

Rotarix®
**(Live Attenuated Human Rotavirus
Vaccine, Oral)**

Vaccines and Related Biological Products Advisory Committee

Briefing Document

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ABBREVIATIONS

ATP	According to Protocol
BLA	Biologic License Application
BPSU	British Paediatric Surveillance Unit
CCID ₅₀	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
DTwP	Diphtheria-Tetanus-whole-cell Pertussis
DTaP	Diphtheria-Tetanus-acellular Pertussis
ELISA	Enzyme-linked ImmunoSorbent Assay
EMA	European Medicines Agency
ERSN	European Rotavirus Surveillance Network
ESPED	Erhebungseinheit for Seltene Paediatrische Erkrankungen in Deutschland
EU	European Union
FDA	Food and Drug Administration
FHA	Filamentous hemagglutinin
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HepB	Hepatitis B
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMSS	Instituto Mexicano de la Seguridad Social
IPV	Inactivated Polio Vaccine
OPV	Oral Polio Vaccine
MedDRA	Medical Dictionary for Regulatory Activities
pfu	plaque forming units
PRN	Pertactin
PRP	Polyribosyl Ribitol Phosphate
PT	Pertussis Toxoid
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SCCS	Self controlled case series
SPSU	Swiss Paediatric Surveillance Unit
U/mL	units/milliliter
UMV	Universal Mass Vaccination
US	United States of America
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. INTRODUCTION

1.1. Key Product Characteristics

Product name: Rotarix® (Live Attenuated Human Rotavirus Vaccine, Oral)

Rotarix is a live attenuated human rotavirus vaccine for oral use to prevent rotavirus gastroenteritis when administered as a two-dose series to infants.

Dosage Forms and Strength: *Rotarix* is available as a vial of lyophilized vaccine to be reconstituted with a liquid diluent in a prefilled oral applicator.

Rotarix contains a live, attenuated (weakened) rotavirus derived from a human rotavirus strain. *Rotarix* is mixed with a liquid diluent that contains calcium carbonate as a buffer and sterile water. *Rotarix* contains no preservatives.

Each 1 mL dose contains at least $10^{6.0}$ median Cell Culture Infective Dose (CCID₅₀) of live, attenuated human rotavirus strain after reconstitution.

Recommended Dose and Schedule: The vaccination series consists of two doses administered orally. The first dose should be administered in infants beginning at 6 weeks of age. There should be an interval of at least 4 weeks between the first and second dose. The two-dose series should be completed by 24 weeks of age.

Proposed indication: *Rotarix* is indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, and G9) when administered as a two-dose series to infants 6 to 24 weeks of age.

Manufactured by: GlaxoSmithKline (GSK) Biologicals

1.2. Background

Rotavirus infection is the leading cause of severe acute gastroenteritis in infants and young children throughout the world. Rotavirus infection is universal and affects nearly all children by the age of 5 years worldwide. Even in developed nations where standards of hygiene are high, rotavirus is the most common cause of diarrhea in children under 5 years of age. In the United States (US), rotavirus accounts for an estimated 600,000 cases requiring a clinic or emergency room visit and 55,000 to 70,000 cases requiring hospitalization each year [Fischer, 2007; Glass, 2006]. Worldwide, rotavirus is estimated to cause approximately 610,000 deaths in children less than 5 years old, most of which occur in Asia (particularly in the Indian subcontinent), Africa and Latin America [Glass, 2006; Parashar, 2006]. Vaccination against rotavirus is recognized as an important preventive strategy to control morbidity and mortality caused by this very common pediatric disease.

On February 20, 2008, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet to review the Biologics Licensing Application (BLA) for *Rotarix*. This briefing document provides information regarding the epidemiology of

rotavirus, the clinical development program and clinical data in support of the licensure of *Rotarix* in the target infant population, and outlines the current post-marketing experience as well as ongoing and planned pharmacovigilance activities.

1.3. Executive Summary

Studies of natural rotavirus infection demonstrate that the initial episode of rotavirus gastroenteritis is the most severe. Subsequent infections typically are progressively milder. The major reason for this observation is that infants develop homotypic and heterotypic immunity following infection [Velazquez, 1996; Ward, 1994]. An attenuated human rotavirus vaccine thus should induce protective immunity, and prevent severe diarrhea and its consequences. The clinical data presented in this briefing document confirm this postulate.

Eleven randomized clinical studies (Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, Rota-023, Rota-033, Rota-036, Rota-039, Rota-048 and Rota-060) were submitted in the BLA to support licensure of *Rotarix* in the US. These studies were designed to evaluate *Rotarix* when administered as a two-dose series in the target infant population.

Clinical Efficacy

Two phase III clinical studies, Rota-036 and Rota-023, provide pivotal efficacy data to support licensure of *Rotarix*. In both studies, surveillance for gastroenteritis started on the day of Dose 1, and continued until the end of the second rotavirus epidemic season after vaccination (Rota-036) or until 24 months of age (Rota-023). In study Rota-036, all gastroenteritis episodes were identified by active surveillance and any medical attention (defined as medical personnel contact/advice/visit, emergency room contact/visit or hospitalization) sought for each gastroenteritis episode was recorded. In study Rota-023, gastroenteritis episodes requiring hospitalization and/or rehydration in a medical facility (clinical definition for severe episodes) were identified by active surveillance. Severity of gastroenteritis episodes was graded using the 20-point Vesikari scale in which episodes with a score ≥ 11 points were considered as severe. Stool specimens were tested for rotavirus antigen (VP6) by enzyme-linked immunosorbent assay (ELISA), and the G and P types were determined using reverse transcriptase-polymerase chain reaction (RT-PCR).

Data from both studies (Rota-023 and Rota-036) showed that two doses of *Rotarix* were highly effective in preventing severe rotavirus gastroenteritis. Protection against severe rotavirus gastroenteritis was 96% in study Rota-036 and 85% in study Rota-023 during the first year of life. Efficacy against rotavirus gastroenteritis of any grade of severity was 87% in study Rota-036. The rate of hospitalization for rotavirus gastroenteritis was reduced significantly in the *Rotarix* group compared to the placebo group. Efficacy against rotavirus hospitalizations was 100% in study Rota-036 and 85% in study Rota-023. In study Rota-036, the need for medical attention was reduced by 92% in the *Rotarix* group. Efficacy persisted during the first 2 years of life when the maximum burden of rotavirus gastroenteritis exists. *Rotarix* provided significant protection against circulating G1 and non-G1 types (including G2, G3, G4, and G9 types). Breast-feeding was not found to reduce the protection against rotavirus gastroenteritis among vaccinated infants.

An overall reduction of gastroenteritis disease regardless of presumed etiology was observed among *Rotarix* recipients compared to placebo recipients. These efficacy results are further described within this briefing document in Section 4.

Clinical Immunogenicity

Rotarix was immunogenic in infants when administered as a two-dose series. The anti-rotavirus IgA seroconversion rate after Dose 2 was 87% and 77% in studies Rota-036 and Rota-023 respectively, where efficacy has been demonstrated. In the phase II study Rota-005 conducted in the US and Canada, the anti-rotavirus IgA seroconversion rate after Dose 2 was 78% in the group receiving the licensure formulation of *Rotarix*. In the phase III study Rota-060 conducted in the US, the anti-rotavirus IgA seropositivity rate was 86% when measured 2 months after, and 79% when measured 3 months after the second dose of *Rotarix*. Antibody responses after two doses of *Rotarix* in studies in US/Canada (Rota-005 and Rota-060) were comparable to those seen in Latin America (Rota-023), and Europe (Rota-036) where efficacy was demonstrated. Efficacy, especially against severe rotavirus gastroenteritis, paralleled but was always higher compared to the antibody response indicating that the antibody response tends to underestimate the level of protective immunity elicited by the vaccine. Consistency of the immune response to three production lots of *Rotarix* has been demonstrated. The *Rotarix* vaccine strain is genetically stable in production. The rate of rotavirus antigen shedding in stool peaked at Day 7 after the first dose of the vaccine and decreased thereafter. It was estimated that 26% of the infants were shedding live vaccine virus at Day 7 after the first dose in two clinical studies. The limited transmission potential of the vaccine strain should be weighed against the high likelihood of acquiring and transmitting natural rotavirus, as nearly all children will be infected with rotavirus by 5 years of age. The coadministration study Rota-060 in the US demonstrated that coadministration of *Rotarix* did not negatively impact the immune response to any of the coadministered antigens [diphtheria, tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), hepatitis B surface antigen (HBsAg), polyribosyl ribitol phosphate (PRP), poliovirus serotypes 1, 2 and 3, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F] that are currently included in the Center for Disease Control and Prevention's (CDC) schedule of recommended immunizations for infants in the US. The immunogenicity results are described in Section 5.

Clinical Safety

The clinical safety database from the 11 clinical studies submitted in the BLA included 75,029 infants: 37,214 infants received at least one dose of the licensure formulation of *Rotarix* (i.e., at least $10^{6.0}$ CCID₅₀ per dose), 3,076 infants received at least one dose of the vaccine at lower potency (i.e., less than $10^{6.0}$ CCID₅₀ per dose), and 34,739 infants received at least one dose of the placebo control. The vaccine exposure in the 11 studies included 72,212 doses of *Rotarix*, 6,037 doses of the vaccine at lower potency, and 67,319 doses of placebo.

Pivotal safety study Rota-023 in which 63,225 infants were vaccinated with *Rotarix* or placebo was specifically designed and powered to evaluate safety of *Rotarix* with regard to the risk of definite intussusception diagnosed within 31 days post-vaccination

compared to the placebo. A case of “definite intussusception” required confirmation at surgery or autopsy or by using imaging techniques such as gas or liquid contrast enema or abdominal ultrasound according to the case definition from the Brighton Collaboration Intussusception Working Group [Bines, 2004a]. Intussusception cases were detected by independent, complementary methods: 1) expedited reporting of intussusception by hospitals in study areas, 2) concurrently conducted prospective hospital-based surveillance, and 3) reporting of the intussusception cases by parents/guardians at scheduled study visits/contacts. All investigator-diagnosed cases of intussusception were adjudicated by an independent blinded expert committee. The pre-specified criteria for meeting the primary safety objective in study Rota-023 were that the upper limit of the 2-sided 95% CI of the risk difference for the percentage of subjects diagnosed with definite intussusception within 31 days (Day 0 to Day 30) after any dose should be below 6/10,000, and the lower limit of the 2-sided 95% CI of the risk difference should be below 0.

There were 13 cases of definite intussusception diagnosed within the 31-day post-vaccination period, 6 in the *Rotarix* group and 7 in the placebo group, with risk difference estimate of -0.32/10,000 [95% confidence interval (CI): -2.91/10,000; 2.18/10,000] and relative risk of 0.85 [95% CI: 0.3;2.42]. There was no temporal cluster of intussusception cases after either dose. The pre-specified criteria were thus met.

Cases of intussusception were also captured in all of the clinical studies, though cases were adjudicated by the independent blinded expert committee only in study Rota-023. There was no evidence of an imbalance in intussusception cases, including all investigator diagnosed reports of intussusception irrespective of adjudication across the 11 studies submitted in the BLA. When considering all investigator-diagnosed intussusception cases reported to occur within the 31-day post-vaccination period in the 11 studies submitted in the BLA, there were 10 cases in vaccine recipients and 7 cases in placebo recipients with a relative risk of 1.3 [95% CI: 0.44; 4.06]. When considering all investigator-diagnosed intussusception cases reported to occur regardless of time-to-onset after vaccination in the 10 placebo-controlled studies submitted in the BLA, there were 18 cases in vaccine recipients and 22 cases in placebo recipients with a relative risk of 0.72 [95% CI: 0.36; 1.41].

Pivotal safety data were provided by a core integrated safety summary comparing safety data in subjects receiving the licensure formulation of *Rotarix* versus placebo. Infants in study Rota-060 received the licensure formulation of *Rotarix*; however, as the study was not placebo-controlled, it was not included in the integrated safety summary. For each safety endpoint, the common relative risk across studies and its 95% CI were calculated based on exact conditional likelihood approach adjusted for the study effect [Proc StatXact 5.0 user manual]. In the integrated safety analyses, imbalances warranting further exploration were identified based on 95% CI for the relative risk across studies excluding 1.

Pivotal data on serious adverse events (SAEs) were provided by a core integrated safety summary of 8 studies (Rota-005, Rota-006, Rota-007, Rota-023, Rota-033, Rota-036, Rota-039 and Rota-048) that assessed SAEs in subjects receiving the licensure formulation of *Rotarix* (36,755 infants) versus placebo (34,454 infants).

The overall safety profile of *Rotarix* was similar to the placebo control. In the core integrated safety summary, there were fewer SAEs associated with gastroenteritis disease in the *Rotarix* group compared to the placebo group (see Section 6.2.2). All other SAEs reported within the 31-day post-vaccination period, including deaths, intussusception, bronchiolitis, pneumonia or nervous system disorder SAEs were reported by similar proportions of subjects in both the *Rotarix* and placebo groups as indicated by the 95% CI for relative risk overlapping 1.0. Pivotal data on solicited adverse events were provided by a core integrated safety summary of 7 studies (Rota-005, Rota-006, Rota-007, Rota-033, Rota-036 (subset), Rota-039 and Rota-048) that assessed solicited adverse events in subjects receiving the licensure formulation of *Rotarix* (3,286 infants) versus placebo (2,015 infants). In the core integrated safety summary, solicited adverse events, including symptoms rated as grade 3 in intensity, occurred at similar rates in the *Rotarix* and placebo groups (see Section 6.2.2.3). No imbalance was noted between *Rotarix* and placebo recipients for fever (rectal temperature >100.4°F or >103.1°F), fussiness/irritability, cough/runny nose, loss of appetite, vomiting, or diarrhea reported within 8 days after Dose 1 and Dose 2 (95% CI of relative risk included 1). Overall, *Rotarix* was well tolerated with a safety profile is similar to the placebo.

Post-Marketing Experience and Pharmacovigilance Plan

Rotarix is currently licensed in over 100 countries worldwide including Canada, Mexico, Australia, and the countries of the European Union (EU). Over 12 million doses of *Rotarix* have been distributed worldwide since launch up to July 11, 2007. The currently available post-marketing data from spontaneous reporting of adverse events outside of the US have shown that *Rotarix* has an acceptable safety profile. These data do not suggest any increased risk for intussusception following vaccination with *Rotarix*, and no new safety signal related to any other events has been detected as summarized in Section 7.

GSK Biologicals is utilizing the worldwide availability of *Rotarix* to study the outcomes of interest (intussusception, Kawasaki disease, convulsions, pneumonia deaths and hospitalizations due to acute lower respiratory tract infections) in the setting in which they can be most appropriately evaluated. Global pharmacovigilance activities are ongoing outside the US and are planned after US licensure as summarized in Section 8. The ongoing pharmacovigilance activities focus on several safety outcomes which include intussusception, Kawasaki disease and pneumonia deaths. In addition, a post-licensure study in the US is planned to assess whether there is an association between *Rotarix* administration and intussusception through epidemiological analysis. This study will also include monitoring of Kawasaki disease, convulsions and hospitalizations due to acute lower respiratory tract infections. The specific study design/protocol for the US post-marketing study is under discussions with Center for Biologics Evaluation and Research (CBER).

Conclusion

Rotarix administered as a two-dose series to infants starting at 6 weeks of age provides significant protection against rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, and G9). In two phase III studies, efficacy against severe

rotavirus gastroenteritis was 96% in study Rota-036 and 85% in study Rota-023 during the first year of life. In the two phase III studies, *Rotarix* reduced hospitalizations for rotavirus gastroenteritis by 100% in study Rota-036 and 85% in study Rota-023. A phase III study in 63,225 infants has demonstrated no increased risk of intussusception within the 31-day period following any dose of *Rotarix* compared to the placebo by meeting the pre-specified criteria as shown by the risk difference estimate of -0.32/10,000 [95% CI: -2.91/10,000; 2.18/10,000] and relative risk of 0.85 [95% CI: 0.3; 2.42]. The overall safety profile for *Rotarix* is similar to the placebo. The results of the clinical studies support the use of *Rotarix* for the US infant population. The risk-benefit ratio for *Rotarix* is overall favorable for the intended population. The availability of *Rotarix* for infants would add measurable value to the current standard of medical care for the infant population in the US.

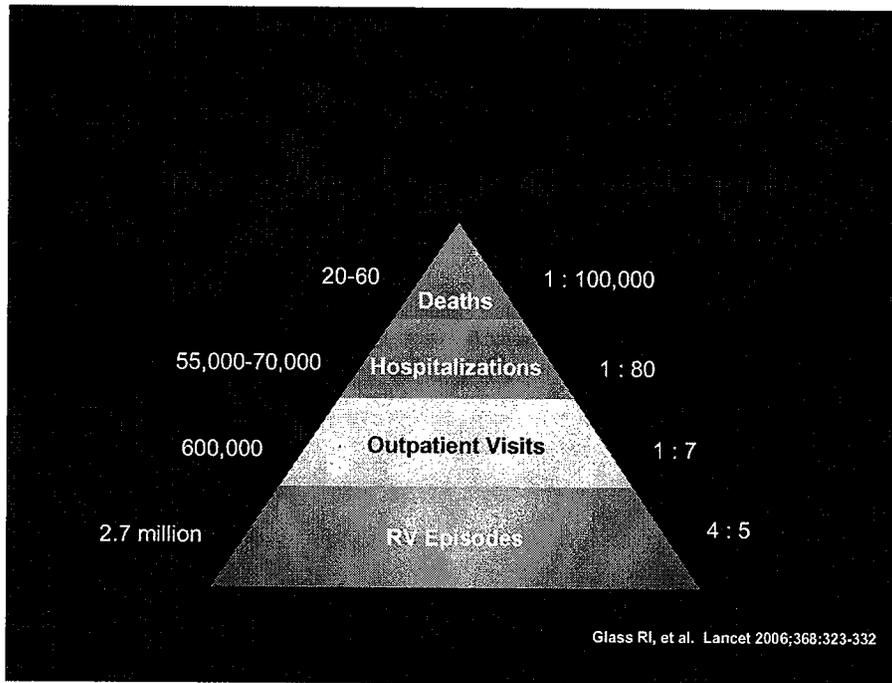
2. ROTAVIRUS VACCINE DEVELOPMENT

2.1. Burden of Rotavirus Disease

Worldwide, rotavirus is estimated to cause approximately 114 million episodes of gastroenteritis, 24 million cases requiring a clinic visit, 2.4 million cases requiring hospitalization and 610,000 deaths in children less than 5 years old [Glass, 2006]. The majority of deaths due to untreated dehydrating rotavirus gastroenteritis occur in Asia (particularly in the Indian subcontinent), Africa and Latin America in countries defined as “low-income” according to the World Bank classification scheme. Rotavirus infection is universal. By the age of 5 years, almost every child will have experienced an episode of rotavirus gastroenteritis, irrespective of whether this child lives in a developing or developed country [Parashar, 2003].

Figure 1 provides the rotavirus disease burden and risk estimates among children less than 5 years of age in the US.

Figure 1 Rotavirus disease burden and risk estimates among children less than 5 years of age in the US



Even in the US where standards of hygiene are high, nearly all children will be infected with rotavirus by their fifth birthday, and an estimated 600,000 cases requiring a clinic or emergency room visit and 55,000-70,000 cases requiring hospitalization occur each year among US children [Fischer, 2007; Glass, 2006]. The most serious rotavirus infections occur in children between 3 months and 36 months of age [Red Book, 2006].

Because there is generally good access to emergency treatment to prevent circulatory collapse resulting from severe dehydration, deaths due to rotavirus are uncommon in developed countries. Nevertheless, 20 to 60 deaths are estimated to occur each year due to rotavirus in the US [Fischer, 2007]. In the US, overall diarrhea-associated deaths declined by 75% from 1968 to 1985 but stabilized since then at about 300 deaths per year. The decrease was greatest during summer months when diarrheal diseases caused by bacteria are more prevalent [Kilgore, 1995]. These data suggest that although the overall death rate of diarrheal disease has decreased, the total number of deaths attributable to rotavirus remain unchanged [Parashar, 2006]. It is likely that there are more infant deaths due to rotavirus than has been estimated because of lack of pathogen identification in the majority of cases [Staat, 2005].

Similarly, during the past 25 years in the US, the rate of rotavirus gastroenteritis hospitalizations has not declined. Rotavirus gastroenteritis still remains an important cause of hospitalizations in the US [Malek, 2006; Charles, 2006]. From 1993 through 2002, 12% to 13% of children less than 5 years of age hospitalized in the US had a diagnosis of acute gastroenteritis at discharge, and overall 18% of all gastroenteritis episodes were coded as rotavirus associated. Among children aged less than 5 years in the US, 20% of the hospitalizations for rotavirus disease occur during the first 6 months

of life, 20% between the ages of 6-11 months, 20% in children 12-23 months old, and 40% in children 24-59 months old [Parashar, 1998].

Rotavirus is a common cause of nosocomially acquired diarrhea in children [Fischer, 2004; Chandran, 2006]. The spread of infections within families and institutions, such as hospitals and day care centers, is common. In the US, up to 14% of the total rotavirus cases among hospitalized children are reported to be due to nosocomially acquired rotavirus infections [Rodriguez-Baez, 2002].

In addition to the direct medical costs due to hospitalization, there are also direct medical costs of rotavirus gastroenteritis not leading to hospitalization, as well as indirect medical costs (such as parental absence at work) and the costs to society [Lee, 2005]. Assuming an estimated 50,000 hospitalizations attributable to rotavirus each year in the US, the medical cost of severe rotavirus infections can exceed 22 million dollars annually [Lee, 2005]. The overall cost of rotavirus disease in the US is estimated to be one billion dollars per year, of which 264 million dollars was attributable to medical costs [Tucker, 1998]. These disease burden data indicate the importance of rotavirus as a cause of severe diarrhea leading to hospitalization among children and underscore the need for effective measures for prevention. A recently published cost-effectiveness analysis for a 3-dose rotavirus vaccine has shown that the costs per case of rotavirus averted (138 US dollars) and per serious case averted (2,636 US dollars) are comparable to the cost effectiveness of pneumococcal vaccine in preventing otitis media (160 US dollars) and pneumonia (3,200 US dollars) in the US [Widdowson, 2007].

2.2. Clinical Features of Rotavirus Disease

Rotavirus is transmitted mainly by the fecal-oral route through close person-to-person contact and through fomites [Butz, 1993]. Ingested virus particles infect the mature enterocytes in the villi of the small bowel, typically leading to villous atrophy [Bernstein, 1998a]. After an incubation period of 2 to 4 days, there is an abrupt onset of diarrhea and vomiting, which can result in severe dehydration that can be fatal if untreated [Kapikian, 2001]. Other common clinical findings include fever and abdominal distress. The diarrheal stools have the features of a secretory diarrhea, are loose and watery, and occur frequently. Mucus is found in 20% of stools but blood is rare. The symptoms typically last from 3 to 9 days. Viral shedding, as measured by ELISA and RT-PCR, peaks at about day 4-5 of illness and then declines [Vesikari, 1981]. Rotavirus can be detected in stool before the onset of diarrhea and can persist for as long as 57 days after the onset of symptoms in immunocompetent hosts [Richardson, 1998]. In immunocompromised children, persistent infection and diarrhea has been reported.

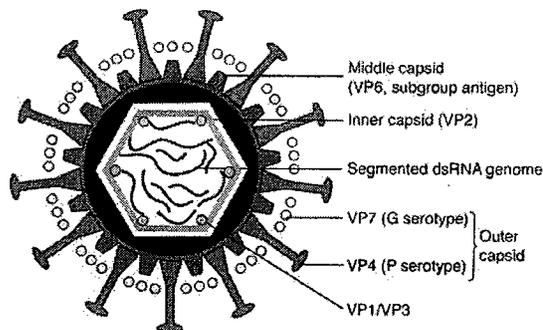
Natural immunity induced by rotavirus infection protects infants from subsequent episodes of severe disease [Bishop, 1983; Velazquez, 1996; Ward, 1994; Bernstein, 1991]. The first rotavirus infection is usually the most severe and subsequent infections cause progressively milder symptoms. Complications of rotavirus gastroenteritis include dehydration, electrolyte imbalance, hospitalization, secondary bacterial infections and death.

No specific antiviral therapy is available and anti-diarrheal agents are not recommended. Treatment is supportive and symptomatic and mainly focuses on preventing dehydration and restoring the patient's fluid and electrolyte balance. Oral rehydration solutions containing water, glucose and electrolytes are widely used. For severe dehydration, intravenous fluid treatment is recommended. Preventive measures against rotavirus infection are limited to good hygienic practices (e.g., frequent washing of hands), chemical disinfection and breast-feeding. Nonetheless, both treatment and preventive measures have had only limited impact on the global rotavirus disease burden. Therefore, vaccination against rotavirus represents an important preventive strategy to control morbidity and mortality caused by this very common pediatric disease.

2.3. Rotavirus Structure and Antigenic Determinants

Rotavirus is an icosahedral, non-enveloped particle 70nm in diameter, and is formed by three protein capsids that encase the genome of 11 segments of double-stranded RNA. Figure 2 presents a schematic of the rotavirus particle. The two outer shell proteins VP7 (a glycoprotein referred to as the G protein) and VP4 (a protease cleaved protein referred to as the P protein) induce neutralizing antibodies which are thought to be involved in disease protection. Rotaviruses are classified into 15 G (VP7) and 23 P (VP4) genotypes. Reassortment between serotypes can lead to unusual diversity of rotavirus strains. However, 5 G-P combinations, G1[P8], G2[P4], G3[P8], G4[P8] and G9[P8], constitute the majority of human rotavirus strains worldwide. The P4 and P8 share cross-reactive epitopes, and the middle capsid protein VP6 is common to all rotavirus strains infecting humans.

