subjects completed the extended safety follow-up phase than the earlier active phase is that some subjects who did not return to the clinic for Visit 6 (blood sample collection visit) at the end of the active phase were able to be contacted, and provided safety information at the end of the extended safety follow-up phase."

2. On page 21 of the Tabular Listing of All Clinical studies, you stated that subjects in Rota-060 were administered *Rotarix* at a potency of $10^{6.5}$ CCID $_{50}$ per dose. However, on page 3 and page 9 of your Rota-060 study report, you state that the vaccine composition was not less than $10^{6.0}$ $CCID_{50}$. Please clarify whether a potency of 10 $^{6.5}$ $CCID_{50}$ per dose was used in Rota-060.

Applicant's response: The applicant stated that in study Rota-060, the potency at release for lot AROTA033A was $10^{6.7}$ $CCID_{50}$ per vial.

Clinical Overview

1. On page 81 of the Clinical Overview, you state that the p-value of the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus) was not statistically significant (p = 0.054). However, as previously stated above in Comment 1 under the Rota-023 section, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two

different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.

Applicant's response: The applicant stated the following: **"**A slight difference in a p-value is possible between GSK and CBER statistical computation. This may be related to the statistical method used for the computation. The method used in study Rota-023 uses the same method as that proposed for the ISS and was shared with CBER during pre-BLA discussions on the ISS analysis plan. The p-value is associated to the null hypothesis that the relative risk equals one, and is ----------. Additional details are provided in the response to Question 11. In addition, interpretation of statistical difference should be made with caution. The objective of the exploratory safety analysis was to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to:

- multiplicity of endpoints and time window considered,
- the power limitation (over-power to detect common clinically meaningless event and under- power to detect rare clinically important event).

As such, the exploratory safety analysis is not intended to be definitive or conclusive with respect to establishing causality. Safety signals identified by this method were reviewed for clinical relevance/plausibility and followed in other studies. More specifically if the vaccine increases rate of fatal pneumonia one would expect to also see an increase in non fatal pneumonia. This was not apparent since, in the study pneumonia-related hospitalizations were reported by 277 (0.87%) of subjects in the *Rotarix* group and 273 (0.87%) subjects in the placebo group (RR -1.01 [0.85-1.2])."

2. On page 85, paragraph 3, you state that 6 cases of definite IS (1 – vaccine, 5-placebo) occurred within 31 days after Dose 1, and 7 cases (2 – vaccine, 5 – placebo) occurred within the same time period after Dose 2. These figures do not match with Table 27 on pg 84. Please clarify.

Applicant's response: The applicant stated the following: **"**There is an error on Page 85 of the Clinical Overview and it should be 'There was no temporal cluster of intussusception cases after either dose: 1 case in the HRV vaccine group and 2 cases in the placebo group were diagnosed within 31 days after Dose 1, and 5 cases in the HRV vaccine group and 5 cases in the placebo group were diagnosed within 31 days after Dose 2.'".

<u>Efficacy Summary</u>

1. On page 69 of the Summary of Clinical Efficacy report, you stats that the exclusion criterion "Previous confirmed occurrence of RV GE" was common to all studies except Rota-023. However, this criterion was not included in the protocol for Rota-036. Please clarify.

Applicant's response: The applicant stated the following: "This is an error on page 69 of the Summary of Clinical Efficacy report and should be 'Previous confirmed occurrence of RV GE was common to all 10 studies submitted in the initial BLA except Rota-023 and Rota-036'".

2. On page 57 of the Summary of Clinical Efficacy, you labeled Table 18 as “Anti-HRV IgA seroconversion rates and GMCs two months after dose 2 in study Rota-007 (ATP cohort for immunogenicity).” However, on page 107 of the Rota-007 Study Report, the same serocnversion rates and GMCs were listed on line PII(M2) which meant “one month after the second dose of HRV vaccine or placebo (Visit 3).” Please clarify.

Applicant’s response: The applicant stated the following: “This is an error on page 57 of the Summary of Clinical Efficacy and Table 18 should be ‘Anti-HRV IgA seroconversion rates and GMCs one month after dose 2 in study Rota-007 (ATP cohort for immunogenicity)’”.

3. On page 120, Table 59 of the Summary of Clinical Efficacy Report, in the Rota-036 Spain category, the numbers of subjects (N, n) for both treatment arms and seroprotection rates for the vaccine antigens were different than corresponding figures for these same antigens in the Spain subset in Tables 36, 38, 39, and 40 in the Rota-036 Year 1 study report. Similarly, on page 121, Table 60 of the Summary of Clinical Efficacy Report, Rota-036 Spain category, the numbers (N) of subjects and anti-PT, anti-FHA, and anti-PRN GMCs for both treatment groups were different than corresponding figures for the same antigens in Table 37 of the Rota-036 Year 1 study report. Please explain the reason(s) for these differences.

Applicant’s response: The applicant stated the following: ***“***As mentioned in the Summary of Clinical Efficacy section 3.3.3.1: “The results of *post hoc* tests of the hypothesis of immunological non-inferiority to coadministered childhood vaccine antigens **post-Dose 2** from studies Rota-005 (subset from the US; 2, 4, 6 month schedule) and Rota-036 (subset from Spain; 2, 4, 6 month schedule) are presented in this section. The analysis of immunogenicity included in Table 59 of the Summary of Clinical Efficacy was based on post dose 2 (visit 3) results from Spain to be compared with Rota-005 post-dose 2 results because post-dose 3 results were not obtained in study Rota-005. In tables 38 to 40 in the Rota-036 Year 1 study report, results are presented for post-dose 3 (visit 4 for Spain).”