Figure 2 Schematic representation of the rotavirus particle



Source: adapted from Cunliffe, 2002

Rotaviruses infecting humans are normally found in two major groups: the “Wa genogroup” which includes G1, G3, G4 and G9 human rotavirus strains, and the “DS-1 genogroup” which includes the G2 human rotavirus strains. Inclusion into the same genogroup requires nucleotide sequence identities between any segments of 89% or more. There is close homology among rotaviruses from different genogroups. For example, the greatest difference in amino acid sequence between the VP6 proteins of any two mammalian rotavirus strains is 11% irrespective of their genogroups. Even though both the VP4 and VP7 segments of two different human rotavirus strains may belong to

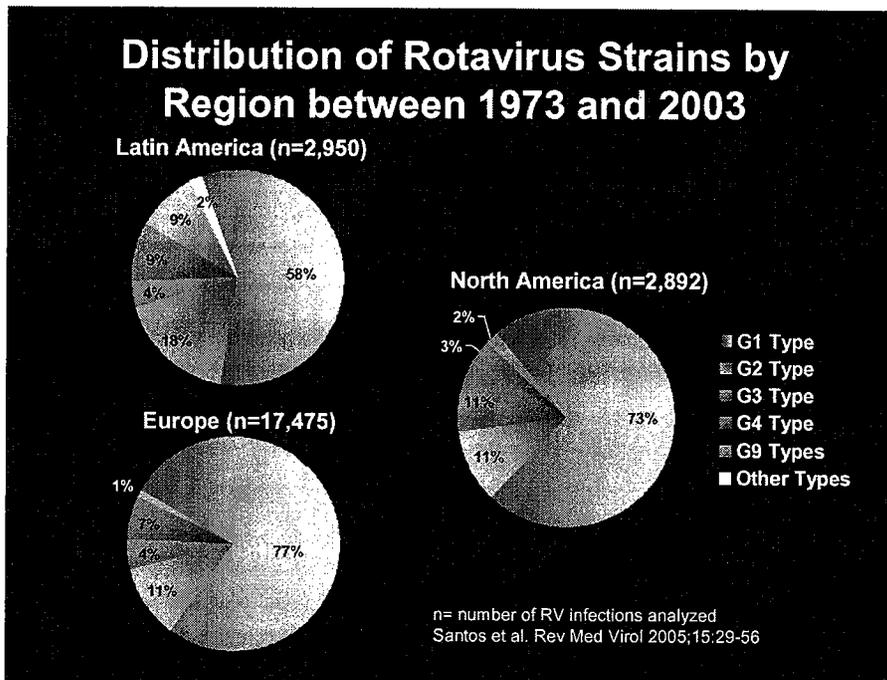
distinct genogroups, their cognate proteins may still contain sufficient common T and B cell epitopes to provide efficient cross protection [Hoshino, 2000]. Despite extensive studies, key proteins that might be essential targets for protection with respect to humoral or cell mediated immune response have not been definitely identified. The VP4 and the VP7 proteins expressed in the outer capsid of the infectious viruses are the two main targets of neutralizing antibodies [Gorrel, 1999]. While some uncertainty remains as to the antigens that are associated with protective responses, key antigens such as VP6, VP7, VP4 and NSP4 are identified as probable key proteins for both immune response induction and protection [Yuan, 2004]. The mechanism of heterotypic protection (immunity against different rotavirus types) may be explained by the significant overlap in epitopes between the various types. Furthermore, data has been published showing that immune response to VP4 could be as high as against VP6 and higher than against VP7 and that responses to VP4 (natural infection or vaccination) are both homotypic and heterotypic [Gorrel, 1999; Yuan, 2004].

2.4. Epidemiology

In the US, there is a marked and well documented seasonality (peak rates in November through March) of rotavirus detection and a geographic progression across the continental states in a general north-easterly direction [Turcios, 2006; Torok, 1997; LeBaron, 1990]. Rotavirus infections are ubiquitous. In North America, most rotavirus infections occur in the first and second year of life [Charles, 2006]. Subsequent infections occur but typically cause much milder symptoms [Ehlken, 2002].

Studies in the US have shown that the common G1, G2, G3 and G4 types represent the majority of the strains each year [Griffin, 2002; Santos, 2005]. The G1 type has been the predominant circulating strain in the US over many years with an average prevalence over 70%. Depending on the year, the prevalence of other frequent types in the US has ranged from 6% to 15% for G2 type, from 1% to 8% for G3 type and from 0% to 2% for G4 type [Griffin, 2002; Griffin, 2000; Ramachandran, 1998]. In the 1990's, the G9 type appeared to be emerging as the fifth most common type, with mostly G9P[8] strains circulating in the US [Ramachandran, 1998]. An annual variation on the distribution of G types is observed. In Philadelphia, for example, the prevalence of the G1 type in the 1997-1998 season was 91% and dropped to 33% during the following season [Clark, 2004]. As shown in Figure 3, the distribution of the predominant rotavirus types in North America is concordant with that in Europe and Latin America where phase III safety and efficacy clinical studies for *Rotarix* were conducted.

Figure 3 Distribution of human group A rotavirus G types by region for strains collected between 1973 and 2003



2.5. Natural Immunity to Rotavirus Disease

Many reports have documented that natural immunity induced by rotavirus infection protects infants from subsequent episodes of severe disease. The first evidence of natural rotavirus infection conferring protection was provided in 1983 [Bishop, 1983]. In this study conducted in Australia, neonatal rotavirus infection was shown to reduce the clinical severity of subsequent rotavirus reinfections. Similarly, nosocomially infected newborns in India were found to be protected against subsequent severe episodes of rotavirus diarrhea [Bhan, 1993].

Longitudinal epidemiology studies performed in very young children (0 -24 months old) have shown that rotavirus infections during the first year of life protect against rotavirus illness (severe reinfection) during the second year of life [Velazquez, 1996]. Importantly, subsequent infections are significantly less severe than first infections, even when the second infection is caused by another G type [Velazquez, 1996]. In most cases homotypic immunity (immunity against the same rotavirus type) is developed after the first natural infection. Successive encounters with rotavirus (even of the same type) are shown to increase and broaden the initial specific immune response allowing for heterotypic protection (immunity against different rotavirus types). Heterotypic protection may be mediated by antibodies directed against antigenically conserved proteins (such as those of the middle capsid) or by rotavirus-specific cytotoxic T-lymphocytes that broadly cross-react with cells infected by different rotavirus types. Given that multiple G and P types can circulate simultaneously, and the temporal and geographic variation in the circulating rotavirus types, the ability of a rotavirus vaccine to generate heterotypic immunity is

critical. Asymptomatic infection observed during the first year of life induces the same level of protection as symptomatic infection [Velazquez, 1996; Ward, 1994; Bernstein, 1991], which is important in the context of development of a live attenuated rotavirus vaccine. The observations from natural immunity studies have provided the basis for development of live attenuated oral vaccines that mimic protective immunity induced by natural infection without causing symptoms.

2.6. Vaccination against Rotavirus

Development of rotavirus vaccines began in the 1970s and most efforts have focused on the development of orally administered live attenuated rotavirus vaccines. Previously developed monovalent bovine rotavirus vaccine candidates, including RIT4237 and WC3, were well tolerated and immunogenic but their efficacy varied across clinical studies. Development of both these vaccines was halted [Vesikari, 1984; Lanata, 1989].

A tetravalent (G1-4) rhesus-human reassortant vaccine (RotaShield® manufactured by Wyeth Lederle Vaccines) was licensed as a three-dose vaccination series by the US Food and Drug Administration (FDA) in August 1998 [CDC, 1999a]. In July 1999, the CDC communicated that intussusception, an unexpected complication, was reported in association with *RotaShield*, and this led to the vaccine's withdrawal within a year of its introduction [CDC, 1999b]. The risk for intussusception among *RotaShield* recipients was initially estimated to be as high as 4/10,000 [Murphy, 2001; Kramarz, 2001], and increased risk was shown during the 3- to 14-day period after the first dose [Murphy, 2001]. Subsequently, the risk estimate was judged to be 1/10,000 [Peter, 2002; Murphy, 2003].

A live oral pentavalent recombinant human-bovine rotavirus vaccine (RotaTeq®, manufactured by Merck & Co Inc.) given as a three-dose vaccination series was shown in clinical trials to not be associated with an increased risk of intussusception relative to placebo by meeting pre-specified criteria, and was efficacious against rotavirus disease [Vesikari, 2006]. *RotaTeq* was licensed for use in the US in February 2006.

3. DEVELOPMENT OF GSK BIOLOGICALS' LIVE ATTENUATED HUMAN ROTAVIRUS VACCINE

3.1. GSK Biologicals' Live Attenuated Human Rotavirus Vaccine – *Rotarix*

Immunity against different rotavirus types, referred to as heterotypic protection, has been observed following the acquisition of natural immunity. Multiple infections with rotavirus, even when they are of the same type, have been shown to increase and broaden the initial specific immune response allowing for heterotypic protection [Pichichero, 1993]. An attenuated human rotavirus vaccine was anticipated to mimic human infection and provide broad, cross-reactive protection against rotavirus gastroenteritis. In addition, human rotavirus has not been demonstrated to be an important cause of intussusception [Rennels, 1998; Velazquez, 2004].

The parent human rotavirus strain first developed as the 89-12 candidate vaccine was derived from the stool samples of a 15-month child participating in an efficacy study of the investigational WC3 bovine vaccine. Efficacy of the investigational WC3 bovine vaccine was not demonstrated but it was observed that infants with evidence of a first rotavirus infection were completely protected against symptomatic reinfection in this two year prospective study [Bernstein, 1991]. The G1P[8] rotavirus strain that was isolated from the naturally infected subject number 12 in the study during the 1988-89 rotavirus season in Cincinnati, Ohio, was developed as the 89-12 vaccine candidate after 33 passages in cell culture. The final preparation of the candidate 89-12 vaccine, which had a titer of $10^{5.0}$ plaque forming units (pfu)/mL underwent pre-clinical safety testing and was licensed by Virus Research Institute (Avant Immunotherapeutics, US) for clinical development. The 89-12 vaccine was well tolerated, immunogenic and efficacious after two doses [Bernstein, 1998b; Bernstein, 1999; Bernstein, 2002].

In 1997, GSK Biologicals acquired rights to the 89-12 vaccine and developed the vaccine further. Cloning and cell culture passages were undertaken to obtain the vaccine known as RIX4414 or *Rotarix*, a live, attenuated human rotavirus vaccine. The *Rotarix* vaccine strain and the original unpassaged isolate genome differ by 12 nucleotide mutations encoding 10 amino acid substitutions. The *Rotarix* vaccine strain is genetically stable throughout the different passages from seed to final vaccine. *Rotarix* is available as a vial of lyophilized vaccine with a liquid diluent in a prefilled oral applicator. *Rotarix* is mixed with liquid diluent that contains the buffer calcium carbonate and sterile water. The diluent is needed to buffer gastric acids and prevent inactivation of the vaccine virus during passage through the stomach. Each 1mL dose of *Rotarix* contains at least $10^{6.0}$ CCID₅₀ of the live, attenuated human rotavirus strain after reconstitution. *Rotarix* contains no preservatives.

3.2. *Rotarix* Clinical Development Program and Regulatory Strategy

GSK Biologicals initiated the clinical development program for the live attenuated human rotavirus vaccine in January 2000 with phase I studies in adults and toddlers, followed by evaluation in the target infant population. The aim of GSK Biologicals' global clinical development plan and registration strategy was to bring *Rotarix* first to the regions of the world where the rotavirus disease burden and the medical need are greatest [Roberts, 2004]. An overview of the clinical studies is provided in 3.2.1.

Rotarix was first launched in Mexico in July 2004. *Rotarix* is currently licensed in more than 100 countries worldwide including Canada, the European Union and Australia, and is recommended in national immunization programs in many countries. *Rotarix* obtained World Health Organization (WHO) prequalification status in February 2007, qualifying GSK to manufacture *Rotarix* for the developing world.

Following a meeting held between GSK Biologicals and CBER in May 2005, CBER considered that data from non-US phase III studies could be pivotal for US licensure of *Rotarix*. The primary endpoints in the pivotal trials, including assessment of intussusception and vaccine efficacy were able to be objectively and independently assessed per protocol and should not be subject to any potential regional differences in

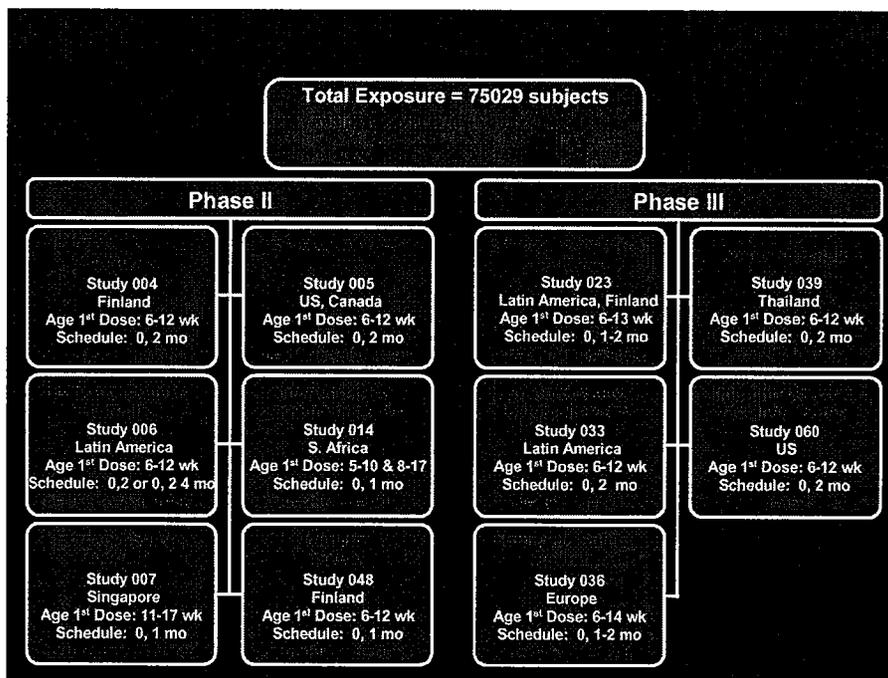
practice. Non-US clinical studies complied with the criteria defined by FDA for acceptance of foreign clinical data. These criteria were as follows: the study design and conduct of the studies were applicable to the US population and relevant to US medical practice; the studies were performed by qualified clinical investigators according to Good Clinical Practices guidelines, and conformed to ethical principles; and the data was validated through on-site inspections. Subsequently, an agreement was reached with CBER regarding the proposed file content in a pre-BLA meeting on 17 July 2006.

3.2.1. Overview of Clinical Studies

Eleven randomized clinical studies (Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, Rota-023, Rota-033, Rota-036, Rota-039, Rota-048 and Rota-060) were submitted in the BLA to support licensure of *Rotarix* in the US. These studies were designed to evaluate *Rotarix* when administered as a two-dose series in the target infant population.

The clinical studies tested the vaccine at potencies ranging from $10^{5.3}$ CCID₅₀ to $10^{6.8}$ CCID₅₀ per dose. Phase III studies including the pivotal efficacy studies Rota-023 and Rota-036, the lot consistency study Rota-033, immunogenicity study Rota-039, and the US coadministration study Rota-060 tested vaccine lots which were released through commercial specifications ensuring an end of shelf life viral titer of at least $10^{6.0}$ CCID₅₀ per dose. All studies were placebo-controlled, except the US coadministration study Rota-060. In all studies, two oral doses of vaccine or placebo were administered to infants at least 6 weeks of age following a 0, 1 or 0, 2 month schedule, with an interval of at least 4 weeks between the first and second dose. The two-dose schedule was to be completed by 24 weeks of age. Figure 4 provides a summary of these studies.

Figure 4 Summary of clinical studies submitted in the *Rotarix* BLA



Efficacy data: Two phase III studies, Rota-023 and Rota-036, provided pivotal efficacy data for *Rotarix*. Two additional studies (Rota-004 and Rota-006) provided supportive efficacy data. An additional study, Rota-007, also had efficacy endpoints but all efficacy objectives could not be evaluated in this study due to the small number of documented rotavirus gastroenteritis cases (parents did not collect the required stool sample in 41% of the gastroenteritis episodes).

Immunogenicity data: The immune response to the vaccine was assessed in all 11 studies submitted in the BLA. In the phase III efficacy studies that are pivotal to the indications, Rota-023 and Rota-036, a pre-defined subset of subjects enrolled at specific centers provided immunogenicity data. Study Rota-033 provided data on lot-to-lot production consistency. Phase II study Rota-005 in the US and Canada, and the phase III US coadministration study Rota-060 provided immunogenicity data in US infants. Study Rota-060 also provided pivotal data to demonstrate that coadministration of *Rotarix* does not impair the immune response to any of the antigens contained in each of the routine infant vaccines currently used in the US. Fecal antigen shedding was evaluated in a subset of subjects in 7 clinical studies (Rota-005, Rota-006, Rota-007, Rota-014, Rota-033, Rota-039 and Rota-048) and live virus shedding was evaluated in studies Rota-039 and Rota-048.

Safety data: Safety data were collected in all vaccinated subjects in the 11 clinical studies submitted in the BLA. Pivotal safety data in the BLA was provided by a core integrated safety summary comparing safety data in subjects receiving the licensure formulation of *Rotarix* versus placebo from 8 studies (Rota-005, Rota-006, Rota-007, Rota-023 (only SAEs), Rota-033, Rota-036, Rota-039 and Rota-048). Infants in study Rota-060 received the licensure formulation of *Rotarix*; however, as the study was not placebo-controlled, it was not included in the integrated safety summary. A supplementary integrated safety summary of 5 studies (Rota-004, Rota-005, Rota-006, Rota-007 and Rota-014) comparing the vaccine at lower potency (i.e., less than $10^{6.0}$ CCID₅₀ per dose) versus the placebo further support the safety of *Rotarix*.

3.3. Populations Evaluated

Healthy male or female infants who were at least 6 weeks of age (at least 5 weeks in study Rota-014) and up to 17 weeks of age at the time of the first dose were eligible for enrollment in the clinical studies. Studies Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, Rota-036 and Rota-048 included only infants who were born after a normal gestation period (i.e., ≥ 36 weeks). Enrolment in study Rota-060 required that the infant had not received a previous dose of hepatitis B vaccine or had received only one dose of hepatitis B vaccine administered at least 30 days prior.

Exclusion criteria were study-specific but essentially consisted of immunodeficiency or immunosuppressant medications, a potential allergy to the vaccine, and chronic gastrointestinal disease or uncorrected gastrointestinal malformation. The phase III efficacy studies Rota-023 and Rota-036, and the US study Rota-060 did not exclude household contact with an immunosuppressed individual or pregnant woman.

Depending on the geographic location of the individual studies, the majority of the

enrolled study participants were either Caucasian/White (Rota-004, Finland; Rota-005, US and Canada; Rota-036, Czech Republic, Finland, France, Germany, Italy and Spain; Rota-048, Finland; Rota-060, US), Hispanic (Rota-006, Brazil, Mexico and Venezuela; Rota-023, Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru and Venezuela; Rota-033, Mexico, Peru and Colombia), Black (Rota-014, South Africa) or Asian (Rota-007, Singapore; Rota-039, Thailand).

The population studied in Europe is similar to that in the US in terms of socioeconomic class, and environmental factors such as disease risk and health outcomes. Study Rota-023 conducted in Latin America included racially and ethnically diverse populations, which are also represented in the US (the efficacy subset of study Rota-023 included 1.1% African; 7.9% White/Caucasian; 85.8% Hispanic; 5.2% other, including Aborigine, Afro-Caribbean, Hindu or Mulatto). Efficacy analyses by race or ethnic groups were not performed in studies Rota-023 and Rota-036 given the predominance of one racial group in the studies (85.8% Hispanic in Rota-023 and 98.3% White/Caucasian in Rota-036). Efficacy among sub-populations in Rota-023 could not be evaluated due to the relatively small number of severe rotavirus gastroenteritis episodes reported in the non-predominant racial groups.

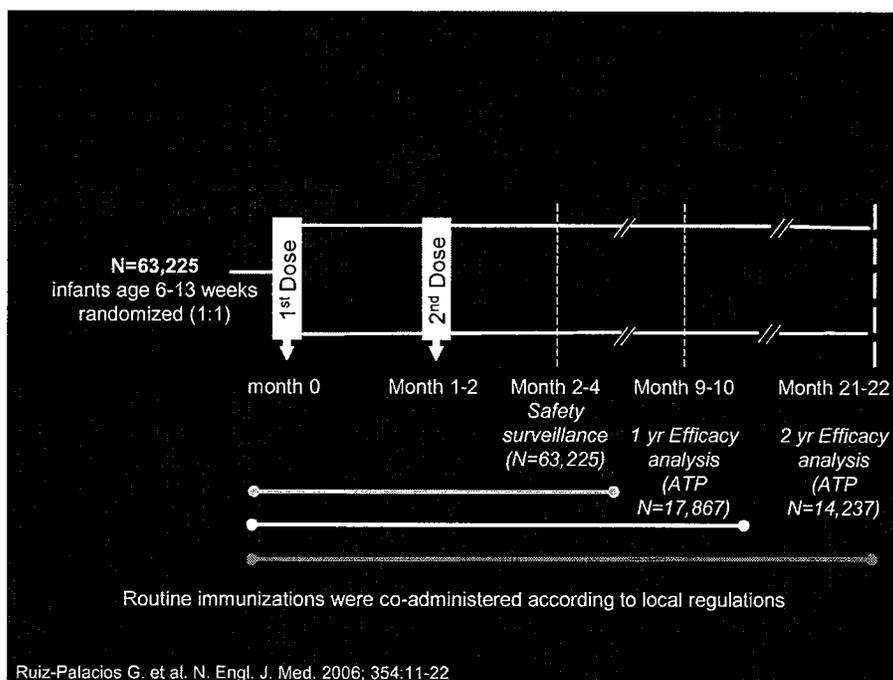
4. CLINICAL EFFICACY

4.1. Efficacy Assessment

Two phase III studies, Rota-023 and Rota-036, provided pivotal efficacy data through two years after *Rotarix* vaccination in infants. Both studies used vaccine lots at the potency of $10^{6.5}$ CCID₅₀ per dose which were released through commercial specifications ensuring an end of shelf life viral titer of at least $10^{6.0}$ CCID₅₀ per dose. Two oral doses of *Rotarix* or placebo were administered to healthy infants starting at 6 weeks of age as a two-dose series following a 0, 1 or 0, 2 month schedule. Unrestricted feeding was permitted during both studies.

Rota-023 was the pivotal phase III, randomized, placebo-controlled, double-blind study conducted in 11 countries in Latin America (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru and Venezuela), and Finland. The design for study Rota-023 is summarized in Figure 5.

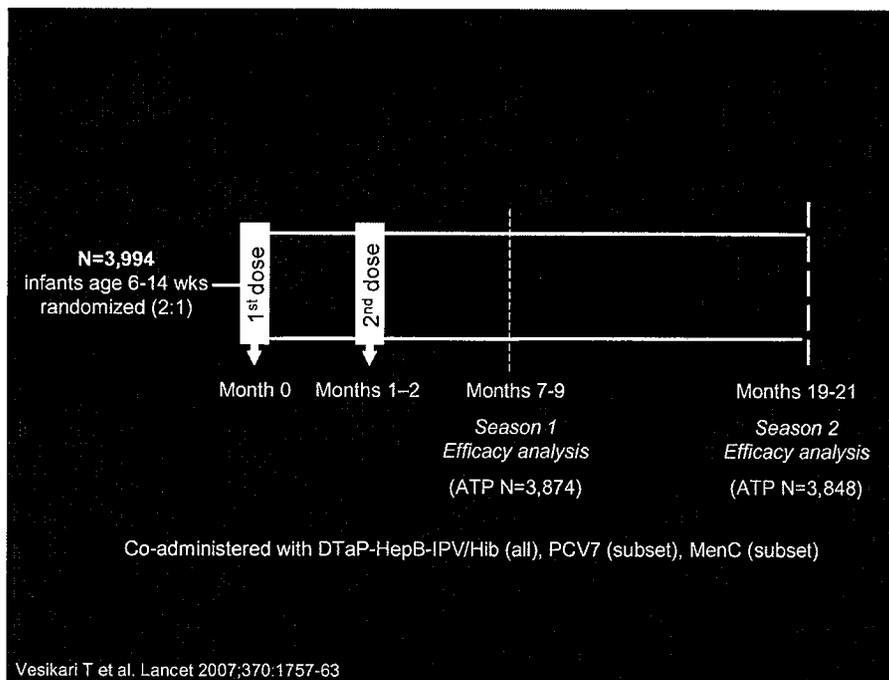
Figure 5 Design of the pivotal phase III efficacy and safety study in Latin America and Finland – study Rota-023



A total of 63,225 infants who were 6 to 13 weeks of age were randomized to receive two doses of *Rotarix* (31,673 infants) or placebo (31,552 infants), and participated in evaluation of safety with regard to intussusception (see Section 6.2.1). Infants received routine pediatric vaccines (such as DTwP or DTaP, Hep B and Hib) according to local regulations. In countries using oral polio vaccine (OPV), its administration was separated from *Rotarix* or placebo dose by 2 weeks. A subset of 20,169 subjects from 10 countries in Latin America (10,159 vaccine recipients and 10,010 placebo recipients) was followed for efficacy and safety assessment until 12 months of age. The according to protocol (ATP) cohort for efficacy until 12 months of age included 9,009 vaccine recipients and 8,858 placebo recipients. A further subset of 15,183 subjects (7,669 vaccine recipients and 7,514 placebo recipients) from 10 of the 11 Latin American countries was followed until 24 months of age (subjects from Peru did not participate in the second year efficacy analysis). The ATP cohort for efficacy until 24 months of age included 7,175 vaccine recipients and 7,062 placebo recipients. The primary efficacy endpoint was prevention of severe rotavirus gastroenteritis (meeting the clinical case definition) caused by naturally occurring rotavirus from 2 weeks after the second dose until 12 months of age. Efficacy was also evaluated against severe rotavirus gastroenteritis with Vesikari score ≥ 11 points, hospitalizations due to rotavirus gastroenteritis and different circulating rotavirus types. Efficacy against severe rotavirus gastroenteritis among infants who received at least one vaccination (total vaccinated cohort) was also evaluated.

Rota-036 was the pivotal phase III, randomized, placebo-controlled, double-blind study conducted in 6 European countries (Czech Republic, Finland, France, Germany, Italy and Spain). The design for study Rota-036 is summarized in Figure 6.

Figure 6 Design of the pivotal phase III efficacy and safety study in Europe – study Rota-036



A total of 3,994 infants who were 6 to 14 weeks of age were randomized to receive two doses of *Rotarix* (2,646 infants) or placebo (1,348 infants) coadministered with the first two doses of specific childhood vaccinations according to the national immunization schedules. Infants in each country received three doses of *Infanrix hexa*TM (combined DTaP, Hep B, IPV and Hib vaccine, manufactured by GSK), except in France where *Infanrix*TM IPV Hib (combined DTaP, IPV and Hib vaccine, manufactured by GSK) was given at the second dose. Infants in Spain also received three doses of *Meningitec*TM (meningococcal group C conjugate vaccine, manufactured by Wyeth Lederle Vaccines), and infants in France and Germany also received three doses of *Prevnar*[®] (pneumococcal 7-valent conjugate vaccine, manufactured by Wyeth Lederle Vaccines).

All subjects were followed for efficacy assessment up to the end of the second rotavirus epidemic season after vaccination. The ATP cohort for efficacy included 2,572 vaccine recipients and 1,302 placebo recipients. The primary efficacy endpoint was prevention of rotavirus gastroenteritis of any grade of severity caused by naturally occurring rotavirus from 2 weeks after the second dose until end of the first rotavirus season after vaccination; efficacy against any grade severity of rotavirus until the end of the second rotavirus season after vaccination was a secondary endpoint. Efficacy was also evaluated against severe rotavirus gastroenteritis, hospitalizations due to rotavirus gastroenteritis, rotavirus gastroenteritis requiring any medical attention, different circulating rotavirus types, and all-cause severe gastroenteritis regardless of presumed etiology. Efficacy against rotavirus gastroenteritis among infants who received at least one vaccination (total vaccinated cohort) was also evaluated. Efficacy follow-up during the third rotavirus season is ongoing in a subset of subjects from Finland.

Surveillance for gastroenteritis and case definitions in studies Rota-023 and Rota-036: In study Rota-023, the clinical case definition of severe rotavirus gastroenteritis was an episode of diarrhea (passage of 3 or more loose or watery stools within a day), with or without vomiting that required hospitalization and/or rehydration therapy (equivalent to WHO plan B or C) in which rotavirus was identified in a stool sample. Surveillance for gastroenteritis started on the day of Dose 1, and continued until 12 months (first efficacy period) and 24 months of age after vaccination (second efficacy period).

Parents/guardians of study subjects were instructed to seek medical advice at the nearest hospital/medical facility in case of symptoms indicative of severe gastroenteritis, and to contact the investigator. Study personnel contacted hospital/medical facilities in the study area at least twice per week to ensure that all severe gastroenteritis cases were identified. Supplemental surveillance was additionally performed by contacting parents/guardians of subjects with a minimum interval of 4 days between contacts. The investigator also specifically solicited the occurrence of severe gastroenteritis at each study visit or study contact.

In study Rota-036, the clinical case definition of rotavirus gastroenteritis was an episode of diarrhea (passage of 3 or more loose or watery stools within a day), with or without vomiting, in which rotavirus was identified in a stool sample. Surveillance for gastroenteritis started on the day of Dose 1, and the first and second efficacy follow-up periods lasted until the end of the first and second rotavirus epidemic seasons (temperate climate) respectively, after vaccination. Rotavirus season was defined as 01 December up to May 31. In this study, 82% of the infants received their first dose of *Rotarix* or placebo, and 10% of the infants had completed the two-dose series prior to the start of the rotavirus season. Study personnel contacted the parents/guardians every week during the rotavirus seasons and every two weeks outside of rotavirus season to collect information about the occurrence of all gastroenteritis episodes irrespective of their severity, and any gastroenteritis related medical care or advice, and hospitalization.

In both studies, individual diary cards were supplied to the parents/guardians of each study subject for the follow-up of gastroenteritis episodes. Gastroenteritis episodes were considered as two separate episodes if there were 5 or more symptom-free days between the episodes. For each gastroenteritis episode, the following information was to be recorded daily until symptoms resolved: body temperature, number of vomiting episodes, number of looser than normal stools, and any treatment given or hospitalization. The data recorded on the diary cards was used to score the intensity of the gastroenteritis episodes using the Vesikari clinical scoring scale (described in detail below). In study Rota-036, information was also recorded on behavioral symptoms (irritable/less playful, lethargic/listless) and seizures experienced by the subject to allow assessment using the Clark clinical scoring scale. Also, any medical attention (defined as medical personnel contact/advice/visit, emergency room contact/visit or hospitalization) sought for each gastroenteritis episode was recorded in study Rota-036. The protocols did not intervene in standard of care practices.

Detection and identification of rotavirus in gastroenteritis stool specimens: The presence of rotavirus antigen in stool samples collected during any gastroenteritis episodes was analyzed using a commercial ELISA kit 'RotaClone' which detects VP6. All stool samples that were rotavirus positive were tested by RT-PCR followed by

reverse hybridization assay (or optional sequencing as needed) to determine the G and P types. This technique also allowed the discrimination between the G1 vaccine virus and wild-type G1 rotavirus.

Evaluation of the severity of a rotavirus gastroenteritis episode: Severity of all gastroenteritis episodes in study Rota-036 was determined at GSK Biologicals using the 20-point Vesikari scale which is a clinical scoring system in which points are assigned based on the duration and intensity of diarrhea and vomiting, the intensity of fever, and use of rehydration therapy or hospitalization for each episode [Ruuska, 1990] (see Table 1). Prospectively, a score of less than 7 was defined as mild, a score of 7 to 10 was defined as moderate and a score of 11 or greater was severe. In study Rota-023, gastroenteritis cases were only evaluated for “severe” episodes using a clinical case definition, in which “severe” rotavirus gastroenteritis was defined as diarrhea (3 or more loose stools in a 24 hr period) with or without vomiting that required hospitalization and/or rehydration therapy in a medical facility. Although only severe gastroenteritis episodes meeting the clinical case definition were collected in study Rota-023, severity of these clinically severe episodes was also scored at GSK Biologicals using the Vesikari scale.

Table 1 20-point Vesikari scale to assess intensity of gastroenteritis episodes

Adverse Experience	Points
Duration of looser than normal stools (days)	
1-4	1
5	2
≥ 6	3
Maximum number of looser than normal stools/24 hours	
1-3	1
4-5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2-4	2
≥ 5	3
Fever* measured rectally (axillary)	
37.1°C – 38.4°C (36.6°C -37.9°C)	1
38.5°C – 38.9°C (38.0°C -38.4°C)	2
≥ 39°C (≥ 38.5°C)	3
Treatment	
Rehydration	1
Hospitalization†	2
Dehydration‡	
1% -5 %	2
≥ 6%	3

*The highest temperature recorded during the episode was scored

†Included less than overnight detention in a treatment facility for dehydration under observation

‡A subject that had a gastroenteritis episode was considered as being dehydrated by 1% to 5% if this subject received oral dehydration medication; a subject was considered as being dehydrated ≥6% if the subject was hospitalized or received intravenous rehydration

Unlike the Vesikari scale, other intensity scales used to assess severity of gastroenteritis episodes, such as the Clark scale used in the *RotaTeq* development program, do not take into account the degree of dehydration and the type of treatment [Clark, 1988].

Calculation of vaccine efficacy

Vaccine efficacy was calculated with its 95% CI. Vaccine efficacy was defined as the percent reduction in the frequency of the efficacy endpoint in vaccine recipients compared with placebo recipients.

The vaccine efficacy was estimated using the formula:

$$\text{Vaccine efficacy} = (1 - \text{Relative Risk}) \times 100\%$$

The according to protocol (ATP) cohort was the primary cohort for efficacy analysis. The ATP cohort included all subjects for whom the randomization code was not broken, who had received two doses of the vaccine or placebo, who had not received a vaccine forbidden by or not specified in the protocol, had no rotavirus other than vaccine strain in

stool samples collected during the period starting on the day of administration of Dose 1 and ending two weeks after Dose 2 was administered, who were seronegative for anti-rotavirus immunoglobulin A (IgA) antibodies on the day of Dose 1 of vaccine or placebo among subjects with serology testing in study Rota-036, and had entered into the efficacy surveillance period. Only rotavirus gastroenteritis episodes occurring at least two weeks after Dose 2 were included in the ATP analysis.

To complement the primary efficacy analysis on the ATP cohort, a secondary analysis was performed on the total vaccinated cohort and included all enrolled subjects who received at least one dose of the vaccine or placebo regardless of adherence to the study protocol. The purpose of performing the two analyses was to ensure that protocol violations, subject drop-outs and withdrawals were not treatment-related and did not lead to any selection bias in the efficacy results. The total vaccinated cohort analysis included all rotavirus gastroenteritis episodes that occurred starting at Dose 1.

4.2. Pivotal Clinical Efficacy Results

The following sections present the pivotal data demonstrating the efficacy of *Rotarix* in preventing rotavirus gastroenteritis obtained in 24,163 infants randomized in two placebo-controlled studies: Rota-023 conducted in 11 countries in Latin America (N=20,169), and Rota-036 conducted in 6 countries in Europe (N=3,994).

In study Rota-023, the primary analysis on efficacy during the first year follow-up (from 2 weeks post-Dose 2 until 12 months of age) was performed on the ATP efficacy cohort of 17,867 subjects (9,009 vaccine recipients and 8,858 placebo recipients). The median age of this cohort was 8 weeks at the time of the first dose and 16 weeks at the time of the second dose. The total vaccinated cohort for efficacy during the first year follow-up (from Dose 1 until 12 months of age) included 20,169 subjects (10,159 vaccine recipients and 10,010 placebo recipients).

In study Rota-036, the primary analysis on efficacy during the first rotavirus season (from 2 weeks post-Dose 2 until end of the first rotavirus season) was performed on the ATP cohort of 3,874 subjects (2,572 vaccine recipients and 1,302 placebo recipients). The median age of this cohort was 12 weeks at the time of the first dose and 20 weeks at the time of the second dose. The total vaccinated cohort for efficacy during the first year follow-up (from Dose 1 until end of the first rotavirus season) included 3,994 subjects (2,646 vaccine recipients and 1,348 placebo recipients).

4.2.1. Protective Efficacy against Rotavirus Gastroenteritis Outcomes

A statistically significant reduction in the occurrence of rotavirus gastroenteritis was demonstrated during the first efficacy follow-up period in studies Rota-023 (see Figure 7) and Rota-036 (see Figure 8). The numbers at the bottom of each efficacy bar represent numbers of cases reported in the *Rotarix* group (“V”), and the placebo group (“P”).

In study Rota-023, efficacy of *Rotarix* against severe rotavirus gastroenteritis episodes meeting the clinical case definition until 12 months of age was 85% [95% CI: 72%; 92%]. Efficacy against severe rotavirus gastroenteritis episodes with Vesikari score ≥ 11

points was 85% [95% CI: 71%; 93%]. Efficacy against any rotavirus gastroenteritis episodes could not be evaluated in this study since only severe rotavirus gastroenteritis episodes were collected as defined in the protocol. *Rotarix* reduced hospitalizations for rotavirus gastroenteritis by 85% [95% CI: 70%; 94%].

In study Rota-036, efficacy of *Rotarix* against rotavirus gastroenteritis of any grade of severity until end of the first rotavirus season after vaccination was 87% [95% CI: 80%; 92%]. Efficacy against severe rotavirus gastroenteritis episodes with Vesikari score ≥ 11 points was 96% [95% CI: 90%; 99%]. Increasing protective efficacy was observed against more severe episodes, with efficacy against the most severe rotavirus gastroenteritis with Vesikari score ≥ 17 points reaching 100% [95% CI: 85%; 100%]. Efficacy against severe rotavirus gastroenteritis as defined by the Clark scale used in the *RotaTeg* development program (i.e., score >16 points) [Clark, 1988] was 93% [95% CI: 71%; 99%]. *Rotarix* reduced hospitalizations for rotavirus gastroenteritis by 100% [95% CI: 82%; 100%]. Significant reduction in the need for medical attention (i.e., medical personnel contact/advice/visit, emergency room contact/visit or hospitalization) was observed among *Rotarix* recipients with efficacy of 92% [95% CI: 84%; 96%].

Figure 7 Vaccine efficacy from 2 weeks post-Dose 2 until 12 months of age in Latin America – study Rota-023 (ATP efficacy cohort)

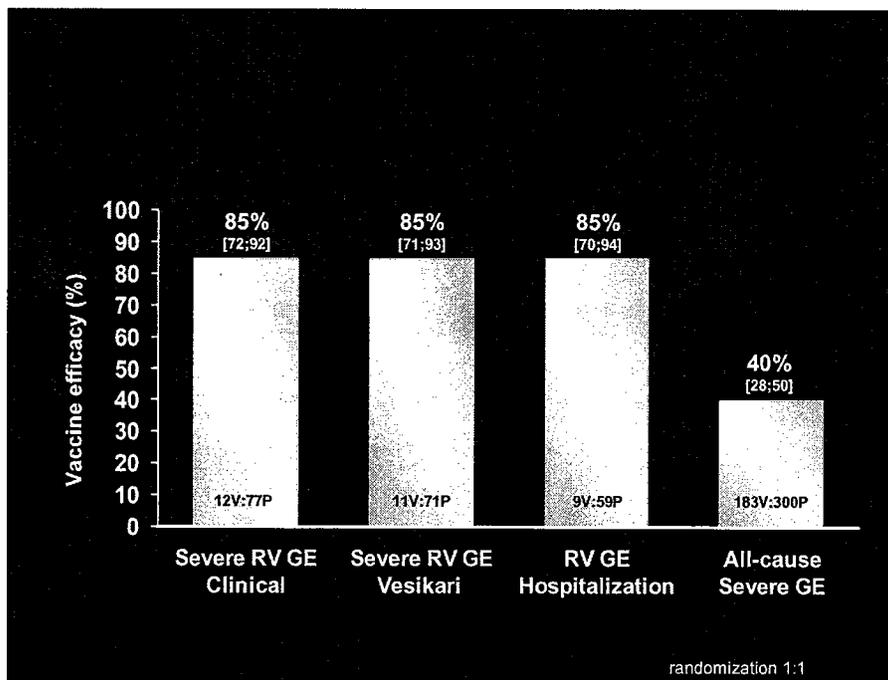
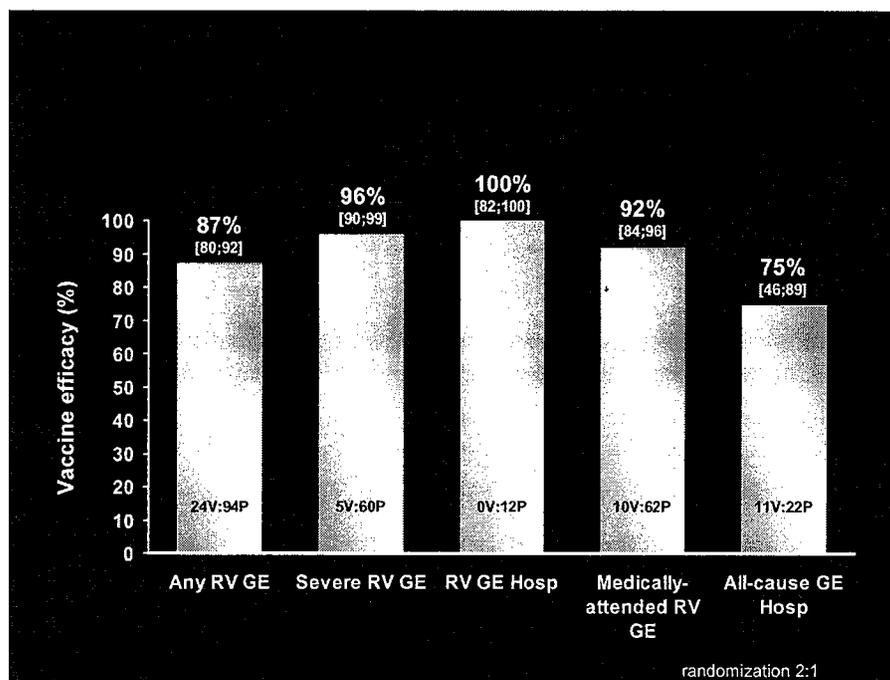


Figure 8 Vaccine efficacy from 2 weeks post-Dose 2 until end of the first rotavirus season in Europe – study Rota-036 (ATP efficacy cohort)



Results of the total vaccinated cohort analyses were fully consistent with the ATP analyses, and showed that *Rotarix* provides significant protection starting from the first dose onwards. In study Rota-023, efficacy was 81% [95% CI: 69%; 89%] against severe rotavirus gastroenteritis according to the clinical definition, and 81% [95% CI: 67%; 89%] based on the Vesikari score ≥ 11 points from Dose 1 until 12 months of age. In study Rota-036, efficacy was 87% [95% CI: 80%; 92%] against any rotavirus gastroenteritis, and 96% [95% CI: 90%; 99%] against severe rotavirus gastroenteritis with Vesikari score ≥ 11 points from Dose 1 until end of the first rotavirus season after vaccination.

4.2.2. Vaccine Efficacy through the Second Year after Vaccination

The efficacy of *Rotarix* until 24 months of age (study Rota-023) and until end of the second rotavirus season after vaccination (study Rota-036) was evaluated since the highest incidence of rotavirus gastroenteritis, and especially of severe disease, occurs during the first 24 months of life (see Figure 9 and Figure 10).

In study Rota-023, the efficacy of *Rotarix* against severe rotavirus gastroenteritis according to the clinical definition was 81% [95% CI: 71%; 87%] until 24 months of age. Hospitalizations for rotavirus gastroenteritis were reduced by 83% [95% CI: 73%; 90%].

In study Rota-036, the efficacy of *Rotarix* against rotavirus gastroenteritis of any grade of severity was 79% [95% CI: 73%; 84%] until end of the second rotavirus season after vaccination. The efficacy against severe rotavirus gastroenteritis was 90% [95% CI: 85%; 94%]. Efficacy against severe rotavirus gastroenteritis as defined by the Clark scale (i.e.,

score >16 points) [Clark, 1988] was 97% [95% CI: 78%; 100%]. Hospitalizations for rotavirus gastroenteritis were reduced by 96% [95% CI: 84%; 100%]. Significant reduction in the need for medical attention was observed among *Rotarix* recipients with an efficacy of 84% [95% CI: 76%; 89%].

Figure 9 Vaccine efficacy from 2 weeks post-Dose 2 until 12 months and 24 months of age in Latin America – study Rota-023 (ATP efficacy cohort)

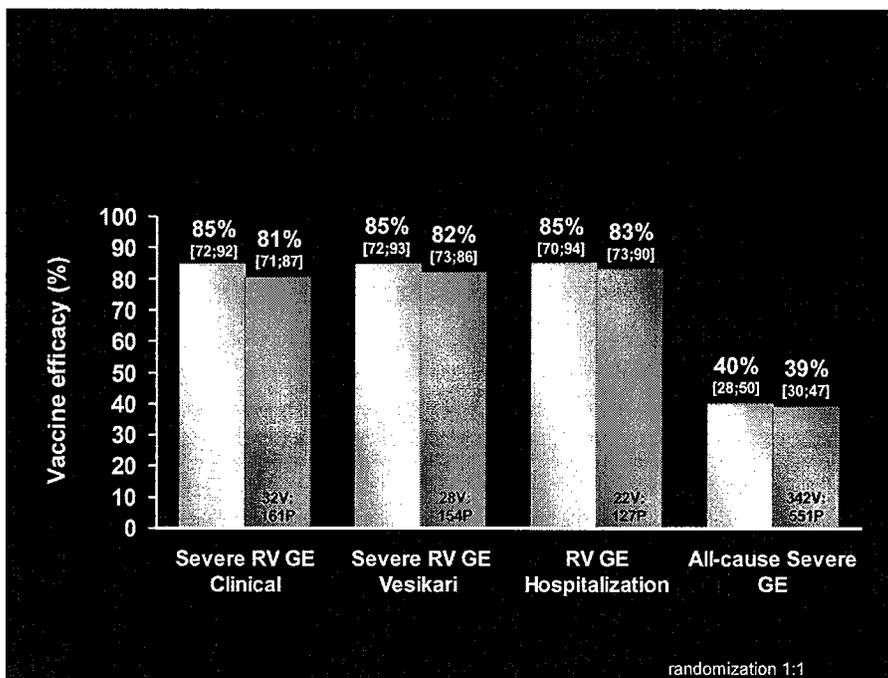
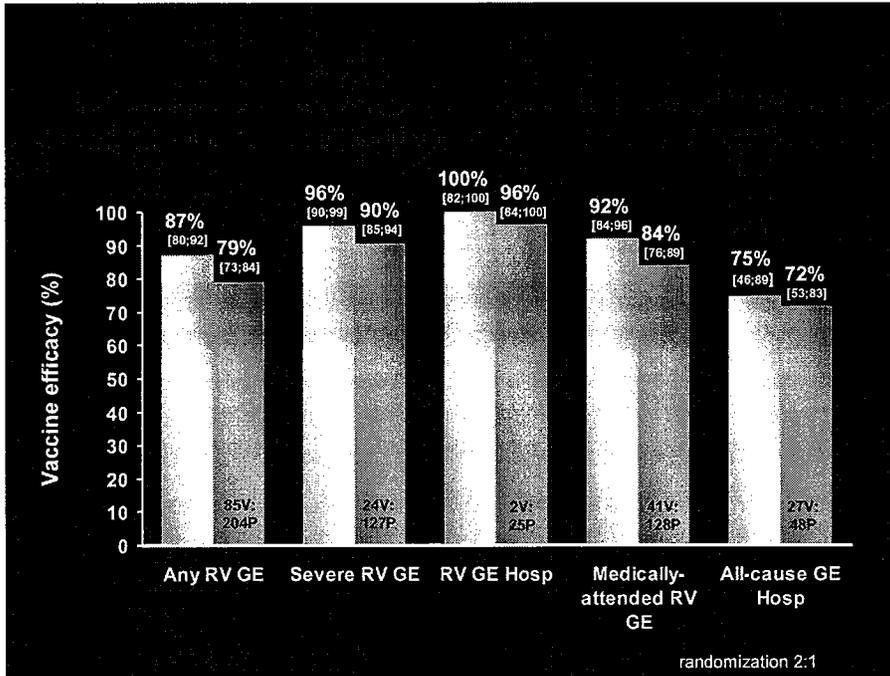


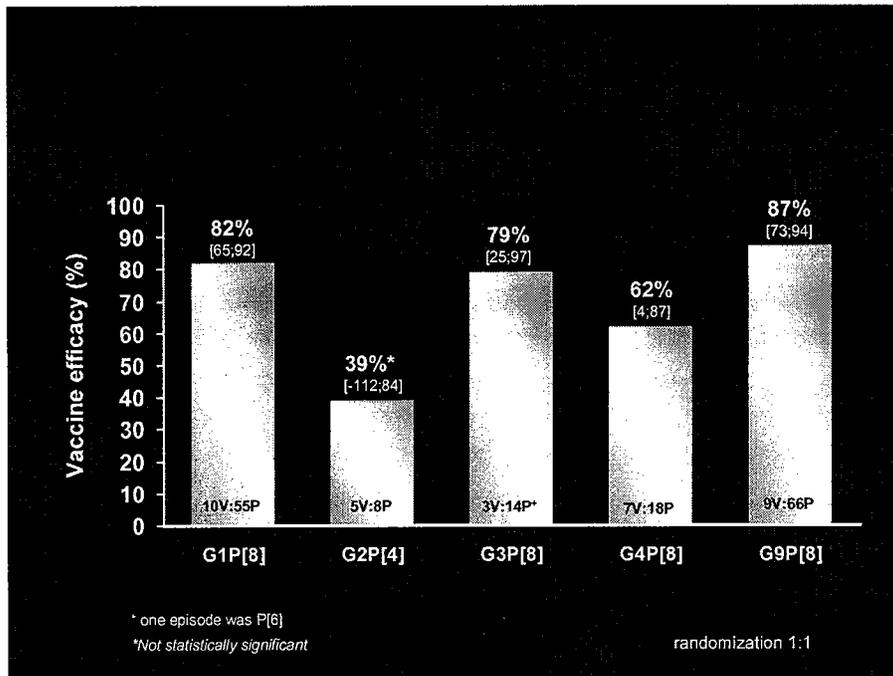
Figure 10 Vaccine efficacy from 2 weeks post-Dose 2 until end of the first and second rotavirus seasons in Europe – study Rota-036 (ATP efficacy cohort)



4.2.3. Vaccine Efficacy against Circulating Rotavirus Types

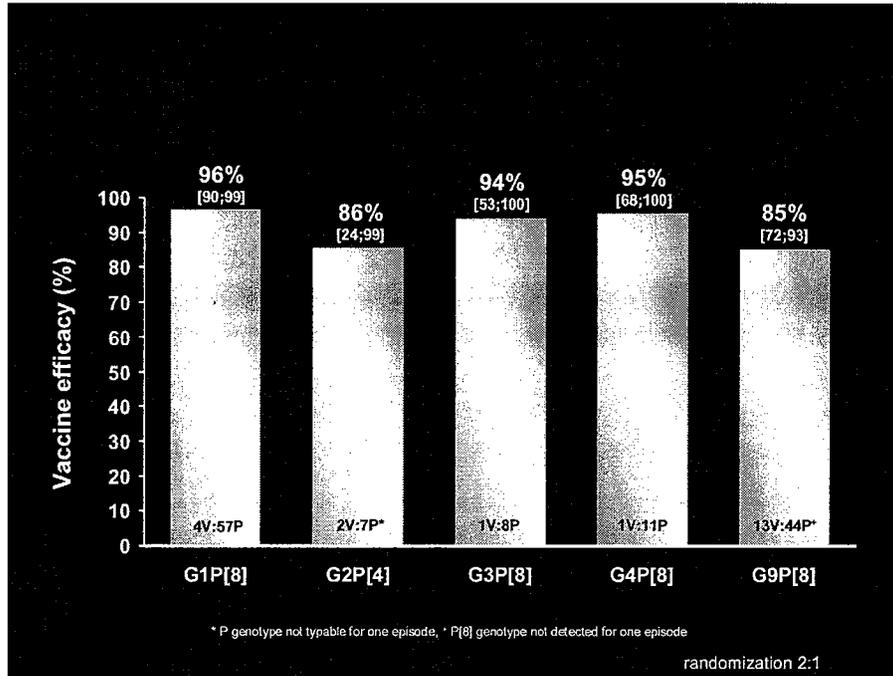
In study Rota-023, the type-specific efficacy against severe rotavirus gastroenteritis caused by G1P[8], G3P[8], G4P[8] and G9P[8], and combined non-G1 types was statistically significant until 24 months of age after vaccination (see Figure 11). Rotavirus infection caused by the G2P[4] type was uncommon in this study. Fewer vaccine recipients reported severe rotavirus gastroenteritis episodes caused by G2P[4] type compared to the placebo recipients but the difference between groups did not reach statistical significance.