<u>Safety Summary</u>

1. On page 78 of the Summary of Clinical Safety Report under the first bullet “13 cases…,” you state that among intussusception cases diagnosed from Day 0-Day 30, “5 cases in the placebo group were diagnosed within 31 days after Dose 1” and “2 cases in the HRV vaccine group…were diagnosed within 31 days after Dose 2.” However, in Table 24 on page 76 of the same report, there were 2 cases of IS in the placebo group under the Day 0-30 post Dose 1 stratum and 5 cases of IS in the Rotarix group under the Day 0-30 post Dose 2 stratum. Please clarify.

Applicant’s response: The applicant stated the following: **“**The data in Table 24 on page 76 of the Summary of Clinical Safety Report is correct. There is an error on Page 78 of the Summary of Clinical Safety Report and it should be ‘There was no temporal cluster of intussusception cases after either dose: 1 case in the HRV vaccine group and 2 cases in the placebo group were diagnosed within 31 days after Dose 1, and 5 cases in the HRV vaccine group and 5 cases in the placebo group were diagnosed within 31 days after Dose 2.’”.

<u>Post-Marketing Report</u>

1. On page 20, section 6.5.2 of the Periodic Safety Update Report, you state that one of the fatal cases was a 2-month-old female subject. However, on page 31 of your Risk Management Plan, you refer to this case as a 2-year-old female subject. Please clarify.

Applicant's response: The applicant stated the following: ***"***On Page 20, Section 6.5.2 of the 3rd Periodic Safety Update Report (covering the period from 12 July 2006 to 11 January 2007), case B0441663A is described as a 2-month-old girl. After verification of the data in the PMS database, the case was reported in a 2-year-old girl. The information provided in the Risk Management Plan (Section 2.2.4.2.3) is correct."

Risk Management Plan

1. On page 46 of your Risk Management Plan, you state that "An additional exploratory analysis showed no imbalance between treatment groups in terms of number of subjects hospitalized for pneumonia during the period from 31 days before through 31 days after each vaccine dose." However, as explained on pages 122-123 of the Rota-023 Visit 1-3 study report, analyses were conducted on pneumonia hospitalizations within 31 days and beyond 31 days after each dose. Please clarify.

Applicant's response: The applicant stated the following: "The Company acknowledges that there is an error on Page 46 (Section 3.1.2) of the Risk Management Plan, where it should read: 'An additional exploratory analysis showed no imbalance between treatment groups in terms of number of subjects hospitalized for pneumonia during the periods within 31 days and beyond 31 days after each dose'. The Company will correct this in an updated RMP."

Kawasaki Disease Report

1. In your Analysis of Kawasaki Reports Following Rotarix, you state that one placebo recipient in Rota-028 (Subject B0405862A) and one Rotarix recipient (Subject B0406754A) in Rota-030 lacked sufficient information to be classified either as Kawasaki disease or incomplete Kawasaki disease. Please provide any follow-up clinical information for these subjects regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

Applicant's response: The applicant provided clinical information on both subjects. Regarding Subject B0405862A, the applicant stated the following: "In the initially submitted document the data available in this report did not meet the criteria of Kawasaki disease. However, meanwhile additional information has been received and the report now meets the criteria of incomplete Kawasaki disease, although echography (date of testing unknown) did not show cardiac aneurysm. The subject was treated with immunoglobulins and aspirin. The case was not reviewed by an expert consultant at this time."

Regarding Subject B0406754A, the applicant stated the following: "Although it is not known for how long the fever persisted, based on the follow up information received, this case meets 4 out of the remaining 5 criteria for Kawasaki disease. Conservatively, the case meets the diagnostic criteria of Kawasaki disease. The subject was treated with immunoglobulins. It should be noted however that the event occurred more than 3 months after the 2nd dose of rotavirus vaccine in an unspecified context of positive Mycoplasma IgM and where reportedly an unspecified viral infection was suspected. The case was not reviewed by an expert consultant at this time."

2. On page 16, Table 4 of the Analysis of Kawasaki Reports Following Rotarix, you included 30,638 Rotarix subjects and 30,527 placebo subjects for Rota-023. However, in the Rota-023 Visit 1-3 study report, you state that 31,673 Rotarix and 31,552 placebo subjects were enrolled and vaccinated, and used these figures for your safety analyses. Please explain the numerical differences between reports. Also, for each study in the Table 4, please provide the

actual numbers of subjects who received at least one dose of Rotarix and placebo, respectively. Please also provide the actual exposure time in person-years for each treatment arm in each study, if available.

Applicant's response: The applicant stated the following: "Table 4 from the "Analysis of Kawasaki reports following *Rotarix*" dated June 18, 2007 (which is reproduced below, see Table 2) represents the studies per geographic area. It should be noted that for study Rota-023, the majority of exposed subjects was from Latin-America (30,638 for Rotarix and 30,527 for placebo), with a minority of subjects exposed from Finland (1,035 for Rotarix and 1,025 for placebo); the latter numbers can be found in Table 4 under the subheading "Europe". The actual number of subjects who received at least one dose of Rotarix and placebo, as well as exposure time in person-years, were also provided in tabular format.

3. Please provide information on race for each case of Kawasaki disease from Rota-028, Rota-29, Rota-30, and Rota -061 that you reported in your Analysis. In addition, please provide the names of any routine childhood vaccinations that were administered or co-administered, the last dose number of these vaccines prior to disease onset, and interval between the last dose and disease onset. For the cases from these studies that received Rotarix, please also provide the dose potency that was administered to each of these cases.

Applicant's response: The applicant provided the information in tabular format.