Figure 11 Type-specific vaccine efficacy from 2 weeks post-Dose 2 until 24 months of age in Latin America – study Rota-023 (ATP efficacy cohort)



In study Rota-036, type-specific efficacy against any grade of severity and severe rotavirus gastroenteritis caused by G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and combined non-G1 (G2, G3, G4, G9) types was statistically significant until end of the second rotavirus season after vaccination (see Figure 12).

Figure 12 Type-specific vaccine efficacy from 2 weeks post-Dose 2 until end of the second rotavirus season in Europe – study Rota-036 (ATP cohort for efficacy)



Of note, the G2P[4] type is fully heterologous to the G1P[8] vaccine strain, according to both G and P types. As discussed in Section 2.3, the molecular characteristics of the rotavirus support the observation that one type can provide broad protection against homotypic and heterotypic rotavirus types. Amino acids analysis between *Rotarix* G1P[8] vaccine strain and G2P[4] shows at least 83% identity for at least 3 proteins likely important for immune protection (90% for VP4, 92% for VP6 and 83% for NSP4). Multiple infections with rotavirus, even when they are of the same rotavirus type, have been shown to increase and broaden the initial specific immune response allowing for heterotypic protection [Pichichero, 1993].

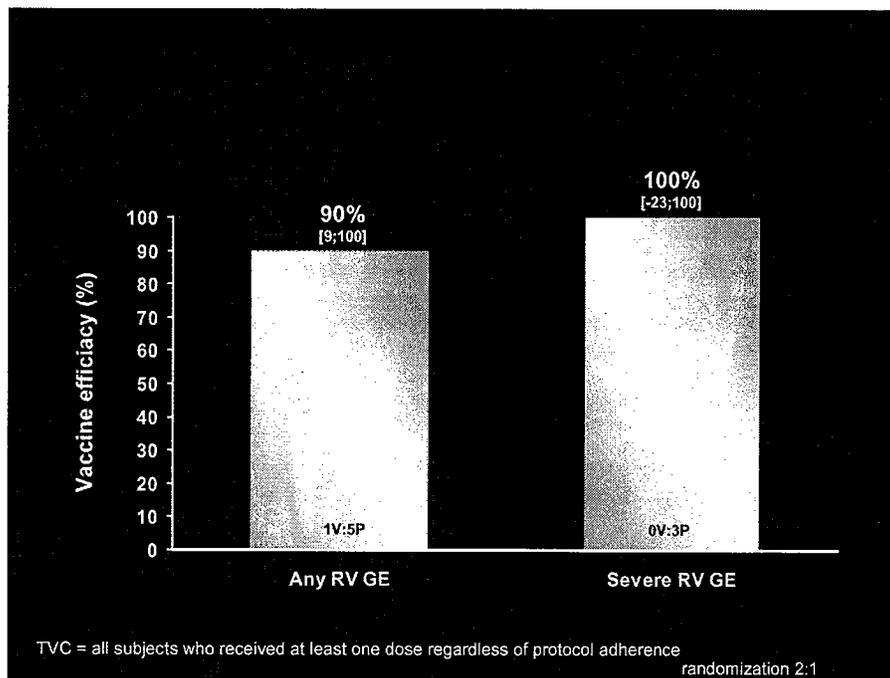
4.2.4. Vaccine Efficacy in Breast-fed Infants

The efficacy of *Rotarix* was evaluated according to feeding status in study Rota-036. Efficacy against severe rotavirus gastroenteritis was 96% [95% CI: 88%; 99%] in breast-fed infants and 96% [95% CI: 74%; 99%] in exclusively formula-fed infants. Efficacy against any rotavirus gastroenteritis was 86% [95% CI: 77%; 92%] in breast-fed infants and 91% [95% CI: 73%; 98%] in exclusively formula-fed infants. Thus, breast-feeding was found not to reduce the protection against rotavirus gastroenteritis among vaccinated infants.

4.2.5. Early Protection: Vaccine Efficacy after the First Dose

Though *Rotarix* is intended as a two-dose series, protection against severe rotavirus gastroenteritis was already observed starting from the first dose onwards at 2 months of age. In study Rota-036, 82% of the infants received their first dose of *Rotarix* or placebo, and 10% of the infants had completed the two-dose series prior to the start of the rotavirus season. Efficacy from Dose 1 up to before Dose 2 was 90% [95% CI: 9%; 100%] against rotavirus gastroenteritis of any grade of severity, and 100% [95% CI: -23%; 100%] against severe rotavirus gastroenteritis (see Figure 13).

Figure 13 Vaccine efficacy from Dose 1 up to before Dose 2 in Europe – study Rota-036 (total vaccinated cohort)



4.2.6. Vaccine Efficacy against All-cause Gastroenteritis

Since the efficacy studies prospectively collected occurrence of gastroenteritis episodes regardless of the etiology or stool testing result, the overall impact of the vaccine administration on gastroenteritis disease regardless of etiology could be evaluated. In study Rota-023, *Rotarix* reduced occurrence of all-cause severe gastroenteritis regardless of presumed etiology by 40% [95% CI: 28%; 50%] until 12 months of age, and by 39% [95% CI: 30%; 47%] until 24 months of age after vaccination. In study Rota-036, *Rotarix* reduced hospitalizations for all-cause gastroenteritis regardless of presumed etiology by 75% [95% CI: 46%; 89%] until end of the first rotavirus season, and by 72% [95% CI: 53%; 83%] until end of the second rotavirus season after vaccination.

4.3. Efficacy Conclusions

The following conclusions can be drawn from the two phase III studies (Rota-036 and Rota-023) providing pivotal efficacy data for *Rotarix* when administered as a two-dose series to infants starting at 6 weeks of age.

- *Rotarix* is highly effective in preventing rotavirus gastroenteritis of any grade of severity and in preventing severe rotavirus gastroenteritis caused by circulating rotavirus types during the first year of life. In two phase III studies, efficacy against severe rotavirus gastroenteritis was 96% in study Rota-036 and 85% in study Rota-023 during the first year of life. Efficacy persisted during the first 2 years of life when the maximum burden of rotavirus gastroenteritis exists.
- *Rotarix* reduced hospitalizations for rotavirus gastroenteritis by 100% in study Rota-036 and 85% in study Rota-023. Also, a significant reduction in need for medical attention for rotavirus gastroenteritis was demonstrated.
- *Rotarix* provides significant protection against each of the commonly circulating rotavirus types: G1, G2, G3, G4, and G9 types.
- Protective efficacy against rotavirus gastroenteritis was evident starting from the first dose onwards.
- Breast-feeding was found to not reduce the protection against rotavirus gastroenteritis among vaccinated infants.
- *Rotarix* reduced occurrence of all cause severe gastroenteritis regardless of presumed etiology including related hospitalizations.

Rotarix provides significant protection against rotavirus gastroenteritis caused by circulating G1 and non-G1 types (including G2, G3, G4, and G9 types). Effective protection can be predicted in the US infant population based on the immunological response (see Section 5.2) observed in this population and the efficacy observed consistently across heterogeneous geographical populations. In addition, epidemiology data show similar G type distribution in the US compared with regions in which efficacy has been demonstrated.

5. CLINICAL IMMUNOGENICITY

5.1. Immunogenicity Assessment

The immune response to the vaccine was assessed in all 11 studies submitted to the BLA. In the pivotal phase III efficacy studies, Rota-023 and Rota-036, a pre-defined subset of subjects enrolled at specific centers were included in the immunogenicity assessment.

A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. However, serum anti-rotavirus IgA antibodies are a commonly used indicator of the immune response to rotavirus [O'Ryan, 1994; Matson, 1993; Coulson, 1992; Franco, 2006]. Therefore, serum anti-rotavirus IgA antibody concentrations measured by standardized and validated ELISAs [assay cut-off

20 units (U)/milliliter (mL)] were used to evaluate immunogenicity of *Rotarix*. Seropositivity was defined as anti-rotavirus IgA antibody concentration greater than or equal to assay cut-off. Seroconversion was defined as post-vaccination anti-rotavirus IgA antibody concentration greater than or equal to the assay cut-off in subjects negative for rotavirus prior to the first dose.

In some cases after vaccination or natural infection, there is no detectable serum IgA antibody response, although rotavirus antigen shedding in stools is detected during several days or weeks, indicating that virus replication has taken place. With oral administration of live rotavirus vaccine, viral antigen shedding when detected several days after vaccination (assessed most often in clinical studies at Day 7) is much lower than the antigen load contained in a vaccine dose. Thus, detection of viral antigen shedding indicates local replication of vaccine virus in the intestinal mucosa, allowing induction of a local mucosal immune response not detected via serum assays. Therefore, in addition to serum IgA antibody seroconversion, “vaccine take” was calculated as a combined endpoint of serum anti-rotavirus IgA antibody seroconversion and/or rotavirus antigen shedding in prospectively collected post-vaccination stool samples in 8 studies (Rota-005, Rota-006, Rota-007, Rota-014, Rota-033, Rota-039 and Rota-048). Of note, vaccine take as a combined measure of serum IgA seroconversion, stool IgA and/or stool culture response (shedding) was also used in studies with the oral rhesus-human reassortant rotavirus vaccine, *RotaShield* [Pichichero, 1990].

5.2. Immunogenicity Results

In all studies, the vaccine was immunogenic in terms of anti-rotavirus IgA seropositivity, seroconversion and/or vaccine take. A range of vaccine titers, from $10^{5.3}$ CCID₅₀ to $10^{6.8}$ CCID₅₀, were used in the phase II studies. A slight dose effect was seen in some studies essentially after the first dose but this effect was not consistent across all studies conducted and was minimal when considering titers from $10^{5.6}$ CCID₅₀ and/or above.

Based on the results in early clinical studies showing immune response and efficacy with vaccine titer of $10^{5.6}$ CCID₅₀ and/or above, and stability testing data, a potency of at least $10^{6.0}$ CCID₅₀ at end of shelf life was chosen for commercial use. In order to guarantee this minimum titer up to the end of shelf-life, the release specification is set at [REDACTED] CCID₅₀ per vial. A two-dose regimen was chosen for *Rotarix* based on several considerations: a high proportion of seroconversion and vaccine take is observed after two doses; a third dose induces only a marginal increase in antibody response; and most importantly, efficacy has been demonstrated with 2 doses during phase II and subsequently during the pivotal phase III studies.

Table 2 presents the anti-rotavirus IgA response observed in the pivotal efficacy studies (Rota-023 and Rota-036), and in the two US studies (Rota-005 and Rota-060). The anti-rotavirus IgA seroconversion rate after Dose 2 was 87% in study Rota-036, and 77% in study Rota-023. In the phase II study Rota-005 conducted in the US and Canada, the anti-rotavirus IgA seroconversion rate after Dose 2 was 78% in the group receiving the licensure formulation of *Rotarix*. In the phase III study Rota-060 conducted in the US, the anti-rotavirus IgA seropositivity rate was 86% when measured 2 months after, and 79% when measured 3 months after the second dose of *Rotarix*. The IgA response rates tended

to be higher in studies conducted in developed regions as compared to developing regions. Vaccine take rates ranged from 73% to 98% (see Table 3), and tended to be higher than IgA response rates, suggesting that in some infants, the vaccine virus replicates without inducing a detectable serological IgA response. No significant difference in vaccine take rates (primary endpoint) was detected between the 10^{5.6} CCID₅₀ (81.5%) and 10^{6.8} CCID₅₀ (88.0%) vaccine groups in study Rota-005.

Although of limited relevance to the US since OPV is not part of the routine infant vaccination schedule, the phase II OPV coadministration study Rota-014 in South Africa, showed that the anti-rotavirus IgA seroconversion rate after two doses was not affected by the concomitant use of OPV.

In all efficacy studies, the protective efficacy, especially against severe rotavirus gastroenteritis, paralleled but was always higher than the anti-rotavirus IgA seropositivity/seroconversion rate and the vaccine take (when measured). This indicates that the anti-rotavirus IgA antibody response tends to underestimate the level of protective immunity elicited by the vaccine. Anti-rotavirus IgA seropositivity/seroconversion rates after two doses of the vaccine in US/Canada (Rota-005 and Rota-060) were comparable to those seen in Europe (Rota-036) and Latin America (Rota-023), where efficacy has been demonstrated.

Table 2 Post-Dose 2 anti-rotavirus IgA antibody response (ATP immunogenicity cohort)

Study (Country)	Post-Dose 2 Seroconversion† Rate			Post-Dose 2 Seropositivity‡ Rate		
	Rota-005 (US and Canada)		Rota-023 (Latin America)	Rota-036 (Europe)	Rota-060 (US)	
	10 ^{5.6} CCID ₅₀ N = 138	10 ^{6.8} CCID ₅₀ N = 133	Rotarix N = 393	Rotarix N = 787	Rotarix co-ad N = 165	Rotarix sep-ad N = 121
Serology Timing	2 months post-Dose 2	2 months post-Dose 2	1 to 2 months post-Dose 2	1 to 2 months post-Dose 2	3 months post-Dose 2	2 months post-Dose 2
% [95% CI]	67 [59; 75]	78 [70; 85]	77 [72; 81]	87 [84; 89]	79 [72; 85]	86 [79; 92]

N = number of subjects with results available

†Seroconversion = appearance of anti-rotavirus IgA ≥20 U/mL in subjects initially negative for rotavirus

‡Seropositivity = anti-rotavirus IgA ≥20 U/mL

Table 3 Vaccine take after Dose 1 and/or Dose 2 of the licensure formulation of Rotarix (ATP immunogenicity cohort)

Study (Country)	Vaccine potency	N tested	Vaccine Take (%)
Rota-005 (US and Canada)	10 ^{6.8} CCID ₅₀	150	88
Rota-006 (Latin America)	10 ^{6.6} CCID ₅₀	106	76
Rota-007 (Singapore)	10 ^{6.6} CCID ₅₀	46	98
Rota-033 (Latin America)	10 ^{6.5} CCID ₅₀	26	73
Rota-039 (Thailand)	10 ^{6.5} CCID ₅₀	167	88
Rota-048 (Finland)	10 ^{6.5} CCID ₅₀	94	89

Vaccine take = Seroconversion and/or rotavirus stool antigen shedding in subjects rotavirus negative prior to the first dose in subset that had blood and stool samples tested

Persistence of Immunogenicity

To assess the persistence of serum anti-rotavirus IgA, concentrations were measured in blood samples taken at approximately one year of age (studies Rota-004, Rota-005 and Rota-006). In each of the three studies, more than 70% of the vaccinated infants were seropositive at approximately one year of age. Natural infections that might have occurred during the follow-up period were not likely to be sufficient to account for the higher seropositivity rates observed in vaccine recipients compared to the placebo recipients. In study Rota-004, anti-rotavirus seropositivity rate at approximately 18 months post-vaccination was 67% [95% CI: 61%; 73%] in vaccine recipients compared to 29% [95% CI: 21%; 38%] in placebo recipients. Thus, vaccine-induced anti-rotavirus IgA persists at least 18 months after vaccination in a high proportion of vaccinees, consistent with the efficacy results through 2 years after vaccination in studies Rota-004, Rota-006, Rota-023 and Rota-036. However, due to continued exposure to circulating wild-type rotavirus, antibody levels observed in the vaccine groups may not solely be attributable to the vaccine. Antibody persistence results in US/Canada (Rota-005) were comparable to those seen in Latin America (Rota-006) and Europe (Rota-004).

Effect of Maternal Antibodies

The impact of maternally derived serum antibodies on the IgA seroconversion rates induced after vaccination was evaluated in studies Rota-004, Rota-006 and Rota-014. Levels of maternally acquired anti-rotavirus immunoglobulin G (IgG) antibodies as well as neutralizing antibodies were higher in non-responders (IgA seronegative) compared to responders (IgA seroconversion). No critical level of maternal antibodies that prevented vaccine response was identified. In general, subjects who seroconverted after the first dose of the vaccine had lower levels of maternally acquired anti-rotavirus IgG and neutralizing antibodies at the pre-vaccination time point. The data also showed that anti-rotavirus IgA seroconversion can be induced upon administration of a second dose of vaccine, despite relatively high levels of maternal antibodies.

Impact of Breast-feeding

As discussed in Section 4, efficacy estimates against any and severe rotavirus gastroenteritis in study Rota-036 were similar for subjects who were breast-fed versus those who were formula-fed. Correspondingly, anti-rotavirus IgA GMCs and seroconversion rates were similar among breast-fed subjects and those who were formula-fed. Based on these results, there are no restrictions on the infant's liquid consumption, including breast milk, either before or after vaccination with *Rotarix*.

Special Infant Populations

Administration of *Rotarix* to pre-term infants, infants with known primary or secondary immunodeficiencies including infants with human immunodeficiency virus (HIV) or infants receiving immunosuppressive therapy has not been specifically evaluated to date. Studies are ongoing to evaluate *Rotarix* in these special populations as described in the pharmacovigilance plan in Section 8.

5.3. Clinical Lot to Lot Consistency

Study Rota-033 was a phase III, randomized, placebo-controlled, double blind study conducted in Mexico, Peru and Colombia to evaluate the consistency of three consecutive production lots of *Rotarix*. A total of 854 eligible infants were randomized in a 2:2:2:1 ratio to receive two doses of *Rotarix* lot A, *Rotarix* lot B, *Rotarix* lot C or placebo according to a 0, 2 month schedule.

The pre-specified criteria for lot-to-lot consistency between three production lots of *Rotarix* were met as shown by the limits of the 90% CI for the ratio of serum anti-rotavirus IgA antibody GMCs two months after Dose 2 being within the pre-specified limit [0.5; 2] for all pairs of lots. This study thus demonstrated the consistency of the *Rotarix* production process. Consistency of three consecutive production lots of *Rotarix* were also demonstrated when data from this same study were reanalyzed using current FDA criteria, i.e., 95% CI for GMC ratio comparisons using the [0.5; 2] clinical limits.

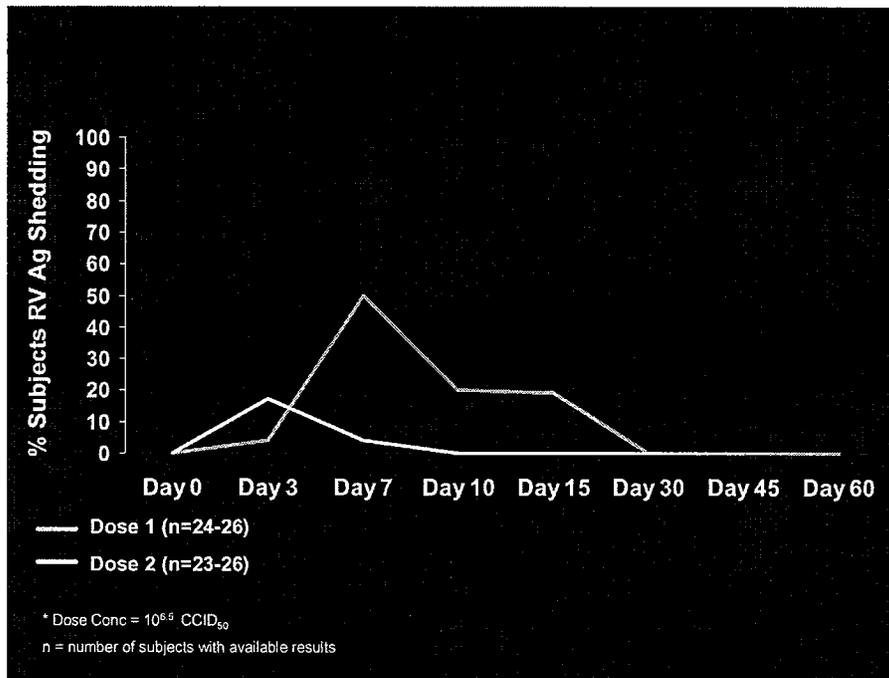
5.4. Rotavirus Antigen and Live Vaccine Virus Shedding

Excretion of the rotavirus antigen in feces is expected after oral administration of a live attenuated vaccine and is an indication of vaccine “take”. However, rotavirus antigen shedding in stool does not necessarily imply the presence of infectious vaccine virus. Among infants with rotavirus antigen shedding post vaccination, live virus is only detected in a subset of infants (see below).

Rotavirus Antigen Shedding

The presence of rotavirus antigen in stool by ELISA was tested in a subset of subjects from 7 clinical studies (Rota-005, Rota-006, Rota-007, Rota-014, Rota-033, Rota-039 and Rota-048). The ELISA test detects presence of viral protein VP6 from infectious particles as well as non-infectious viral debris. The rate of rotavirus antigen shedding in stool peaked at Day 7 after the first dose of the vaccine and decreased thereafter. Among subjects receiving the licensure formulation of *Rotarix*, the median proportion of subjects with rotavirus antigen shedding at Day 7 was 55% (range: 44% to 80%) after Dose 1 and 13% (range: 10% to 18%) after Dose 2. Figure 14 presents data on rotavirus antigen shedding in stools from phase III study Rota-033 conducted in Colombia, Mexico and Peru in which antigen shedding was assessed at multiple time points after each dose of *Rotarix*.

Figure 14 Rotavirus antigen shedding in stool among *Rotarix* recipients – study Rota-033



The antigen shedding rates observed following vaccination were consistent with reported rates of excretion of rotavirus following natural infection. In study Rota-033, the longest post dose time point at which rotavirus antigen shedding was detected was Day 15 after the first dose. Longer duration of rotavirus antigen shedding is reported following natural infection. A study evaluating the duration of rotavirus shedding in children hospitalized for severe diarrhea showed that replication of rotavirus in the gut leading to antigen or viral genome rotavirus antigen shedding for extended periods is a feature of wild-type rotavirus infection [Richardson, 1998]. Importantly, although *Rotarix* replicates well in the gastrointestinal tract, *Rotarix* was not associated with an increase in gastroenteritis symptoms (diarrhea, vomiting or fever) in vaccine recipients as compared to placebo recipients (see Section 6.2.2.3).

Rotavirus Live Vaccine Virus Shedding

Rotavirus antigen shedding in stool does not necessarily imply the presence of infectious vaccine virus. Electron micrographs of stool suspensions from patients with rotavirus gastroenteritis generally show empty (non-infectious) viral particles and capsid fragments in excess of full viral particles that represent infectious virions. Presence of live rotavirus particles in stool was therefore assessed in two studies (Rota-039 and Rota-048) by a titration assay using African Green Monkey Cells (MA-104 cells) as substrate with the live vaccine virus identified by indirect fluorescence. Only stool samples that were positive for rotavirus antigen and with sufficient quantity of stool were tested for live vaccine virus. The percentage of vaccinees with live vaccine virus detected in stool was extrapolated by multiplying the proportion of stools that were rotavirus antigen positive by the proportion of rotavirus antigen positive stools containing live vaccine virus. The

shedding of infectious particles among rotavirus antigen shedders was found to be relatively limited. At Day 7 after the first dose, 46.2% (Rota-039) and 45.5% (Rota-048) of the antigen shedders tested positive for live vaccine virus. It was estimated that 25.6% and 26.5% of the infants were shedding live vaccine virus at Day 7 after the first dose in these two studies (see Figure 15).

The quantity of live rotavirus shedding after wild-type (natural) infection appears to be much higher than quantity of live rotavirus detected post-vaccination. Analysis of residual stool samples from clinical studies showed that the vaccine viral load (mean titer) in post-vaccination (Day 7 post-Dose 1) stool samples was 2.5-fold lower as compared to the viral load in rotavirus gastroenteritis stool samples after wild-type infection.

Figure 15 Live vaccine virus shedding in vaccine recipients at Day 7 post-Dose 1

039 (Thailand)	90/162 (55.6%)	6/13 (46.2%)	25.6 % (95% CI 10 – 41)
048 (Finland)	49/84 (58.3%)	15/33 (45.5)	26.5 % (95% CI 16-38)

* all ELISA positive samples with remaining stool cultured for live virus

In clinical studies, vaccine strain antigen was detected in stool samples from 7 placebo recipients. Four out of the seven placebo recipients had seroconverted after two doses. None of these 7 subjects reported any symptoms associated with gastroenteritis (diarrhea, vomiting or fever) close to the time of stool collection. They were all in good health and not immunosuppressed. Two subjects had a twin enrolled in the vaccine group in the same study sites at the same time, and this may have favored transmission of the vaccine strain because of close contact. The potential for horizontal transmission of vaccine virus was not evaluated in the pre-authorization phase; a study is currently ongoing to evaluate horizontal transmission of the vaccine strain between twins within families (see Section 8).

5.5. Immunogenicity of Concomitant Vaccinations Administered with *Rotarix*

Coadministration of routine pediatric vaccines was allowed in all studies except Rota-004 and Rota-048. In studies Rota-006, Rota-023, Rota-033 and Rota-039 conducted in regions where OPV is in use, either the administration of OPV was separated from vaccine or placebo dose by at least two weeks or IPV was used instead of OPV (Rota-039). Study Rota-014 specifically evaluated coadministration of OPV. Immunogenicity of coadministered routine childhood vaccinations (DTaP, DTwP, HepB, Hib, IPV, OPV, pneumococcal 7-valent conjugate vaccine and meningococcal group C conjugate vaccine) was evaluated in vaccine recipients compared to placebo recipients in studies Rota-005, Rota-006, Rota-007, Rota-014 and Rota-036.

In all studies including Rota-005 in the US and Canada, and the phase III efficacy study Rota-036 in Europe, a robust immune response to the childhood vaccine antigens was observed with no apparent interference in vaccine recipients as compared to placebo recipients. Importantly, efficacy against rotavirus gastroenteritis was demonstrated in study Rota-036 (see Section 4.2) where subjects received *Rotarix* or placebo coadministered with routine infant vaccine antigens including diphtheria, tetanus, PT, FHA, PRN, HBsAg, PRP, poliovirus serotypes 1, 2 and 3, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F that are also routinely administered to infants in the US.

Study Rota-060 conducted in the US was a prospective, randomized, controlled study designed with pre-specified endpoints to demonstrate that *Rotarix* does not impair the immune response to licensed vaccines included in the CDC's recommended immunization schedule for infants up to the age of 6 months. These vaccine antigens are diphtheria, tetanus, PT, FHA, PRN, HBsAg, PRP, poliovirus serotypes 1, 2 and 3, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The routine vaccines used in this study were Pediarix® [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined, manufactured by GSK], ActHIB® [*Haemophilus influenzae* type b (Hib) conjugate vaccine, manufactured by Sanofi Pasteur] and *Prevnar* [pneumococcal 7-valent conjugate vaccine, manufactured by Wyeth Lederle Vaccines].

Subjects were randomized to receive two doses of *Rotarix* with the routine infant vaccines either coadministered (co-ad group; 249 subjects) or given separately (sep-ad group; 235 subjects). In the co-ad group, subjects were administered *Rotarix* at 2 and 4 months of age and the routine infant vaccines at 2, 4 and 6 months of age; in the sep-ad group, subjects were administered the routine infant vaccines at 2, 4 and 6 months of age and *Rotarix* at 3 and 5 months of age. Serum samples were collected at one month after Dose 3 of the routine vaccines to measure antibody responses to each of the antigens contained in the routine vaccines.

The pre-specified criteria for demonstrating non-inferiority of antibody responses at one month after Dose 3 of routine infant vaccines were met for all 17 antigens contained in the routine infant vaccines licensed in the US:

- The lower limits of the standardized asymptotic 95% CI for the treatment difference (co-ad group minus sep-ad group) in seroprotection rate were \geq -10% (pre-defined limit) for anti-PRP, anti-HBsAg, anti-poliovirus serotypes 1, 2 and 3, anti-diphtheria and anti-tetanus antibodies, and
- The lower limits of the 95% CI for the GMC ratios (co-ad group over sep-ad group) were \geq 0.67 (pre-defined limit) for anti-PT, anti-FHA and anti-PRN antibodies, and were \geq 0.5 for antibodies to *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

By meeting the pre-specified criteria for non-inferiority, study Rota-060 demonstrates that coadministration of *Rotarix* with licensed routine infant vaccines recommended in the US (*Pediarix*, *Prevnar* and *ActHIB*) does not negatively impact the immune response to any of the antigens (PRP, HBsAg, poliovirus serotypes 1, 2 and 3, diphtheria, tetanus, PT, FHA, PRN, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) that are currently included in the CDC's schedule of recommended immunizations for infants.

5.6. Immunogenicity Conclusions

- *Rotarix* is immunogenic in infants when administered as a two-dose series. Lot-to-lot consistency of the *Rotarix* production process has been demonstrated. The *Rotarix* vaccine strain, which is an attenuated human rotavirus, is genetically stable in production. Anti-rotavirus IgA response rates after two doses of the vaccine in US/Canada (Rota-005 and Rota-060) were comparable to those seen in Europe (Rota-036), and Latin America (Rota-023) where efficacy was demonstrated. Efficacy, especially against severe rotavirus gastroenteritis, paralleled but was always higher compared to the antibody response indicating that the antibody response tends to underestimate the level of protective immunity elicited by the vaccine.
- The rate of rotavirus antigen shedding detected by ELISA in stool peaked at Day 7 after the first dose of the vaccine and decreased thereafter. It was estimated that 26% of the infants were shedding live vaccine virus at Day 7 after the first dose in two clinical studies. The limited transmission potential should be weighed against the high likelihood of acquiring and transmitting natural rotavirus.
- Study Rota-060 demonstrated that coadministration of *Rotarix* with licensed routine infant vaccines (*Pediarix*, *Prevnar* and *ActHIB*) does not negatively impact the immune response to any of the antigens (PRP, HBsAg, poliovirus serotypes 1, 2 and 3, diphtheria, tetanus, PT, FHA, PRN, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) that are currently included in the CDC's schedule of recommended immunizations for infants in the US.

6. CLINICAL SAFETY

Safety data were collected in all vaccinated subjects in the 11 clinical studies submitted in the BLA (Rota-004, Rota-005, Rota-006, Rota-007, Rota-014, Rota-023, Rota-033, Rota-036, Rota-039, Rota-048 and Rota-060). Safety assessments performed were: 1) Safety

with regard to intussusception; 2) Occurrence of SAEs; 3) Occurrence of specific solicited general adverse events; 4) Occurrence of unsolicited adverse events. An Independent Data Monitoring Committee (IDMC) consisting of external clinical experts and a biostatistician has monitored the safety aspects of the *Rotarix* clinical development program since May 2002.

Pivotal safety study Rota-023 in which 63,225 infants were vaccinated with *Rotarix* or placebo was specifically designed and powered to evaluate safety of *Rotarix* with regard to the risk of definite intussusception diagnosed within 31 days post-vaccination compared to the placebo as described in Section 6.2.1. The pivotal safety results presented in this briefing document focus on the core integrated safety summary comparing safety data in subjects receiving the licensure formulation of *Rotarix* (i.e., potency of at least $10^{6.0}$ CCID₅₀ per dose) *versus* placebo. Infants in study Rota-060 received the licensure formulation of *Rotarix*; however, as the study was not placebo-controlled, it was not included in the integrated safety summary. A supplementary integrated safety summary comparing the vaccine at lower potency (i.e., less than $10^{6.0}$ CCID₅₀ per dose) *versus* the placebo provides further supportive data. Safety endpoints evaluated in the integrated summary of safety were: 1) solicited adverse events; 2) unsolicited adverse events; 3) SAEs; and 4) deaths. The relative risk of *Rotarix* versus placebo was estimated with the 95% CI for each endpoint. The common relative risk across studies and its 95% CI were based on exact conditional likelihood approach adjusted for the study effect [Proc StatXact 5.0 user manual]. It should be noted that since the relative risk accounts for study effect, it is different from a crude ratio of the percentages aggregated across studies. Imbalances warranting further exploration were identified based on 95% CI for the relative risk across studies excluding 1.

It is recognized that the use of any method to identify imbalances has the potential to identify a large number of events which may or may not have a causal relationship to the treatment due to multiplicity of endpoints, the difference in data processing between studies, and the power limitation (over-powered to detect common less clinically relevant events and under-powered to detect rare clinically important events). Any identified imbalances therefore should be interpreted cautiously taking clinical relevance into account since statistically significant findings were likely to occur by random chances.

6.1. Extent of Exposure

In the 11 clinical studies submitted in the BLA, a total of 75,029 infants received at least one dose of the vaccine or placebo. Of these, 37,214 infants received at least one dose of the licensure formulation of *Rotarix*, 3,076 infants received at least one dose of the vaccine at lower potency, and 34,739 infants received at least one dose of the placebo (control). The vaccine exposure in the 11 studies included 72,212 doses of *Rotarix*, 6,037 doses of the vaccine at lower potency, and 67,319 doses of placebo.

6.2. Pivotal Safety Results in Clinical Studies

6.2.1. Safety with Regard to Intussusception

In view of the temporal relationship between intussusception and *RotaShield* vaccination [Murphy, 2001], demonstration of safety with regard to intussusception is an important safety parameter for new rotavirus vaccines.

Intussusception occurs infrequently and yet is one of the most common abdominal emergencies in pediatric surgery [Wyllie, 2000]. Intussusception is the invagination of one portion of the intestine into a distal segment. Symptoms include severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. If diagnosed promptly, intussusception usually can be successfully reduced with a contrast or air enema. If there is a delay in diagnosis, intestinal ischemia may lead to necrosis of the bowel, perforation, peritonitis, and rarely, death. The etiology of intussusception is unknown. Most cases in infants and young children are idiopathic. Adenovirus is the most common infectious agent associated with intussusception. The condition can present at any age but only 10% to 25% of the cases occur after the age of 2 years. The peak incidence is between 5 to 9 months of age, and overall 60% to 70% of intussusceptions occur in males [Stringer, 1992]. Accurate estimates of the incidence of intussusception are not available for most developing countries and many developed countries [WHO, 2002]. Overall, the expected annual incidence of acute intussusception for developed countries is <100 per 100,000 live births in children less than one year of age [Parashar, 2000; Justice, 2005].

To allow assessment of the potential risk of intussusception among vaccine recipients as compared with placebo recipients, a large sample size was required because intussusception is an uncommon event. GSK initiated a large phase III study (Rota-023) in 63,225 infants that was specifically designed and powered with pre-specified criteria to demonstrate safety of *Rotarix* with regard to the risk of definite intussusception diagnosed within the 31-day post-vaccination period compared to the placebo. This study was conducted in Latin America (61,165 subjects), and Finland (2,060 subjects), the country in which most of the phase II data were generated, was included as a reference industrialized country. The healthcare infrastructure in Latin America enabled the conduct of this large clinical study with robust surveillance for adverse events.

Because knowledge of the background incidence rates is critical in interpreting data for a geographic region, the incidences of intussusception among children in Latin America *versus* children in the US were assessed by reviewing information on intussusception incidences reported in different regions. Review of the available data indicates that annual incidence of intussusception among children in Latin America is not substantially different from those reported in developed countries (e.g. US) [O’Ryan, 2003; Perez-Schael, 2003]. An overall background rate of 43.9 per 100,000 person-years in the first year of life was estimated for Latin America based on the intussusception incidence observed in a GSK conducted epidemiological study in Latin America [Breuer, 2004].

6.2.1.1. Assessment of Intussusception in Study Rota-023

Study Design: Rota-023 was a phase III, randomized, placebo-controlled, double-blind, multicenter study conducted in Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela and Finland. Healthy infants 6 to 13 weeks of age were randomized in a 1:1 ratio to receive two doses of *Rotarix* or placebo given 1 to 2 months apart. Infants received routine pediatric vaccines (such as DTwP or DTaP, Hep B and Hib) according to local regulations. In countries using OPV, its administration was separated from *Rotarix* or placebo dose by 2 weeks. The safety surveillance period for the entire cohort started at Dose 1 and ended at the third follow-up visit planned at 30-90 days after Dose 2. A subset from the 11 Latin American countries was followed until 12 months of age, and a subset from 10 of the 11 Latin American countries was followed until 24 months of age for efficacy and safety evaluations. See Figure 5 for design of study Rota-023.

The primary safety objective of study Rota-023 was to determine the safety of *Rotarix* with respect to definite intussusception within 31 days (Day 0 to Day 30) after each dose. A case of definite intussusception required confirmation at surgery or autopsy or by using imaging techniques such as gas or liquid contrast enema or abdominal ultrasound according to the case definition from the Brighton Collaboration Intussusception Working Group [Bines, 2004a]. The analysis of the primary safety endpoint included only cases adjudicated as “definite” intussusception among all intussusception cases reported and only those with the date of diagnosis within the 31 days post-vaccination period. The pre-specified criteria for meeting the primary safety objective in study Rota-023 were:

- The upper limit of the 2-sided 95% CI of the risk difference for the percentage of subjects diagnosed with definite intussusception within 31 days (Day 0 to Day 30) after any dose should be below 6/10,000, a limit based on the study sample size and the anticipated intussusception incidence rate, and
- There should be no statistically significant increase in the percentage of subjects diagnosed with definite intussusception within 31 days (Day 0 to Day 30) after any dose (the lower limit of the 2-sided 95% CI of the risk difference should be below 0).

Considering an incidence rate of 3 to 5 cases of definite intussusception per 10,000 infants within 31 days in the placebo group, the sample size of 63,225 subjects in this study had more than 86% power to meet the primary objective if the risk difference was truly zero.

The criteria for meeting the primary safety objective in study Rota-023 corresponded to observing a relative risk below 3 and a risk increase below 2.5/10,000, which are lower than risk estimates for *RotaShield* (the risk increase for *RotaShield* was 4/10,000 which corresponds to a relative risk between 14.33 and 5.44).

Surveillance for Intussusception: Intussusception cases were detected by independent, complementary methods: 1) expedited reporting by hospitals in study areas of intussusception cases during the study, 2) concurrently conducted prospective hospital-based surveillance study, and 3) reporting of the intussusception cases by

parents/guardians at scheduled study visits/contacts. All hospitals in the study areas were informed about the study. Relevant departments at the hospitals were advised to contact the study personnel and inform them regarding each case of intussusception evaluated. Parents/guardians of participating infants were informed about symptoms consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C). Parents/guardians were instructed to seek medical advice at the nearest hospital if symptoms indicative of intussusception appeared, and to inform the investigator. At each study visit or contact, the investigators queried each subject's parent/guardian on whether the subject had been evaluated in a hospital or emergency department for a complaint that led to abdominal surgery or had an abdominal radiology procedure involving an enema in order to identify occurrence of any intussusception cases during the study. Every affirmative answer was followed with a complete case investigation by the study personnel. The investigator was required to document all available information for each intussusception case on the SAE report pages in the electronic case report form and on a supplied Intussusception Form. An IDMC separately reviewed all intussusception cases reported during the study and had the authority to unblind.

Adjudication Procedure: All investigator-diagnosed cases of intussusception reported during the safety surveillance period were adjudicated by an independent blinded expert Clinical Events Committee composed of a pediatric gastroenterologist, surgeon and radiologist. Using the case definition from the Brighton Collaboration Intussusception Working Group [Bines, 2004a], the Clinical Events Committee categorized intussusception cases as definite, probable or possible according to diagnostic certainty.

6.2.1.2. Pivotal Results on Safety with Regard to Intussusception in Study Rota-023

For the total vaccinated cohort of 63,225 infants (31,673 subjects in the *Rotarix* group and 31,552 subjects in the placebo group), the median age was 7 weeks at Dose 1 and 15 weeks at Dose 2. The gender distribution was 49.0% females and 51.0% males. The study included 81.3% Hispanic, 10.9% White/Caucasian, 1% African and 6.8% other races. Overall, 98% of the subjects were followed for a period of at least 31 days (Day 0 to Day 30) after each dose of *Rotarix* or placebo with no difference between the groups. The median duration of the safety surveillance period (from Dose 1 up to the third follow-up visit planned at 30-90 days after Dose 2) was 100 days after Dose 1.

Twenty-seven investigator-diagnosed cases of intussusception were reported during the safety surveillance period. The independent Clinical Events Committee adjudicated 26 cases as 'definite' intussusception. One case diagnosed 22 days after Dose 2 in the *Rotarix* group was adjudicated as 'probable' intussusception since this subject had a normal ultrasound and improved without treatment, and no supporting investigations or treatment were performed to enable adjudication of this case as 'definite' intussusception according to the case definition or exclude a 'possible' intussusception that may have spontaneously resolved. One case of definite intussusception (58 days after Dose 2) was diagnosed after the infant had concluded participation in the study (this subject was not part of the efficacy subset and therefore was not followed beyond the third follow-up

visit). Thus, 25 cases of definite intussusception were diagnosed during the safety surveillance period.

Of these 25 cases of definite intussusception, 13 cases (6 in the *Rotarix* group and 7 in the placebo group) were diagnosed within the 31-day post-vaccination period after any dose (see Figure 16). There was no temporal cluster of intussusception cases after either dose. There were no reports of intussusception within 14 days after the first dose which was the period of highest risk of intussusception for the previous rhesus rotavirus tetravalent vaccine, *RotaShield* [Murphy, 2001] (see Figure 17). Clinical characteristics of the intussusception cases in the *Rotarix* and placebo recipients were similar. All subjects with intussusception had a complete recovery.

Figure 16 Occurrence of definite intussusception from Dose 1 up to end of the safety surveillance period – study Rota-023 (total vaccinated cohort)

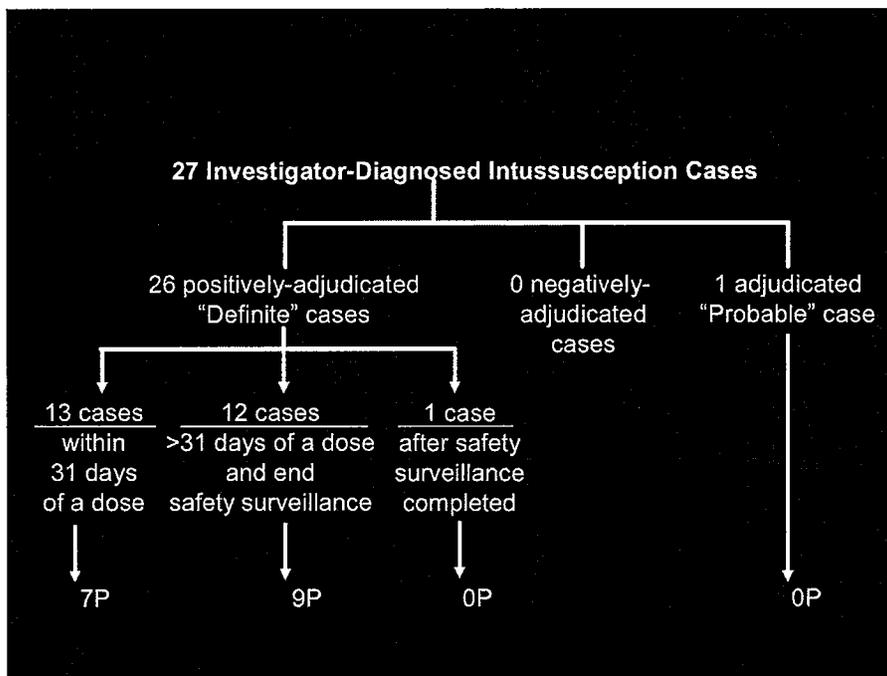
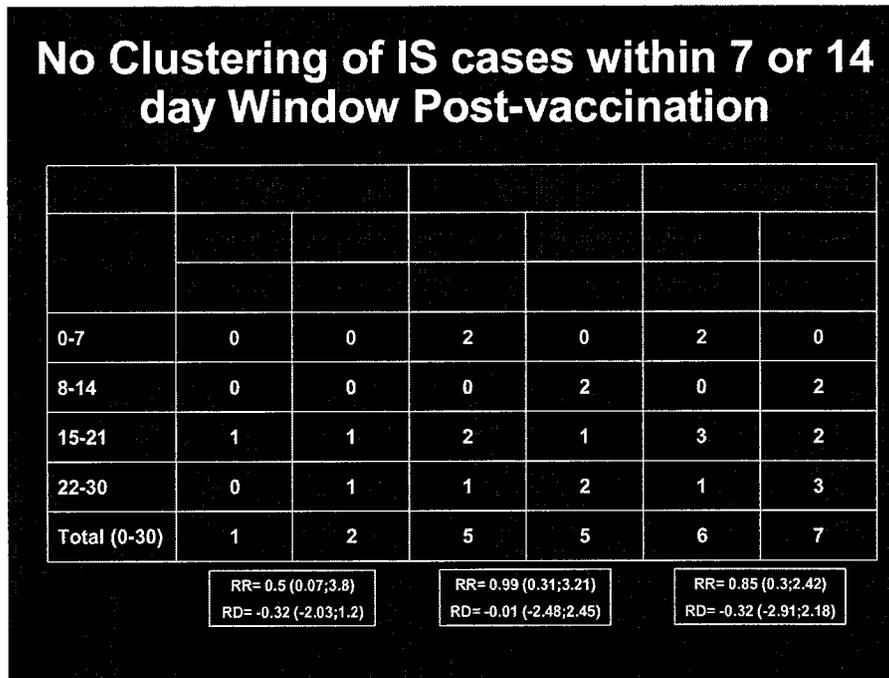
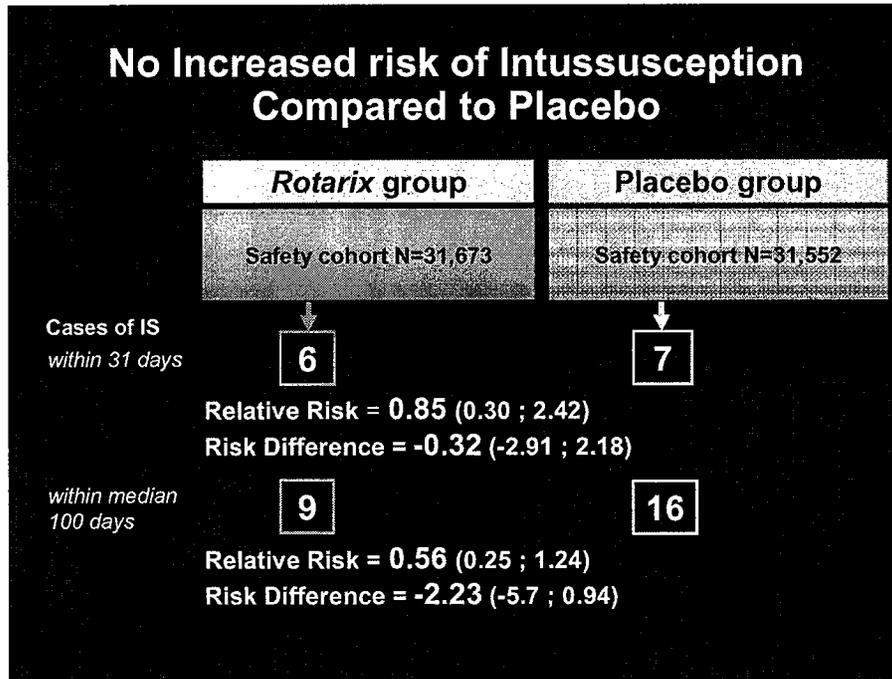


Figure 17 Occurrence of definite intussusception within 31 days of any dose by day range – study Rota-023 (total vaccinated cohort)



The criteria specified for fulfilling the primary safety objective were reached by the observed risk difference estimate after any dose of -0.32/10,000 [95% CI: -2.91/10,000; 2.18/10,000] as shown in Figure 18. As determined by the pre-defined criteria, this study demonstrated that there is no increased risk of intussusception diagnosed within 31 days (Day 0-Day 30) after each dose of *Rotarix*.

Figure 18 Relative Risk for occurrence of definite intussusception diagnosed from Dose 1 up to end of the safety surveillance period – study Rota-023 (total vaccinated cohort)



The upper limit of the 95% CI for the observed risk difference (2.18/10,000) is below the risk difference of 4/10,000 that had prompted the withdrawal of *RotaShield* in the US [Murphy, 2001; Kramarz, 2001]. The observed risk difference of -0.32/10,000 is also far below the subsequently published consensus risk difference for *RotaShield* (1/10,000) [Peter, 2002; Murphy, 2003].

The entire cohort was followed for intussusception during the safety surveillance period starting at Dose 1 and ending at the third follow-up visit planned to be 30-90 days after Dose 2. During the safety surveillance period (median duration: 100 days after Dose 1), 9 cases of definite intussusception were reported in the *Rotarix* group and 16 cases were reported in the placebo group (see Table 4).

A subset of 20,169 infants (10,159 receiving *Rotarix* and 10,010 receiving placebo) from the 11 Latin American countries was followed until 12 months of age after vaccination. Beyond the safety surveillance period during the first year, 3 subjects in the *Rotarix* group and 4 subjects in the placebo group were diagnosed with intussusception. From Dose 1 up to 12 months of age, there were 4 cases of intussusception in the *Rotarix* group compared with 14 cases of intussusception in the placebo group (see Table 4). It should be noted that some subjects who had experienced intussusception during the safety surveillance period were not followed beyond the third follow-up visit.

A subset of 15,183 children (7,669 receiving *Rotarix* and 7,514 receiving placebo) from 10 of the 11 Latin American countries was followed up to two years of age after vaccination. No intussusception cases were reported during the second year. Some

subjects who had experienced intussusception during the first year were not part of the subset followed during the second year. This resulted in fewer number of intussusception cases in the longer follow-up cohort. From Dose 1 to two years of age, there were 4 cases of intussusception in the *Rotarix* group compared with 11 cases of intussusception in the placebo group (see Table 4).

Table 4 Risk Difference and Relative Risk for definite intussusception over sequential follow-up periods – study Rota-023 (total vaccinated cohort)

	Rotarix		Placebo		Risk Difference			Relative Risk			p-Value
	N	n	N	n	per 10,000	95% CI		per 10,000	95% CI		
						Lower Limit	Upper Limit		Lower Limit	Upper Limit	
Secondary endpoint											
Within 100 days of Dose 1	31673	9	31552	16	-2.23	-5.70	0.94	0.56	0.25	1.24	0.159
Dose 1 to 12 months of age	10159	4	10010	14	-10.05	-19.95	-2.02	0.28	0.10	0.81	0.017
Dose 1 to 24 months of age	7669	4	7514	11	-9.4	-21.6	0.6	0.36	0.12	1.06	0.065

N = number of subjects in the considered cohort

n = number of subjects reporting definite intussusception

Per 10,000 = number of subjects per 10,000 reporting definite intussusception

p-value = results of comparison of percentage of subjects reporting definite intussusception between groups by 2-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significant level of alpha = 0.05)

6.2.1.3. Supportive Results on Safety with Regard to Intussusception

Cases of intussusception were also captured in all of the clinical studies, though cases were adjudicated by the independent Clinical Events Committee only in study Rota-023. There was no evidence of an imbalance in intussusception cases, including all investigator diagnosed reports of intussusception irrespective of adjudication across the 11 studies submitted in the BLA.

When considering all investigator-diagnosed intussusception cases (irrespective of adjudication) reported to occur within the 31-day post-vaccination period in the 11 studies submitted in the BLA, there were 10 cases in vaccine recipients and 7 cases in placebo recipients with a relative risk of 1.3 [95% CI: 0.44; 4.06].

When considering all investigator-diagnosed intussusception cases (irrespective of adjudication) reported to occur regardless of time-to-onset after vaccination in the 10 placebo-controlled studies submitted in the BLA, there were 18 cases in vaccine recipients and 22 cases in placebo recipients with a relative risk of 0.72 [95% CI: 0.36; 1.41].

6.2.1.4. Conclusion on Safety with Regard to Intussusception

Study Rota-023 has demonstrated no increased risk of intussusception within the 31-day period following any dose of *Rotarix* compared to the placebo by meeting the pre-specified criteria as shown by the risk difference estimate of -0.32/10,000 [95% CI: -

2.91/10,000; 2.18/10,000] and relative risk of 0.85 [95% CI: 0.3; 2.42]. There was no temporal cluster of intussusception cases after either dose. Additionally, no increased risk for intussusception was observed for the 100-day follow-up after the first dose, up to 12 months of age, and up to 24 months of age. In conclusion, results of the pivotal safety study Rota-023, and the results from other clinical studies included in the BLA, provide a high level of confidence in the safety of *Rotarix* with regard to intussusception.

6.2.2. Serious Adverse Events

SAEs that occurred during the entire study period were reported in all studies. Each SAE was classified using Medical Dictionary for Regulatory Activities (MedDRA) with every verbatim term matched to the MedDRA Preferred Term and the corresponding primary System Organ Class.

The pivotal data on SAEs and deaths for *Rotarix* compared to placebo was provided by the core integrated safety summary of 8 studies (Rota-005, Rota-006, Rota-007, Rota-023, Rota-033, Rota-036, Rota-039 and Rota-048) that assessed SAEs in subjects receiving the licensure formulation of *Rotarix* (36,755 infants) versus placebo (34,454 infants). In the integrated safety summary, imbalances warranting further exploration were identified based on 95% CI for the relative risk across studies excluding 1, and clinical relevance was taken into account when interpreting any statistically significant findings.

6.2.2.1. Deaths

In the core integrated safety summary, 33 deaths (0.09%) in *Rotarix* recipients and 20 deaths (0.06%) in placebo recipients were reported to occur within the 31-day post-vaccination period with a relative risk of 1.64 [95% CI: 0.92; 3.02]. The most frequent cause of deaths within the 31-day post-vaccination period was pneumonia, which was observed in 7 (0.02%) vaccine recipients and 5 (0.01%) placebo recipients with a relative risk of 1.39 [95% CI: 0.38; 5.57]. During the course of the studies regardless of time-to-onset, there were 68 (0.19%) deaths following administration of *Rotarix* and 50 (0.15%) deaths following placebo administration with a relative risk of 1.31 [95% CI: 0.89; 1.93]. All reported deaths were assessed by the investigators as not related to vaccination. No imbalance was noted for deaths reported to occur within the 31-day post-vaccination period and for deaths reported to occur during the entire course of studies regardless of time-to-onset (95% CI of relative risks included 1).

6.2.2.2. Serious Adverse Events

In the core integrated safety summary, 2,219 (6.04%) *Rotarix* recipients and 2,300 (6.68%) placebo recipients reported the occurrence of at least one SAE during the entire course of the studies.

Table 5 presents results of the core integrated safety summary for SAEs occurring within the 31-day post-vaccination period including the most frequently reported SAEs (reported with frequency of >0.1%) and events for which an imbalance was identified between the groups (95% CI of relative risks excluded 1).

At least one SAE occurring within the 31-day post-vaccination period was reported by 627 (1.71%) vaccine recipients and 659 (1.91%) placebo recipients. The most common SAEs occurring within the 31-day post-vaccination period were bronchiolitis (reported in 0.35% vaccine recipients and 0.40% placebo recipients), pneumonia (0.33% and 0.35%), and gastroenteritis (0.20% and 0.32%).

An imbalance (95% CI for relative risk excluded 1.0) between *Rotarix* and placebo groups was observed for SAEs of diarrhea (reported in 0.02% vaccine recipients versus 0.07% placebo recipients), gastroenteritis (0.20% versus 0.32%), and dehydration (0.02% versus 0.06%) within the 31-day post-vaccination period. The imbalance was in favor of *Rotarix* as most likely reflects efficacy of *Rotarix* against gastroenteritis related symptoms of rotavirus etiology.

All other SAEs reported within the 31-day post-vaccination period including investigator-diagnosed cases of intussusception (reported in 0.02% vaccine recipients and 0.02% placebo recipients) and nervous system disorder SAEs (reported in 0.05% vaccine recipients and 0.07% placebo recipients) were reported by similar proportions of subjects in both the *Rotarix* and placebo groups with no imbalance between groups (95% CI for relative risk included 1.0).

Table 5 Core Integrated Safety Summary of SAEs within the 31-day post-vaccination period – studies Rota-005, Rota-006, Rota-007, Rota-023, Rota-033, Rota-036, Rota-039 and Rota-048 (total vaccinated cohort)

Serious Adverse Event (SAE)	Rotarix N = 36755		Placebo N = 34454		Relative Risk
	n	%	n	%	(95% CI)
At least one SAE	627	1.71	659	1.91	0.90 (0.81; 1.01)
Most frequent SAEs (reported with frequency of >0.1% in either group)					
Bronchiolitis	127	0.35	137	0.40	0.88 (0.68; 1.13)
Pneumonia	122	0.33	122	0.35	0.99 (0.76; 1.28)
Gastroenteritis	72	0.20	111	0.32	0.62 (0.45; 0.84)§
SAEs with imbalance between groups (95% CI on Relative Risk excluded 1)					
Diarrhea	9	0.02	25	0.07	0.35 (0.14; 0.78)§
Dehydration	9	0.02	21	0.06	0.43 (0.17; 0.97)§
Gastroenteritis	72	0.20	111	0.32	0.62 (0.45; 0.84)§

N = number of subjects that received at least one dose

n/% = number/percentage of subjects reporting at least once a specified symptom

Relative Risk adjusted for study effect

Imbalances were noted based on 95% CI for the relative risk across studies excluding 1

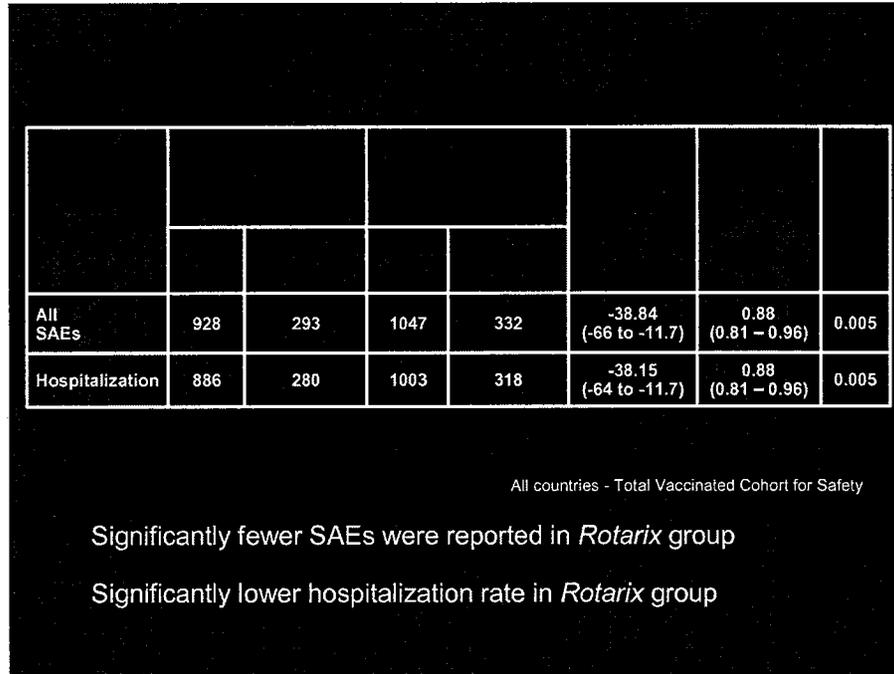
§ = 95% CI on Relative Risk excludes 1

SAEs and Hospitalizations Associated with Gastroenteritis Disease – study Rota-023

A secondary safety objective in study Rota-023 was to assess the occurrence of all SAEs during the safety surveillance period (from Dose 1 up to the third follow-up visit planned at 30-90 days after Dose 2) in the entire cohort of 31,673 *Rotarix* recipients and 31,552 placebo recipients. Significantly fewer numbers of SAEs and hospitalizations were observed in *Rotarix* recipients compared to placebo recipients (see Figure 19). Consistent with the integrated safety summary, this was primarily driven by fewer SAEs and hospitalizations associated with gastroenteritis disease in the *Rotarix* group: there were

significantly fewer numbers of SAEs of diarrhea, vomiting, gastroenteritis, dehydration and hypovolaemic shock reported in the *Rotarix* group compared to the placebo group (2-sided p-value <0.05 for each comparison).

Figure 19 Occurrence of SAEs and hospitalizations from Dose 1 up to end of the safety surveillance period – study Rota-023 (total vaccinated cohort)



Discontinuations (i.e., any subject who missed a study visit, any subject who missed the planned concluding visit, or any subject who missed a vaccine/placebo dose) due to SAEs or non-serious adverse events were similar between the vaccine recipients and placebo recipients. In the core integrated safety summary, 0.43% vaccine recipients and 0.39% placebo recipients discontinued due to an SAE or non-serious adverse event.

6.2.2.3. Serious Adverse Events of Clinical Interest

Events of clinical interest, for rotavirus vaccines in general (such as hematochezia, Kawasaki disease and seizures in addition to intussusception) and/or identified upon review of the individual studies included in the integrated safety summary, are summarized in this section. It is important to note that there were no imbalances observed for any of these events of clinical interest in the core integrated safety summary.

In individual studies, imbalances warranting further exploration were identified based on 2-sided p-value <0.05. Clinical relevance was again taken into account when interpreting any statistically significant findings.

Hematochezia

It is recognized that intussusception might present with symptoms of bloody stools or hematochezia [Bines, 2004b]. Bloody stools were reported as part of the clinical spectrum of gastrointestinal-related illness in post-licensure surveillance of *RotaShield* [Haber, 2004]. Possible explanations were that the reports of bloody stools may represent occult cases of intussusception that resolved spontaneously before they were diagnosed, coinfection with another organism that causes bloody diarrhea at the time of or shortly after vaccination with *RotaShield*, or that the vaccine virus of *RotaShield* is more invasive than wild rotavirus, causing these events [Haber, 2004].

Hematochezia was not prospectively solicited in any of the studies but would be expected to have been captured as an unsolicited event. Hematochezia may have been reported as part of the symptom complex in subjects diagnosed with intussusception in both the *Rotarix* and placebo groups, and in those subjects the SAE was reported by the investigators as intussusception. In the core integrated safety summary for SAEs including 36,755 *Rotarix* recipients and 34,454 placebo recipients, there were no reports of SAEs coded to the MedDRA Preferred Term “Hematochezia” during the 31-day post-vaccination period in the *Rotarix* group or the placebo group. During the course of the studies regardless of time-to-onset, SAEs coded to the MedDRA Preferred Term “Hematochezia” were reported by 1 subject in each group.

As hematochezia was not prospectively solicited in any of the studies, a review of unsolicited reports of hematochezia in clinical studies was performed to assess the occurrence of this adverse event. Varied terms were used for reporting adverse events related to blood in stools across the studies. Therefore, adverse events coded to the MedDRA High Level Term (HLT) “gastrointestinal hemorrhages” were analyzed. In the core integrated safety summary including 36,755 *Rotarix* recipients and 34,454 placebo recipients, at least one adverse event within the MedDRA HLT “gastrointestinal hemorrhages” was reported by 19 (0.05%) vaccine recipients and 9 (0.03%) placebo recipients regardless of time-to-onset from vaccination (see Figure 20). No imbalance was noted between the *Rotarix* and the placebo groups for each of the considered MedDRA Preferred Terms under the MedDRA HLT “gastrointestinal hemorrhages” (the 95% CI for relative risk included 1.0). Of these, 24 cases [17 (0.046%) in vaccine recipients and 7 (0.020%) in placebo recipients] had symptom onset within the 31-day post-vaccination period. The events resolved in all cases. None of these 28 subjects were reported to have intussusception.

Figure 20 Core Integrated Safety Summary of “Gastrointestinal Hemorrhages” adverse events regardless of time-to-onset – studies Rota-005, Rota-006, Rota-007, Rota-023, Rota-033, Rota-036, Rota-039 and Rota-048 (total vaccinated cohort)

At least one GE Hemorrhage symptom	19 (0.05%)	9 (0.03%)	1.22 (0.52 – 3.09)
Diarrhea hemorrhagic	1	0	8 (0.03 – 8)
Gastritis hemorrhagic	1	0	8 (0.03 – 8)
GI hemorrhage	1	0	8 (0.03 – 8)
Hematochezia	15 (0.04%)	7 (0.02%)	1.13 (0.43 - 3.28)
Rectal hemorrhage	0	2 (0.01%)	0 (0 – 3.76)
Upper GI hemorrhage	1	0	8 (0.03 – 8)

Relative Risk adjusted for study effect

Kawasaki Disease

During the course of the 11 studies submitted in the BLA, four cases of Kawasaki disease were reported: 1) a case was reported 7 months after the second dose of the vaccine in study Rota-006 in Latin America, 2) a case was reported 55 days after the second dose of the vaccine in study Rota-007 in Singapore, 3) a case was reported 3 months after the second dose of the vaccine in study Rota-007 in Singapore, and 4) a case was reported 19 months after the second dose of the vaccine in study Rota-023 in Latin America. None was fatal and all were reported as not related to vaccination by the investigator. No pattern was identified with regard to time-to-onset of these cases. In two studies (Rota-006 and Rota-007), three times as many children received *Rotarix* compared to placebo. The randomization ratio in study Rota-023 was 1:1. The differences in randomization ratio and background rates should be taken into consideration when assessing the number of Kawasaki disease reports arising in these studies.

Convulsions

In study Rota-023 (31,673 subjects in the *Rotarix* group and 31,552 subjects in the placebo group), 29 subject each in the *Rotarix* and placebo groups reported SAEs coded to the MedDRA System Organ Class “Nervous system disorders” during the safety surveillance period (2-sided p-value = 0.988). An imbalance warranting further exploration, based on the pre-defined exploratory 2-sided asymptotic p-value <0.05 significance level, was observed for SAEs coded to the MedDRA Preferred Term

“Convulsions”: 16 subjects in the *Rotarix* group versus 6 subjects in the placebo group reported convulsion SAEs (2-sided asymptotic p-value = 0.034). All cases were assessed as not related to vaccination by the investigators. Because SAEs coded to multiple Preferred Terms related to convulsions were reported in study Rota-023, all SAEs during the safety surveillance period coded to convulsion disorders were reviewed; these included convulsions, epilepsy, grand mal convulsion, status epilepticus, and tonic convulsion. An imbalance was no longer noted when these terms were pooled: 20 cases in the *Rotarix* group versus 12 in the placebo group (2-sided exact p-value = 0.219). Additionally, a temporal association between pooled terms convulsion and *Rotarix* vaccination was not established: 7 subjects in the *Rotarix* group versus 9 in the placebo group within the 31-day post-vaccination period. Most cases in the *Rotarix* group had other concurrent and/or pre-existing conditions that could have accounted for the convulsion.

In all of the other clinical trials, and in the core integrated safety summary, an imbalance was not noted in convulsion SAEs within the 31-day post-vaccination period and during the entire course of studies regardless of time-to-onset.

Although the currently available data do not show a consistent relationship between *Rotarix* and convulsions, GSK will be monitoring convulsions in the post-marketing setting as outlined in the pharmacovigilance plan in Section 8.

Pneumonia-related Deaths

In study Rota-023 (31,673 subjects in the *Rotarix* group and 31,552 subjects in the placebo group), there were 56 (0.18%) deaths in the *Rotarix* group and 43 (0.14%) deaths in the placebo group during the safety surveillance period. An imbalance warranting further exploration, based on the pre-defined exploratory 2-sided asymptotic p-value <0.05 significance level, was observed for fatal events coded to the MedDRA Preferred Term “Pneumonia” reported during the safety surveillance period: 14 deaths in the *Rotarix* group versus 5 deaths in the placebo group (2-sided asymptotic p-value = 0.040). These fatal events were reported in Latin American countries where acute respiratory infections, especially pneumonia, account for dramatically greater numbers and proportions of infant deaths in Latin America, as compared to the US [Benguigui, 1999]. It should be noted that, in the core integrated summary of safety, no imbalance was noted for deaths including fatal pneumonia events reported to occur within the 31-day post-vaccination period and for deaths reported to occur during the entire course of studies regardless of time-to-onset as described in Section 6.2.2.1 (note: in the core integrated safety summary, all deaths within the 31-day post-vaccination period among *Rotarix* recipients occurred in study Rota-023).

Further exploratory analyses were performed to assess this observed imbalance using exact statistical method for rare events. All fatal events during the safety surveillance period coded to Preferred Terms related to pneumonia were reviewed. In addition to the 19 fatal pneumonia events, 2 bronchopneumonia deaths and one cytomegalovirus pneumonia death were identified. All pneumonia-related terms with fatal outcomes were grouped together for an exploratory analysis. There was no imbalance noted between groups for pneumonia-related deaths based on the pre-defined exploratory 2-sided p-

value <0.05 significance level: 16 deaths in the *Rotarix* group versus 6 deaths in the placebo group were reported (2-sided exact p-value = 0.054). Additionally, there was no imbalance between the groups for pneumonia-related fatal events within the 31-day post-vaccination period: 7 deaths in the *Rotarix* group versus 3 deaths in the placebo group, 2-sided exact p-value = 0.34 and relative risk 2.32 [95% CI: 0.53; 13.93].

Pneumonia SAEs and Hospitalizations

To further assess the observed imbalance in pneumonia deaths in study Rota-023, an additional exploratory analysis was performed on pneumonia SAEs and hospitalizations. During the safety surveillance period, SAEs coded to the various MedDRA Preferred Terms “Pneumonia” within the System Organ Class “Infections and infestations” were reported by 280 subject in the *Rotarix* group versus 277 subjects in the placebo group (2-sided p-value = 0.934). The majority of these SAEs were hospitalizations: pneumonia-related hospitalizations were reported by 277 (0.87%) subjects in the *Rotarix* group and 273 (0.87%) subjects in the placebo group (2-sided p-value = 0.9). There was also no imbalance between the *Rotarix* and placebo groups for pneumonia-related hospitalizations within 31 days and beyond 31 days after each dose (2-sided p-value >0.05 for each comparison). Based on these exploratory analyses, the imbalance in pneumonia deaths was not confirmed by analysis of hospitalizations associated with pneumonia. Clinically, it does not appear plausible that a vaccine effect would be seen on pneumonia mortality but not at all on pneumonia hospitalizations.

In study Rota-036 conducted in Europe (2,646 subjects in the *Rotarix* group and 1,348 subjects in the placebo group), an imbalance warranting further exploration was noted for pneumonia SAEs reported from Dose 1 until end of the second rotavirus season after vaccination: 24 (0.9%) subjects in the *Rotarix* group versus 4 (0.3%) subjects in the placebo group reported pneumonia SAEs (2-sided asymptotic p-value = 0.03). The majority of cases (19 out of 28 cases) were reported to occur remotely from vaccination during the second rotavirus season, and only one case in the *Rotarix* group occurred within the 31-day post-vaccination period. There was no imbalance noted for pneumonia SAEs reported within the 31-day post-vaccination period (1 *Rotarix* group and 0 placebo group), and during follow-up from Dose 1 until end of the first rotavirus season (7 *Rotarix* group and 2 placebo group; 2-sided p-value >0.05). Also, there was no imbalance noted for unsolicited reports of pneumonia within the 31-day post-vaccination period: 4 (0.2%) subjects in the *Rotarix* group versus 2 (0.1%) subjects in the placebo group (2-sided p-value = 0.983). No deaths were reported in this study.

In all of the other clinical trials, and in the core integrated safety summary, an imbalance was not noted for pneumonia or other pneumonia-related SAEs within the 31-day post-vaccination period and during the entire course of studies regardless of time to-onset.

The currently available data do not show a consistent relationship between *Rotarix* and pneumonia-related deaths, SAEs and hospitalizations. Nevertheless, GSK will further investigate pneumonia-related deaths and hospitalizations due to acute lower respiratory tract infections in the post-marketing setting as outlined in the pharmacovigilance plan in Section 8.

6.2.3. Solicited Adverse Events

The occurrence of specific solicited general adverse events was actively collected from the infant's parent/guardian during the 8-day or 15-day post-vaccination period after each dose in all studies using diary cards completed by the infant's parent/guardian with the exception of Rota-023 and Rota-060 in which only SAEs were collected.

Parents/guardians completed a diary card daily during the specified follow-up period (8-day or 15-day post-vaccination period) after each dose to record any fussiness/irritability, cough/runny nose, the infant's temperature, loss of appetite, vomiting, or diarrhea; cough/runny nose was not solicited in study Rota-033. For each solicited adverse event, definitions of "severity" were provided to the parents/guardians for guidance.

Coadministration of routine pediatric vaccines according to local regulations (such as DTaP or DTwP, Hep B, Hib, IPV or OPV, pneumococcal 7-valent conjugate vaccine and meningococcal group C conjugate vaccine) was allowed in all studies except Rota-048. Due to concomitant administration of routine pediatric vaccines during the studies, it was not possible to determine the causal relationship of general symptoms to the individual vaccines administered. Therefore, the investigators assessed whether the general adverse events were causally related to vaccination rather than to the individual vaccines.

The pivotal data on solicited adverse events for *Rotarix* compared to placebo was provided by the core integrated safety summary of 7 studies (Rota-005, Rota-006, Rota-007, Rota-033, Rota-036 (subset of subjects), Rota-039 and Rota-048) that assessed solicited adverse events in subjects receiving the licensure formulation of *Rotarix* (3,286 infants) *versus* placebo (2,015 infants). Solicited adverse events occurred at similar rates among *Rotarix* and placebo recipients, and grade 3 symptoms were not frequently reported (see Figure 21 and Figure 22). No imbalance was noted between *Rotarix* and placebo recipients for fussiness/irritability, cough/runny nose, fever (rectal temperature >100.4°F or >103.1°F), loss of appetite, vomiting, or diarrhea reported within the 8-day post-vaccination period after Dose 1 and Dose 2 (95% CI of relative risk included 1).

Figure 21 Core Integrated Safety Summary of solicited adverse events of any intensity reported to occur within the 8-day post-vaccination period – studies Rota-005, Rota-006, Rota-007, Rota-033, Rota-036, Rota-039 and Rota-048 (total vaccinated cohort)

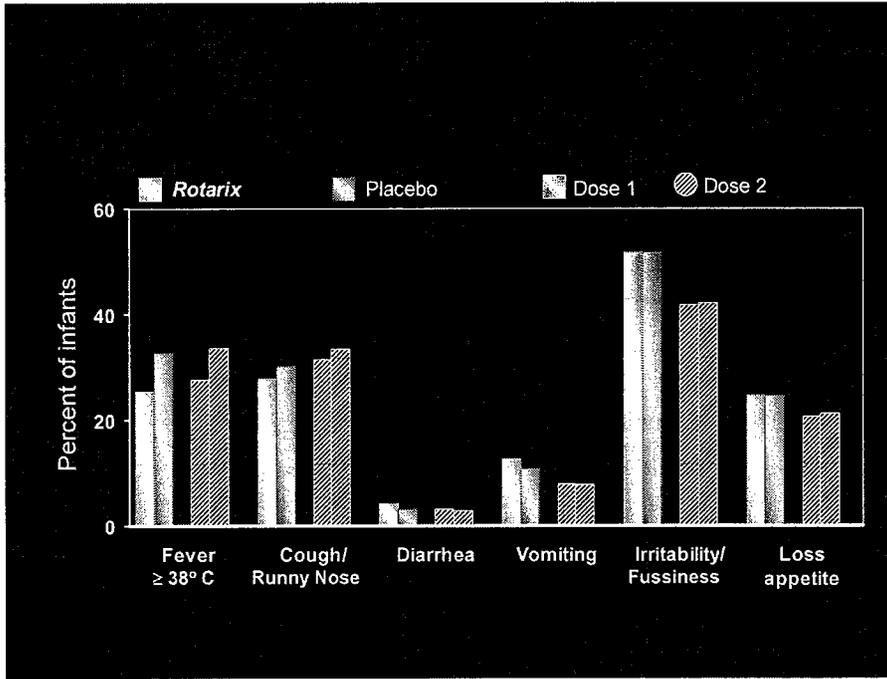
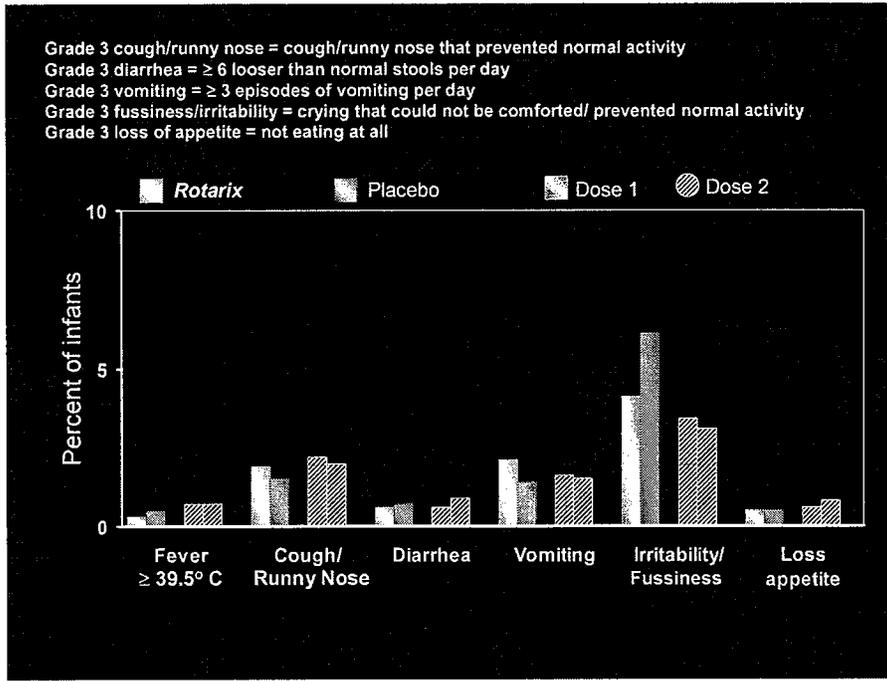


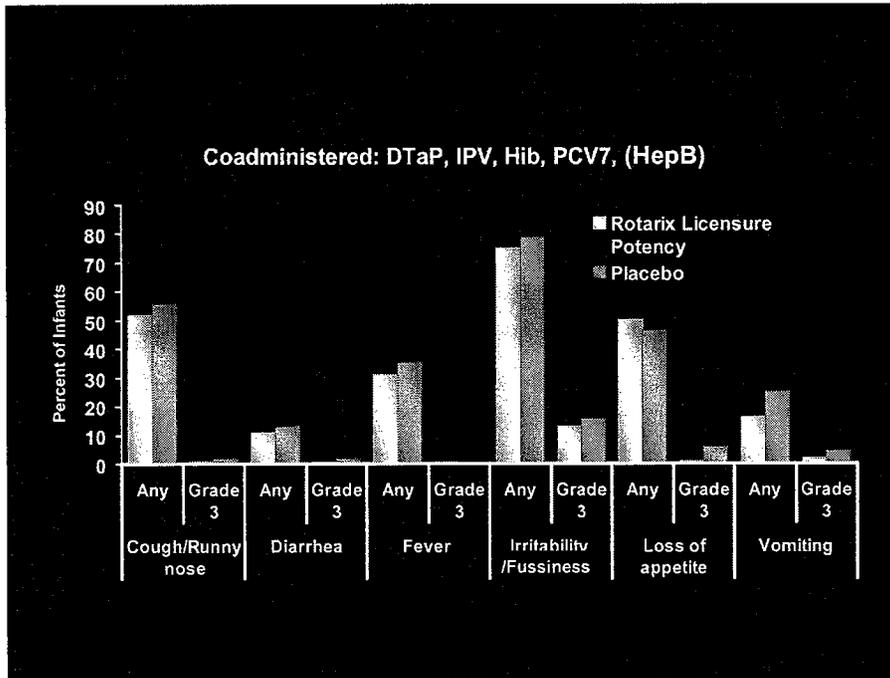
Figure 22 Core Integrated Safety Summary of solicited adverse events of grade 3 intensity reported to occur within the 8-day post-vaccination period – studies Rota-005, Rota-006, Rota-007, Rota-033, Rota-036, Rota-039 and Rota-048 (total vaccinated cohort)



When considering individual studies included in the core integrated safety summary, the incidences of solicited adverse events were comparable between the vaccine and placebo groups in each study, irrespective of the potency of the vaccine tested. As examples, the incidences of solicited adverse events in studies Rota-005 (US and Canada) and Rota-036 (Europe) are summarized.

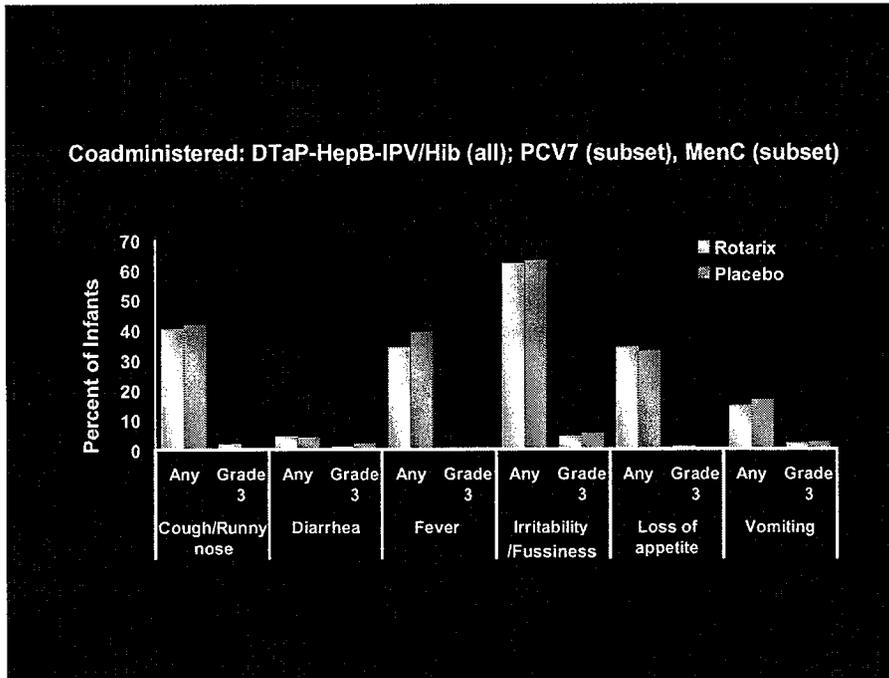
In the phase II dose-ranging study Rota-005 conducted in the US and Canada, 529 infants were enrolled and received at least one dose of $10^{5.3}$ CCID₅₀ vaccine (N=212), $10^{6.8}$ CCID₅₀ vaccine (N=209) or placebo (N=108) according to 0, 2-month schedule. Routine vaccines coadministered were Infanrix® (DTaP), OmniHIB® (Hib) or ActHIB (Hib) or Comvax® (Hib and HepB), IPOL® (IPV) and *Prevnar* (pneumococcal 7-valent conjugate vaccine) to the US subjects (N=448), and Pentacel® (combined DTaP, IPV and Hib) to the subjects in Canada (N=81). Consistent with the core integrated safety summary, the incidence of solicited adverse events were comparable between the licensure formulation of *Rotarix* ($10^{6.8}$ CCID₅₀ vaccine group) and the placebo as shown in Figure 23. This study also included a co-primary objective to compare the percentages of subjects reporting grade 2 or grade 3 fever (rectal temperature $>38.5^\circ\text{C}$ to $\leq 39.5^\circ\text{C}$ or $>39.5^\circ\text{C}$), vomiting (2 or ≥ 3 episodes per day) or diarrhea (4-5 or ≥ 6 looser than normal stools per day) during the 15-day post-vaccination period after any doses between the vaccine and placebo groups. Statistically significant differences were not detected between each vaccine group and the placebo group with respect to the percentage of subjects reporting grade 2 or grade 3 fever, vomiting or diarrhea during the 15-day post-vaccination period (2-sided p-value >0.10).

Figure 23 Occurrence of solicited adverse events within the 15-day post-vaccination period after any dose in US and Canada – study Rota-005 (total vaccinated cohort)



In the phase III study Rota-036 conducted in Europe, reactogenicity data was evaluated in a subset of 1,404 subjects (914 *Rotarix* recipients and 490 placebo recipients). Routine pediatric vaccines coadministered were three doses of *Infanrix hexa* (combined DTaP, Hep B, IPV and Hib vaccine), except in France where *Infanrix IPV Hib* (combined DTaP, IPV and Hib vaccine) was given at the second dose. Infants in Spain also received three doses of *Meningitec* (meningococcal group C conjugate vaccine), and infants in France and Germany also received three doses of *Prennar* (pneumococcal 7-valent conjugate vaccine). The incidences of solicited adverse events were similar in the vaccine and placebo groups when coadministered with routine pediatric vaccines (see Figure 24). Statistically significant differences were not detected between groups as shown by the 2-sided p-value >0.05 for each comparison.

Figure 24 Occurrence of solicited adverse events within the 8-day post-vaccination period after any dose in Europe – study Rota-036 (total vaccinated cohort)



6.2.4. Unsolicited Adverse Events

Unsolicited adverse events occurring during the 31-day or 43-day post-vaccination period after each dose were collected in all studies except Rota-023 and Rota-060 in which only SAEs were collected. Each recorded adverse event was classified using MedDRA with every verbatim term matched to the MedDRA Preferred Term and the corresponding primary System Organ Class.

The pivotal data on unsolicited adverse events for *Rotarix* compared to placebo was provided by the core integrated safety summary of 7 studies (Rota-005, Rota-006, Rota-007, Rota-033, Rota-036, Rota-039 and Rota-048) that assessed unsolicited adverse events in subjects receiving the licensure formulation of *Rotarix* (5,082 infants) versus placebo (2,902 infants).

At least one unsolicited adverse event occurring within the 31-day post-vaccination period was reported by 2,709 (53.3%) vaccine recipients and 1,455 (50.1%) placebo recipients. The most frequently reported unsolicited adverse events were pyrexia (reported in 13.5% vaccine recipients and 12.8% placebo recipients) and irritability (reported in 11.4% vaccine recipients and 8.7% placebo recipients). At least one grade 3 unsolicited adverse event occurring within the 31-day post-vaccination period was reported by 5.3% vaccine recipients and 4.9% placebo recipients. The most frequently reported grade 3 unsolicited adverse events occurring within the 31-day post-vaccination period were pyrexia (reported in 1.3% vaccine recipients and 1.2% placebo recipients) and otitis media (reported in 1.2% vaccine recipients and 1.2% placebo recipients).

Unsolicited reports of hematochezia within the 31-day post-vaccination period were reported by 14 (0.28%) vaccine recipients and 6 (0.21%) placebo recipients. There were no reports of grade 3 hematochezia.

An imbalance between the vaccine and placebo groups was noted (95% CI for relative risk excluded 1.0) for unsolicited adverse event reports of irritability (reported in 11.4% vaccine recipients *versus* 8.7% placebo recipients), flatulence (2.2% *versus* 1.3%), rhinorrhea (0.9% *versus* 1.9%), grade 3 bronchiolitis (0.1% *versus* 0.5%) and grade 3 rhinorrhea (0.0% *versus* 0.2%). The observed imbalances are not considered to be clinically relevant given that the differences observed between groups were small, and the majority of irritability and flatulence reports were of mild or moderate intensity.

6.3. Supportive Safety Results in Clinical Studies

Supportive safety data was provided by a supplementary integrated safety summary comparing the vaccine at lower potency (i.e., less than $10^{6.0}$ CCID₅₀ per dose) to the placebo in 4,689 infants (3,076 vaccine recipients and 1,613 placebo recipients) from 5 studies (Rota-004, Rota-005, Rota-006, Rota-007 and Rota-014).

Consistent with the core integrated safety summary, no imbalance was noted between vaccine and placebo groups for solicited symptoms reported within the 8-day post-vaccination period after Dose 1 and Dose 2. Also, there was no imbalance noted between the vaccine and the placebo for deaths and SAEs within the 31-day post-vaccination period and during the entire course of studies regardless of time-to-onset. There were 5 (0.16%) deaths in vaccine recipients and 6 (0.37%) deaths in placebo recipients regardless of time-to-onset. Three (0.10%) deaths in vaccine recipients and 4 (0.25%) deaths in placebo recipients occurred within the 31-day post-vaccination. All reported deaths were assessed by the investigators as not related to vaccination. At least one SAE within the 31-day post-vaccination was reported by 56 (1.82%) vaccine recipients and 24 (1.49%) placebo recipients. There were three cases of investigator-diagnosed intussusception (irrespective of adjudication) reported during the course of the studies: two (0.07%) cases in vaccine recipients and one (0.06%) case in a placebo recipient. Of these, one case in a vaccine recipient occurred during the 31-day post-vaccination period.

An imbalance warranting further exploration was noted for unsolicited adverse events of any intensity coded to the MedDRA Preferred Term “Bronchitis” within the 31-day post-vaccination period: 1.85% subjects in the vaccine group and 0.74% subjects in the placebo group with a relative risk of 2.39 [95% CI: 1.27; 4.90]. This imbalance was driven by an imbalance in the incidence of unsolicited bronchitis of any intensity in study Rota-006. No imbalance in the incidence of grade 3 bronchitis unsolicited reports or bronchitis SAEs within the 31-day post-vaccination period was observed between groups in the supplementary integrated safety summary. In addition, no imbalance in the incidence of unsolicited bronchitis (any or grade 3 intensity) or bronchitis SAEs was noted in the core integrated safety summary. Of note, the incidence of unsolicited bronchitis was similar in the *Rotarix* and placebo groups in study Rota-036 (2,646 *Rotarix* recipients and 1,348 placebo recipients): 1.5% subjects in the *Rotarix* group and 1.5% subjects in the placebo group (2-sided p-value = 0.981). The observation related to unsolicited bronchitis in study Rota-006 has not been observed in the subsequent larger

study Rota-036 or in the integrated safety summary analyses. Nevertheless, hospitalizations due to acute lower respiratory tract infections will be monitored in the post-marketing setting as outlined in the pharmacovigilance plan in Section 8.

Pre-term Infants

Data on safety of *Rotarix* in pre-term infants was obtained from 254 subjects (134 vaccine recipients and 120 placebo recipients) identified as pre-term infants (i.e., gestational age less than or equal to 36 weeks) in study Rota-023. Mean gestational age was 34.6 weeks. Of note, the pre-term infants were vaccinated in Rota-023 according to their chronological age as other infants (and not according to their gestational age). All 254 subjects were followed for safety from Dose 1 up to the third follow-up visit (planned at 30-90 days after Dose 2). During this follow-up, 5.2% vaccine recipients and 5.0% placebo recipients reported at least one SAE (p-value = 0.94). Of the 254 pre-term infants, 52 (29 vaccine recipients and 23 placebo recipients) were part of the subset that was followed during the first year. During the first year, 17.2% vaccine recipients and 21.7% placebo recipients reported at least one SAE (p-value = 0.68). No intussusception cases or fatal cases were reported in any pre-term subjects. With regard to immunogenicity/efficacy data in pre-term infants, no blood samples were tested from this subset of pre-term vaccine recipients. Severe rotavirus gastroenteritis was reported by one pre-term subject in each group (1 case of severe rotavirus gastroenteritis caused by the G2[P4] type in a vaccine recipients and 1 case of severe rotavirus gastroenteritis caused by the G1 type in a placebo recipient). These clinical data do not raise safety concerns regarding administration of *Rotarix* in pre-term infants. A study is ongoing to evaluate *Rotarix* in pre-term infants as described in the pharmacovigilance plan in Section 8.

Known or Suspected Immunodeficiency

Study Rota-014 was a phase IIb, randomized, placebo-controlled study conducted in South Africa to evaluate immunogenicity and safety of two doses of $10^{5.6}$ CCID₅₀ vaccine formulation when coadministered with OPV or IPV *versus* placebo. The study was conducted in two parts. In part 1, the first dose was administered between 5-10 weeks of age, and in part 2, the first dose was administered between 8-17 weeks of age. In both parts of the study, the second dose was administered 1 month after the first dose.

A cluster of fatalities (7 deaths among 271 infants enrolled) during Rota-014 study part 1 led to an investigation by the IDMC. Of the 6 fatal cases for which the HIV status was known, all were found to be HIV positive. Proportionally more deaths were reported in the placebo group than in the vaccine group: 4 deaths among 90 placebo recipients (4.4%) and 3 deaths among 181 vaccine recipients (1.7%). The investigation, which was done without unblinding (except for the IDMC), indicated that most of the cases were due to opportunistic infections related to the HIV status of the infants. Before enrollment in part 2 began, the protocol was amended as recommended by the IDMC so that the HIV status of mothers was ascertained, and that only infants whose mothers were HIV-negative were enrolled in part 2 of the study. One death was reported during study part 2 (a placebo recipient died from pneumonia 76 days after the 2nd dose) and it was not a complication of HIV disease.

Except for the 6 fatal cases from study part 1 mentioned above, the HIV status was not known for the remaining subjects enrolled in study part 1 of the study. In order to retrospectively assess the use of the vaccine in asymptomatic immunodeficient subjects, HIV testing was performed in 172 subjects from study part 1 whose parents/guardian gave consent. Of those tested, 5 subjects were confirmed HIV positive (2 vaccine recipients and 3 placebo recipients). One subject from the placebo group reported diarrhea during the solicited 15-day post-vaccination period after the first dose. All unsolicited adverse events reported for these 5 subjects were of mild or moderate intensity and none reported a SAE. None of these subjects had seroconverted for anti-rotavirus IgA post-Dose 2. Although limited, these clinical data do not raise safety concerns regarding administration of *Rotarix* in HIV positive subjects. A study is ongoing to evaluate *Rotarix* in HIV-infected infants as described in the pharmacovigilance plan in Section 8.

6.4. Clinical Safety Conclusions

- Study Rota-023 has demonstrated no increased risk of intussusception within the 31-day period following any dose of *Rotarix* compared to the placebo by meeting the pre-specified criteria as shown by the risk difference estimate of -0.32/10,000 [95% CI: -2.91/10,000; 2.18/10,000] and relative risk of 0.85 [95% CI: 0.3; 2.42]. There was no temporal cluster of intussusception cases after either dose. Also, no increased risk for intussusception was observed during 100-day follow-up after the first dose, up to 12 months of age, and up to 24 months of age. In conclusion, results of pivotal safety study Rota-023, and the additional supportive safety studies in the BLA provide a high level of confidence in the safety of *Rotarix* with regard to intussusception.
- The overall safety profile of *Rotarix* was similar to the placebo control. In the core integrated safety summary, there were fewer SAEs associated with gastroenteritis disease in the *Rotarix* group compared to the placebo group. All other SAEs reported within the 31-day post-vaccination period, including deaths, intussusception, bronchiolitis, pneumonia or nervous system disorder SAEs were reported by similar proportions of subjects in both the *Rotarix* and placebo groups as indicated by the 95% CI for relative risk overlapping 1.0. An imbalance warranting further exploration for pneumonia SAEs was observed in one study (Rota-036), for pneumonia-related deaths was observed in one study (Rota-023), and for unsolicited bronchitis was observed in one study (Rota-006). However, in all of the other clinical trials, and in the core integrated safety summary, no imbalance was noted for acute lower respiratory tract infections. Nevertheless, acute lower respiratory tract infections will be monitored in the post-marketing setting as outlined in the pharmacovigilance plan in Section 8.
- *Rotarix* was well tolerated when coadministered with routine pediatric vaccines such as DTaP, Hep B, IPV, Hib, pneumococcal 7-valent conjugate vaccine and meningococcal group C conjugate vaccine with no increase in post-vaccination fever or other adverse events compared to placebo administration.

7. POST-MARKETING EXPERIENCE OUTSIDE US

Rotarix is currently licensed in over 100 countries including Canada, Mexico, Australia, and countries of the European Union. From launch on 12 July 2004 to 11 July 2007, approximately 12.3 million doses of *Rotarix* were distributed worldwide (including Brazil: 8.7 million; Mexico: 1.5 million; Europe: 406,000). As *Rotarix* is a two-dose vaccine, the number of subjects exposed can be estimated as between a minimum of 6 million and a maximum of 12.3 million.

Up to 11 July 2007, GSK Biologicals has received a total of 802 spontaneous adverse event reports following *Rotarix* administration, of which 323 were serious. The overall reporting rate was thus 6.5 reports per 100,000 doses distributed. For comparison, 1,251 reports had been made on *RotaTeq* following distribution of 6.2 million doses [CDC, 2007]. The reporting rate for *RotaTeq* was thus 20.2 reports per 100,000 doses distributed. However, any comparison of reporting rates is limited by the differences in the geographic distributions of the vaccines, the times during which data were collected, and other factors (e.g., public awareness of the potential association of intussusception after *RotaShield*). The most frequently reported events for *Rotarix* were those that were expected based on the clinical development experience (diarrhea and vomiting) or that are of special interest (intussusception) (see Table 6).

Table 6 Summary of the most frequently reported events for *Rotarix* through spontaneous reporting

System Organ Class	Preferred Term	Number of Events [†]	Reported Frequency per 100,000 doses
Serious and non-serious combined			
Gastrointestinal disorders	Diarrhea	252	2.05
Gastrointestinal disorders	Vomiting	174	1.41
Gastrointestinal disorders	Intussusception	133	1.08

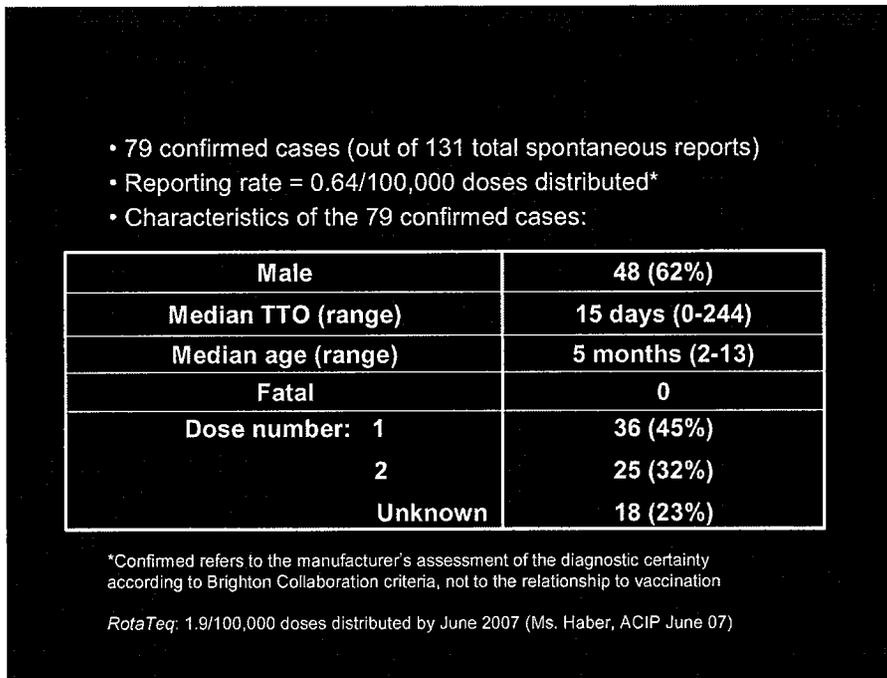
[†] Including regulatory non serious and consumer reports, excluding clinical trial cases

7.1. Adverse Events of Interest in Post-marketing Reports

7.1.1. Intussusception

From launch to 11 July 2007, a total of 140 reports of intussusception have been made to the Company: 131 were spontaneous reports and 9 were from phase IV clinical studies. Of the spontaneous reports, 79 can be considered to be confirmed intussusception cases according to the case definition from the Brighton Collaboration Intussusception Working Group [Bines, 2004a], and 50 cases occurred within 31 days following vaccine administration (See Figure 25).

Figure 25 Post-marketing Experience: Intussusception



The overall reporting rate for confirmed intussusception cases is 0.64 reports per 100,000 doses distributed. For comparison, the reporting rate for confirmed intussusception cases following *RotaTeq* was 1.9 reports per 100,000 doses distributed by June 2007 [CDC, 2007]; comparison of reporting rates is limited as mentioned previously.

As shown in Figure 26, the distribution of the time-to-onset for intussusception indicates no unexpected clustering; the relatively higher rates in the first days after vaccination fits with the overall reporting profile for any other adverse event.

Figure 26 Post-marketing Experience: Distribution of the time-to-onset for intussusception within 31 Days after vaccination with *Rotarix*

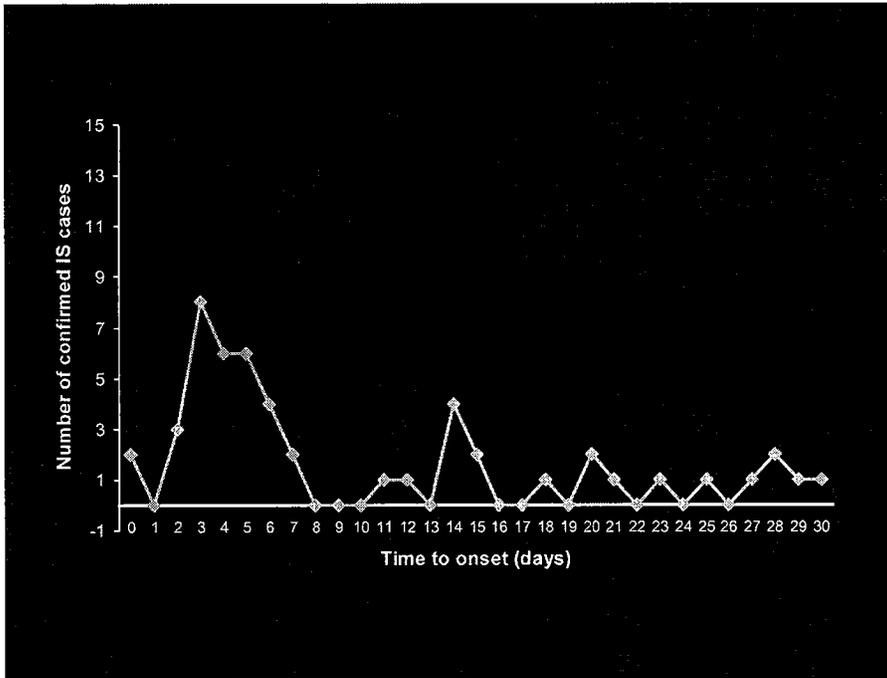


Figure 27 compares the time to onset distribution of spontaneous reports of intussusception following the first dose of three different rotavirus vaccines (*Rotarix*, *RotaTeq* [Haber, 2007] and *RotaShield* [Zanardi, 2001]). As can be seen from Figure 27, the distribution of the time-to-onset is very comparable for *Rotarix* and *RotaTeq* but shows a peak in the 3-7 days interval after vaccination for *RotaShield*.

Figure 27 Post-marketing Experience: Time-to-onset between vaccination and first symptoms, after first dose of *Rotarix*, *RotaTeq* and *RotaShield*

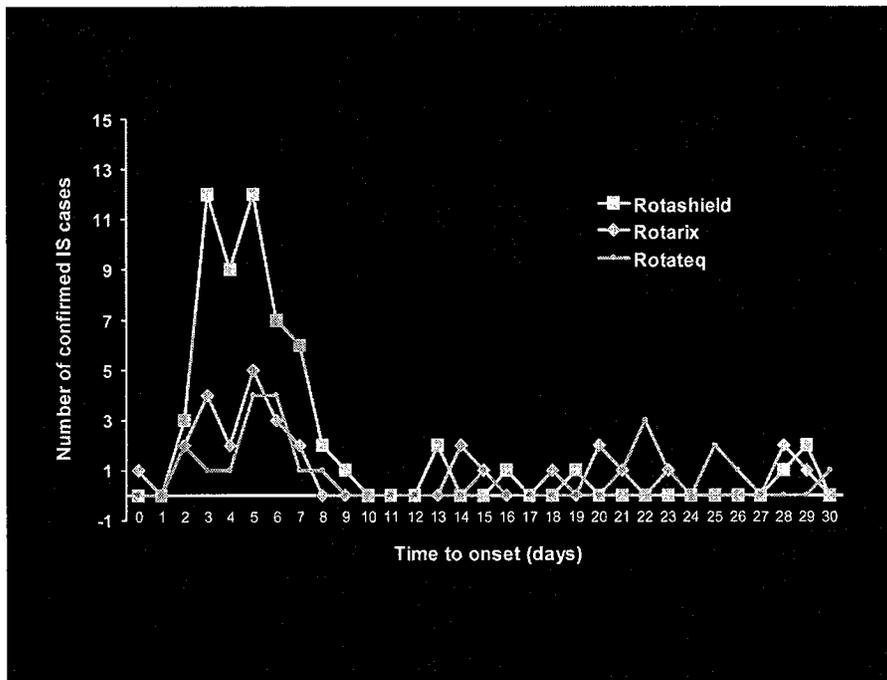


Figure 28 compares the number of observed intussusception cases to the expected number of intussusception cases expected in the vaccinated population based on the known background incidence of intussusception in children under the age of one year, and the number of *Rotarix* doses distributed. An overall background rate of 43.9 and 49.3 per 100,000 person-years in the first year of life was used for Latin America and Europe, respectively, based on the intussusception incidence observed in a GSK conducted epidemiological study in Latin America [Breuer, 2004] and a recently published survey in Switzerland [Buettcher, 2007]. For the countries outside of the EU and Latin America, the lower of these two rates was applied.

The numbers of observed intussusception cases are fewer than the cases expected to occur normally in this population. Aside from providing reassurance about the intussusception rates, the very low observed number is suggestive of underreporting in some countries where the vaccine is currently available. Therefore, an additional comparison was done between the number of cases reported and those expected in Europe only, where the reporting rate is expected to be high. This comparison again shows that the number of cases reported thus far is well below the number expected.

At the October 2007 CDC Advisory Committee on Immunization Practices meeting, consensus was reached that analyses of observed *versus* expected intussusception rates through post-licensure surveillance should include a sensitivity analysis in which the number of cases observed is 75% of the actual number, and that the number of doses distributed is 75% of the actual number. In accordance with these discussions, the Company performed an additional sensitivity analysis (see Figure 28) in which it was assumed that only 75% of all intussusception cases that occurred within 31 days of

vaccination were reported and that the actual number of doses administered would equal 75% of those distributed. Under this scenario, the number of intussusception cases observed would also not exceed the number expected worldwide or in Europe. When applying similar assumptions to the analysis restricted to the less than 7 days interval, the number of cases observed would not exceed the number expected on a global level and would only slightly but not statistically significantly exceed the number expected in Europe (observed/expected ratio = 1.65, 95% CI: 0.45; 4.23).

Figure 28 Post-marketing Experience: Observed versus expected analysis for intussusception cases within 31 days after vaccination with *Rotarix*

Observed versus expected analyses:				
	Observed	Expected	Ratio	95% CI
global	58	496	40	116
EU	8	19	4	5

Sensitivity analysis: 75% of cases reported and 75% of doses distributed				
	Observed	Expected	Ratio	95% CI
global	77	386	53	90
EU	11	14	6	4

In summary, the similarity between the demographics of the spontaneously reported intussusception cases and those observed before the use of rotavirus vaccines, the absence of any unexpected clustering in the time-to-onset of the reported cases, and the observation that the number of cases reported does not exceed the number expected by coincidence do not indicate an increased risk of intussusception following the administration of *Rotarix* in the post-marketing setting.

7.1.2. Blood in stool

From launch to 11 July 2007, GSK Biologicals received 57 reports of blood in stool (0.46 reports per 100,000 doses distributed), excluding reports in which blood in stool was reported in a context of intussusception. Thirty-six reports (63%) were from Latin American countries, where the event blood in stools frequently occurs and where the etiology is heterogeneous. Fifteen reports (26%) were from Europe. Six reports (10.5%) were from the rest of the world. In 33 cases (57.9 %) the event occurred after the first dose, in 7 cases (12.3%) after the second dose, and in 17 cases (29.8%) the dose was reported as unknown.

Rotarix is currently marketed in countries where bloody diarrhea is a common occurrence, and where the etiology for this event includes underlying bacterial and parasitic infections [Black, 1993]. The information received in the reports of blood in stools has insufficient information to rule out the most common alternative causes. The presence of bloody stool after *RotaShield* was also reported by the CDC [Haber, 2004]. According to the authors, these cases may represent occult cases of intussusception that resolved spontaneously before they were diagnosed. Another proposed explanation was that these reports represent coinfection with another organism that causes bloody diarrhea at the time of or shortly after vaccination with *RotaShield*. In the absence of any association between *Rotarix* and intussusception, coinfection with other pathogen is the more likely explanation for the events reported after *Rotarix*.

7.1.3. Kawasaki Disease

In the context of the June 2007 update of the US Prescribing Information of *RotaTeq* with data on Kawasaki disease from post-marketing and clinical studies, GSK Biologicals has reviewed cases of Kawasaki disease reported after administration of *Rotarix*.

Kawasaki disease is a disease of unknown cause, although an infectious agent is suspected. It consists of a variety of symptoms and the natural incidence is different from one region to another, the highest incidence being reported in Asia.

To identify any potential cases of Kawasaki disease, the global post-marketing safety database was searched for any of the following terms: mucocutaneous lymph node syndrome, Kawasaki's syndrome, Kawasaki's disease, Kawasaki syndrome, infantile polyarteritis nodosa, infantile periarteritis nodosa, medium-sized vessel vasculitis, medium vessel vasculitis, vasculitis of medium vessels, or periarteritis nodosa. Since launch of the vaccine on 12 July 2004 in Mexico, no case suggestive of Kawasaki disease has been identified in the global post-marketing safety database.

Up to 11 July 2007, a total of 27 cases of Kawasaki disease have been reported in clinical studies with *Rotarix*. None was fatal and all were reported as not related to the study vaccine. Time-to-onset after last dose of study medication ranged from 3 to 578 days (median 152 days).

The majority of the clinical trial cases (22 of the 27 reported cases) occurred in an ongoing double blind study in Asia enrolling over 10,000 infants randomized in a 1:1 ratio to receive *Rotarix* or placebo. The background rate of Kawasaki disease is known to be much higher in Asia than in other parts of the world (approximately 100 Kawasaki disease cases per 100,000 children-years for children under 5 years of age in Asia, compared to 9-19 cases per 100,000 children less 5 years of age in the US). On 16 June 2007, the Company unblinded these 22 SAEs to allow a more thorough evaluation of any potential association between *Rotarix* and Kawasaki disease. Of the 22 reported cases, 13 occurred among *Rotarix* recipients and 9 among placebo recipients. The associated relative risk of this distribution is not statistically significant [relative risk = 1.4, 95% CI: 0.6; 3.4 (Taylor series)]. The time-to-onset does not suggest any clustering in time-to-onset of the cases overall, nor for the cases occurring in the *Rotarix* group. Only one case

in the vaccine group and one case in the placebo group occurred within 31 days of vaccination.

The five remaining cases occurred following *Rotarix* in studies without placebo group or from studies with imbalanced randomization. The difference in numbers in each exposure group should be taken into consideration when assessing the number of Kawasaki disease cases reported in these studies. These cases did also not present any specific pattern with regard to time-to-onset after last dose of vaccine. One case occurred 12 days after administration of first dose of vaccine; four cases occurred after the second dose of vaccine (55 days, 3 months, 7 months, and 19 months after the second dose, respectively).

To further assess the importance of the cases reported in the clinical studies, the Company compared these numbers to the number of Kawasaki disease cases expected to occur naturally for the vaccine recipients in each of these studies. The number expected was calculated by multiplying the background incidence of Kawasaki disease in the region where the study was conducted with the person-time contributed by each group in the given study. Overall, in the vaccine group the number of reports observed (18 cases) corresponds to the expected number of reports (18 cases).

In summary, the absence of any spontaneous reports of Kawasaki disease since launch, the absence of an imbalance of cases in clinical studies, the absence of any clustering in time and the comparability of the numbers reported to those expected do not indicate an increased risk of Kawasaki disease following the administration of *Rotarix*.

7.1.4. Respiratory Events

From launch to 11 July 2007, there have been 33 reports (reporting frequency 0.26 per 100,000 doses distributed) related to a variety of upper and lower respiratory tract events: bronchospasm (2 cases), pharyngitis and nasopharyngitis (5 cases), pneumonia (4 cases), cough (4 cases), apnea (2 cases), cyanosis (3 cases), dyspnea (4 cases), bronchiolitis (3 cases), respiratory infection (4 cases), and unspecified respiratory disorder (2 cases). The low reporting rate and the heterogeneity of reports related to the respiratory system do not suggest any causal association between these events and *Rotarix* vaccination.

7.1.5. Neurological Events

From launch to 11 July 2007, there were 5 reports of seizures (reporting frequency 0.04 per 100,000 doses distributed). The median age at onset was 3 months (range from 2 to 6 months) and the median time-to-onset was 2 days (range from 0 to 4 days). Three cases reported concomitant vaccinations known be associated with seizures.

Other neurological events reported spontaneously were somnolence (15 cases), depressed level of consciousness (1 case), decreased activity (3 cases), and insomnia and sleep disorder (9 cases). All these reports are rather uninformative, of a mild nature and do not suggest a causal link to the vaccine. Based on the low reported frequency of neurological cases, GSK considers that there is no safety concern with respect to *Rotarix* vaccination and neurological symptoms.

7.1.6. Cases with Fatal Outcome

From launch to 11 July 2007, GSK Biologicals has received 7 reports of fatal cases (0.056 cases per 100 000 doses distributed). Four reports were allegedly associated with an episode of intussusception, but were never medically confirmed. Moreover, the Brazilian Ministry of Health, which made two of these four reports to the Company, later suggested that these cases most likely did not occur.

In the other 3 reports, causes of deaths were reported as follows: an adenovirus infection complicated by severe dehydration, an idiopathic thrombocytopenic purpura 3 hours after vaccination with *Rotarix*, and a rotavirus infection that would have occurred 9 months after vaccination, respectively. For the last case, the Company has received conflicting information on whether or not *Rotarix* was actually administered.

7.1.7. Maladministration

From launch to 11 July 2007, a total of 120 reports of incorrect route of administration (parenteral) of *Rotarix* have been received by the Company.

Of these 120 cases, 27 were associated with non-serious adverse events and 3 were associated with SAEs, all of which resolved. The first SAE was a report of injection site reaction after intramuscular injection (verbatim reported: “except a trace on the skin after injection, no local or systemic reaction occurred”); the subject was hospitalized for observation. The second SAE was a case of respiratory syncytial virus pneumonia one week after vaccination. In the third SAE anaphylactic shock was reported, but the description of the events (tachycardia, pallor, hypotonia, fall in blood pressure and swelling of thigh 30 minutes after vaccination) and of the corrective treatment (monitoring and intravenous glucose) were inconsistent with the reported diagnosis of anaphylactic shock as there were no respiratory or cutaneous symptoms, and epinephrine, corticosteroids, and oxygen were not required to resolve the reaction.

The Company has implemented several measures to reinforce the correct route of administration of *Rotarix*. Pediatricians in countries where *Rotarix* was available were reminded of the appropriate route of administration of *Rotarix* through an “information letter” and other means such as telephone contacts or visits of sales representatives. Additional efforts were also made through changes to the product label, package and leaflet to further emphasize the oral administration route and consequently reduce the risk of maladministration.

7.2. Conclusion

Currently available post-marketing data from spontaneous reporting system, taking into account the intrinsic limitations of such systems, do not suggest any increased risk for intussusception following *Rotarix*, and no new safety signal related to any other events has been detected.

8. PHARMACOVIGILANCE PLAN

Clinical studies and currently available post-marketing data from spontaneous reporting of adverse events outside of the US have shown that *Rotarix* has an acceptable safety profile. These data do not suggest any increased risk for intussusception following vaccination with *Rotarix*, and no new safety signal related to any other events has been detected.

GSK Biologicals is utilizing the worldwide availability of *Rotarix* to study the outcomes of interest in the setting in which they can be most appropriately evaluated. Global pharmacovigilance activities are ongoing outside the US and are planned after US licensure. The ongoing pharmacovigilance activities focus on several safety outcomes which include: intussusception, Kawasaki disease and pneumonia deaths. In addition, a post-licensure study in the US is planned to assess whether there is an association between *Rotarix* administration and intussusception through epidemiological analysis. This study will also include monitoring of Kawasaki disease, convulsions and hospitalizations due to acute lower respiratory tract infections. The specific study design/protocol for the US post-marketing study is under discussions with CBER.

Post-licensure study in the US: In order to generate US specific post-licensure safety data, an observational study is planned to confirm the safety profile regarding any temporal association of intussusception and *Rotarix*, in a routine use setting. The study will also monitor Kawasaki disease, convulsions and hospitalizations due to acute lower respiratory tract infections. The specific study design/protocol is under discussion with CBER. The study is to be designed based on the following considerations: cohort of infants vaccinated in a routine pediatric health care setting; safety data collected prospectively; sufficient (80%) power to detect an increased relative risk of intussusception of 2.5 or greater. The study will be conducted through an existing computerized administrative health database in the US in coordination with CDC and FDA. GSK is currently in the process of identifying sites in the US that will be participating in this post licensure study. The criteria used to select the US health database will be based on, but are not limited to: access to population sufficiently large to provide the required power, a pediatric care setting that allows for routine vaccination with *Rotarix*; ability to link health data files (e.g., a unique identifier for each subject); ability to reliably capture all childhood vaccinations with possibility to identify manufacturer; capacity to reliably capture all outcomes of interest; access to medical records for review; proven track record in conducting drug safety investigations and timely delivery of results. US sites not currently participating in the VSD databases will be preferred.

Active surveillance for intussusception: GSK Biologicals is currently collaborating with researchers at pediatric surveillance units in both Germany [Erhebungseinheit for Seltene Paediatrische Erkrankungen in Deutschland (ESPED)] and the United Kingdom [British Paediatric Surveillance Unit (BPSU)] to assure that intussusception active surveillance systems are established in a European setting. These surveillance systems will provide data for observed *versus* expected comparisons to assess the intussusception risk once *Rotarix* is available, as well as allow monitoring of any large increases in intussusception rates following the introduction of the vaccine. Participating research

organizations provide reports on intussusception active surveillance to GSK Biologicals every six months. These reports are shared with regulatory authorities upon receipt. Initially, GSK Biologicals will commit to active intussusception surveillance in Germany and the UK for two years, after which time, these and other available data will be discussed with Authorities to guide the future of these activities. The pediatric surveillance units use a common method to perform surveillance on selected conditions (monthly surveys of hospital pediatric units and subsequent follow-up through extensive targeted questionnaires). Such an approach has already been used by the Swiss Paediatric Surveillance Unit (SPSU) to provide baseline estimates of intussusception incidence in Switzerland (3.9 per 10,000 live births). In the event that a potential safety signal for any rare disease (such as Kawasaki disease) is identified in ongoing clinical trials and in the US post marketing setting, GSK would liaise with the independent boards governing the conduct of the German ESPED and UK BPSU surveillance studies and propose that, if applicable, the event of interest be added to the list of diseases under surveillance.

Enhanced passive surveillance, including observed *versus* expected analysis for intussusception: GSK Biologicals will closely monitor all worldwide spontaneously reported intussusception cases in markets where *Rotarix* is available. Follow-up of reports will include use of a questionnaire to obtain a more standardized and detailed description of the cases. The number of confirmed intussusception reports following *Rotarix* vaccination will be compared to the number of intussusception cases expected to have occurred by chance in the 31-day post-vaccination period in the population receiving *Rotarix*. The expected estimate will be based on data available from the previously described intussusception active surveillances as well as from published sources. A summary of all reported cases of intussusception will be provided to regulatory authorities every 6 months. Observed *versus* expected analyses are also conducted at 6-month intervals, and reports of these analyses are provided to regulatory authorities.

Self controlled case series (SCCS) post-authorization study in Mexico: This study is planned to continue the assessment of any potential for a temporal association between *Rotarix* administration and intussusception through epidemiological analysis (SCSS analysis) on data gathered actively (daily review of log books/clinical files) and passively through intussusception surveillance in the Instituto Mexicano de la Seguridad Social (IMSS) network throughout Mexico once Universal Mass Vaccination (UMV) starts in Mexico. The study protocol was endorsed by a panel of international experts that included 3 scientists from North America. The final protocol was submitted to CBER, the EMEA as well as to Mexican health authorities. A pilot phase has been started during 2007 and the study launch is planned in early 2008. Analyses will be performed at the conclusion of case enrolment: 660 intussusception cases for the self-controlled case series analysis. An interim analysis is also planned when a total of 360 intussusception cases are recruited. It is anticipated that the interim results will be available 2 years after the initiation of the study and the final case series analysis will be available 3 or more years after study start. The latter assumes that more than 1.5 million infants will have been vaccinated with *Rotarix* by then. GSK will evaluate, in collaboration with the IMSS, the feasibility of actively monitoring hospitalizations due to acute lower respiratory tract infections in a subset of hospitals. The latter investigation would be performed under a separate protocol.

Infants admitted to or cared for at participating pediatric hospitals for definite, probable, possible or suspected intussusception will be identified through daily reviews. Only those intussusception cases classified as definite intussusception will be part of the final analysis. A sample size of 660 subjects (definite intussusception cases) vaccinated with Dose 1 will allow to rule out with 2.5% type I error a relative risk increase within 31 days following Dose 1 above 2.67. Of note, the 95% CI for the relative risk in study Rota-023 is below 2.67, therefore this study will provide additional clinical evidence that *Rotarix* does not increase rates of intussusception.

Because pneumonia-related post-neonatal infant deaths still occur with frequency in Latin America, the setting of the Mexican study will also be used to assess the temporal association between *Rotarix* vaccination and pneumonia-related post-neonatal infant mortality. As mentioned in Section 6.2.2.1, an imbalance warranting further exploration for pneumonia-related deaths was observed in one study (Rota-023) but was not confirmed in subsequent analyses including the integrated safety summary including 36,755 infants receiving *Rotarix* and 34,454 infants receiving placebo from 8 studies. GSK Biologicals has planned to assess the temporal association between *Rotarix* vaccination and pneumonia-related post-neonatal infant mortality through epidemiological analysis (self-controlled case series analysis) on data gathered actively (daily review of log books/clinical files/morgue) and passively through the IMSS network throughout Mexico. Analyses will be performed at the conclusion of case enrolment: 200 pneumonia-related post-neonatal infant deaths.

Strain surveillance through the European Rotavirus Network: To confirm that the introduction of *Rotarix* reduces the relative detection during gastroenteritis episodes of rotavirus strains for which the vaccine is effective, and to monitor for changes in strain distribution after vaccine introduction, GSK Biologicals will monitor the circulation of rotavirus types as *Rotarix* coverage increases through the European Rotavirus Surveillance Network (ERSN). The ERSN is based in a laboratory surveillance system established to detect and characterize circulating rotavirus strains in at least 11 EU countries (Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Slovenia, Spain, Sweden, and United Kingdom) before and after introduction of *Rotarix*. This will allow for the detection and monitoring of rotavirus strains (including the vaccine strain) and characterization of uncommon strains. This surveillance will allow early analyses to detect potential safety signals by comparing observed *versus* expected cases of intussusception.

Vaccine effectiveness: To confirm the effectiveness of *Rotarix* in routine use settings with regard to rotavirus gastroenteritis requiring hospitalization and with regard to circulating rotavirus strains (homotypic and heterotypic protection), GSK Biologicals will assess the effectiveness of *Rotarix* in a site(s) with sufficient vaccine coverage (>30% in children < 1 year of age) with a case-control study. GSK Biologicals intends to adapt the “Generic protocol for Monitoring Impact of Rotavirus Vaccination on Gastroenteritis Disease Burden and Viral Strains” developed by the WHO and CDC with input from internal and external expert partners to conduct a study assessing *Rotarix* effectiveness among children born after the launch of *Rotarix* in Belgium, Singapore and Panama. In Belgium, *Rotarix* was launched in June 2006 and recommended in November 2006 to be

part of the national childhood immunisation schedule. The vaccine has achieved a high level of infant population coverage (around 80%) since its launch.

Genetic stability of vaccine virus: To monitor for the potential occurrence of genetic drifts and shifts in the vaccine strain after introduction in the market, targeted sequencing of a subset of G1P[8] samples from individuals known to have no rotavirus vaccination history will be performed. A setting with sufficient vaccine coverage (>30% for children < 1 year), availability of vaccination history data, and good rotavirus surveillance are critical for this investigation. As mentioned for evaluation of vaccine effectiveness, Belgium is being considered as a study site for evaluation of genetic stability of the vaccine virus.

Vaccine virus transmission: In clinical trials, vaccine strain antigen was detected in stool samples from 7 placebo recipients. A phase IIIB study (Rota-052) is ongoing under US IND to assess horizontal transmission of the vaccine strain between twins within families (a situation with known close contact), and results are anticipated in the third quarter of 2008.

Preterm infants: A phase IIIB study (Rota-054) is ongoing in Europe to assess immunogenicity, reactogenicity and safety of *Rotarix* in preterm infants, and results are anticipated in the third quarter of 2008.

Immunocompromised individuals: A phase II study (Rota-022) is ongoing in South Africa to assess safety, reactogenicity and immunogenicity of *Rotarix* in HIV-infected infants, and results are anticipated in the third quarter of 2008.

9. CONCLUSIONS

Studies of natural rotavirus infection demonstrate that the initial episode of rotavirus gastroenteritis is the most severe. Subsequent infections typically are progressively milder. The major reason for this observation is that infants develop homotypic and heterotypic immunity following infection [Velazquez, 1996; Ward, 1994]. An attenuated human rotavirus vaccine thus should induce protective immunity, and prevent severe diarrhea and its consequences. The clinical data presented in this briefing document confirm this postulate.

Two phase III studies have demonstrated that GSK Biologicals' *Rotarix* live attenuated human rotavirus vaccine administered as a two-dose series to healthy infants starting at 6 weeks of age is highly effective in preventing severe rotavirus gastroenteritis and any rotavirus gastroenteritis during the first year of life. In the two phase III studies, efficacy against severe rotavirus gastroenteritis was 96% in study Rota-036 conducted in Europe and 85% in study Rota-023 conducted in Latin America. Efficacy persisted during the first 2 years of life when the maximum burden of rotavirus gastroenteritis exists. In the two phase III studies, *Rotarix* reduced hospitalizations for rotavirus gastroenteritis by 100% in study Rota-036 and 85% in study Rota-023. In study Rota-036, the need for medical attention was reduced by 92% in *Rotarix* recipients. Significant protection was demonstrated against all major circulating types including G1, G2, G3, G4, and G9 (rotavirus type G9 has more recently emerged as a circulating type in the US). An overall reduction of gastroenteritis disease regardless of presumed etiology was observed among

Rotarix recipients compared to placebo recipients. Importantly, breast-feeding was found to not reduce the protection against rotavirus gastroenteritis among vaccinated infants.

The clinical development program of *Rotarix* comprised clinical studies that enrolled infants from different regions of the world, permitting assessment of protective efficacy in different settings. The population studied in Europe is similar to that in the US in terms of socioeconomic class, and environmental factors such as disease risk and health outcomes. In addition, epidemiology data show similar G type distribution in the US compared with regions in which efficacy has been demonstrated.

The coadministration study Rota-060 in the US demonstrated that coadministration of *Rotarix* does not negatively impact the immune response to any of the antigens (PRP, HBsAg, poliovirus serotypes 1, 2 and 3, diphtheria, tetanus, PT, FHA, PRN, and *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) that are currently included in the CDC's schedule of recommended immunizations for infants in the US.

Study Rota-023 in 63,225 infants has demonstrated no increased risk of intussusception within the 31-day period following any dose of *Rotarix* compared to the placebo by meeting the pre-specified criteria as shown by the risk difference estimate of -0.32/10,000 [95% CI: -2.91/10,000; 2.18/10,000] and relative risk of 0.85 [95% CI: 0.3; 2.42]. There was no temporal cluster of intussusception cases after either dose.

The overall safety profile of *Rotarix* was similar to the placebo control. In the core integrated safety summary, there were fewer SAEs associated with gastroenteritis disease in the *Rotarix* group compared to the placebo group. All other SAEs reported within the 31-day post-vaccination period, including deaths, intussusception, bronchiolitis, pneumonia or nervous system disorder SAEs were reported by similar proportions of subjects in both the *Rotarix* and placebo groups. *Rotarix* was well tolerated when coadministered with routine pediatric vaccines such as DTaP, Hep B, IPV, Hib, pneumococcal 7-valent conjugate vaccine and meningococcal group C conjugate vaccine with no increase in post-vaccination fever or other adverse events compared to placebo administration. The potential for horizontal transmission of vaccine virus was not evaluated in the pre-licensure studies, and is currently being evaluated. Nearly all children will be infected with natural rotavirus by 5 years of age. The limited potential of transmission of vaccine virus should be weighed against the high likelihood of acquiring and transmitting natural rotavirus.

Over 12 million doses of *Rotarix* have been distributed worldwide since launch up to July 11, 2007. The currently available post-marketing data do not suggest any increased risk for intussusception following *Rotarix*, and no new safety signal related to any other events has been detected. GSK Biologicals is utilizing the worldwide availability of *Rotarix* to study the outcomes of interest (intussusception, Kawasaki disease, convulsions, pneumonia deaths and hospitalizations due to acute lower respiratory tract infections) in the setting in which they can be most appropriately evaluated. Global pharmacovigilance activities are ongoing outside the US and are planned after US licensure. The ongoing pharmacovigilance activities focus on several safety outcomes which include intussusception, Kawasaki disease and pneumonia deaths. In addition, a post-licensure study in the US is planned to assess whether there is an association

between *Rotarix* administration and intussusception through epidemiological analysis. This study will also include monitoring of Kawasaki disease, convulsions and hospitalizations due to acute lower respiratory tract infections. The specific study design/protocol for the US post-marketing study is under discussions with CBER.

When administered as a two-dose series to infants starting at 6 weeks of age, *Rotarix* provides significant protection against rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, and G9). Safety with regard to intussusception was demonstrated by meeting the pre-specified criteria, and the overall safety profile for *Rotarix* is similar to the placebo. The results of the clinical studies support the use of *Rotarix* for the US infant population. The risk-benefit ratio for *Rotarix* is overall favorable for the intended population. The availability of *Rotarix* for infants would add measurable value to the current standard of medical care for the infant population in the US.

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