FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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WEDNESDAY,
FEBRUARY 20, 2008

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The Committee convened at 8:30 a.m. in the Hilton Washington, DC North, 620 Perry Parkway, Gaithersburg, MD, John Modlin, MD, Acting Chair, presiding.

PRESENT:

JOHN MODLIN, MD, ACTING CHAIR
CHRISTINE WALSH, RN, EXECUTIVE SECRETARY
SETH HETHERINGTON, MD, INDUSTRY REPRESENTATIVE
VICKY DEBOLD, PHD, RN, CONSUMER REPRESENTATIVE
LISA JACKSON, MD, MPH, MEMBER
JACK STAPLETON, MD, MEMBER
JOSE ROMERO, MD, MEMBER
PABLO SANCHEZ, MD, MEMBER
ERMIAS BELAY, MD, TEMPORARY VOTING MEMBER
ROBERT DAVIS, MD, MPH, TEMPORARY VOTING MEMBER
FRANK DESTEFANO, MD, MPH, TEMPORARY VOTING MEMBER
BRUCE GELLIN, MD, MPH, TEMPORARY VOTING MEMBER
PAMELA MCINNES, DDS, MSC, TEMPORARY VOTING MEMBER
STEVEN SELF, PHD, TEMPORARY VOTING MEMBER
MELINDA WHARTON, MD, MPH, TEMPORARY VOTING MEMBER

PRESENT: (CONT.)

STEVEN ROSENTHAL, MD, FDA
DOUGLAS PRATT, MD, FDA
NORMAN BAYLOR, PHD, FDA

A G E N D A

P-R-O-C-E-E-D-I-N-G-S

(8:33:15 a.m.)

DR. MODLIN: Good morning, everyone. My name is John Modlin, and I am serving as the Acting Chair for this meeting of the VRBPAC Committee. I would like to start out by welcoming the new members to the Committee, Dr. Pablo Sanchez, Dr. Jose Romero, and Dr. Vicky Debold. And I think I'll now turn things over to Christine.

EXEC. SECRETARY WALSH: Good morning, everyone. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the Advisory Committee.

Today and tomorrow's sessions will consist of presentations that are open to the public, as described in the Federal Register Notice of February 1st, 2008.

I would also like to request that

any media inquiries be directed to Ms. Karen Riley from the FDA, Office of Public Affairs.

I would like to request that everyone please check your cell phones, and pagers, and Blackberries to make sure they are off, or in the silent mode. I would now like to read into public record the conflict of interest statement for today's meeting.

The Food and Drug Administration, FDA, is convening the February 20-21st, 2008 meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the Industry Representative, all participants of the Committee are Special Government Employees, SGEs, or Regular Federal Employees from other agencies, and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this Advisory Committee's compliance

with federal ethics and conflict of interest laws, including, but not limited to 18 USC 208 and 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants at this meeting, and to the public.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC 208, Congress has authorized FDA to grant waivers to Special Government Employees, and Regular Government Employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to Special Government Employees, and Regular Government Employees with potential financial conflicts when necessary to afford the Committee their essential

expertise.

Related to the discussion of this meeting, members and consultants of this Committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for the purpose of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and also primary employment.

The Committee will discuss and make recommendations on the safety and efficacy of a rotavirus Vaccine manufactured by GlaxoSmithKline. This is a particular matter involving specific parties, Topic 1.

For Topic 2, the Committee will discuss and make recommendations on the selection of strains to be included in the influenza virus for the 2008-2009 influenza

season. This is a particular matter of general applicability.

For Topic 3, the Committee will discuss clinical development of influenza vaccines for pre-pandemic uses. This is a particular matter of general applicability.

Based on the agenda and all financial interests reported by members and consultants, conflict of interest waivers have been issued in accordance with 18 USC 208(b)(3), and 712 of the Food, Drug, and Cosmetic Act.

Related to Dr. John Modlin, Dr. Modlin's waivers include a consulting arrangement with two firms that could be affected by the Committee's discussions, Topics 1, 2, and 3. The waivers allow Dr. Modlin to participate fully and vote on the Committee discussion.

Related to Dr. Robert Couch, Dr. Couch's waivers include a contract with a firm that could be affected by the Committee's

discussions, Topics 2 and 3. The waivers will allow Dr. Couch to participate fully and vote on the Committee discussions.

FDA's reason for issuing the waivers are described in the waiver documents, which are posted on the FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the written waivers may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building, Rockville, Maryland.

With regard to FDA's guest speaker, the Agency has determined that the information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments.

For Topic 2, Dr. Tony Colgate is the Influenza Technical Affairs Manager at Novartis Vaccines in the United Kingdom. He is a member of several European groups which focus on influenza vaccines and pandemic

issues.

Dr. Seth Hetherington is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Icogen, Incorporated. In addition, Dr. Hetherington's spouse is employed by GlaxoSmithKline. Industry representatives are not Special Government Employees, and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remember members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda, for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with

the Sponsor, its product, and if known, its direct competitors.

I also have one additional announcement, and that is that Dr. Bruce Gellin will be present for this morning's presentations, and will be participating in the morning's discussions. However, he does have an unavoidable obligation this afternoon, and will not be able to return to the meeting after lunch.

That ends the conflict of interest statement. Dr. Modlin, I turn the meeting back over to you.

DR. MODLIN: Thanks, Christine.

I'd like to next ask the members of the Committee to introduce themselves, and where they're from. And I think we'll begin with Dr. Jackson.

DR. JACKSON: I'm Lisa Jackson from the Group Health Center for Health Studies in Seattle.

DR. SANCHEZ: Pablo Sanchez from

University of Texas Southwestern Medical Center in Dallas. I'm a Neonatologist in Pediatric ID.

DR. SELF: Steve Self from Hutchinson Cancer Research Center, University of Washington.

DR. MCINNES: Pamela McInnes, National Institutes of Health.

DR. ROMERO: Jose Romero, University of Nebraska, Omaha, Pediatric Infectious Diseases.

DR. HETHERINGTON: Seth Hetherington from Icogen Research, Triangle Park, North Carolina.

DR. DEBOLD: And Vicky Debold from the National Vaccine Information Center here in Vienna, Virginia.

DR. BELAY: Ermias Belay from the Centers for Disease Control and Prevention in Atlanta, Georgia.

DR. GELLIN: I'm Bruce Gellin with the National Vaccine Program Office,

Department of Health and Human Services.

DR. DAVIS: Bob Davis, Kaiser Permanente Georgia.

DR. STAPLETON: Jack Stapleton, University of Iowa, Iowa City, Iowa.

DR. DeSTEFANO: Frank DeStefano, RTI International in Atlanta.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention, Atlanta.

DR. BAYLOR: Norman Baylor, Food and Drug Administration, Office of Vaccines.

DR. PRATT: Douglas Pratt, Division of Vaccine Applications, Office of Vaccines, FDA.

DR. ROSENTHAL: Steve Rosenthal, Division of Vaccines, FDA.

DR. MODLIN: Thank you. As Christine mentioned, our purpose here today is to provide advice to the Agency, to the Vaccines Division on the safety and efficacy of the GSK Human rotavirus Vaccine. Dr.

Rosenthal, I understand you'll be leading off with the introductory remarks.

DR. ROSENTHAL: Thank you, Dr. Modlin. Good morning. I want to thank everyone, Members of the Advisory Committee for coming today to help the Agency in its evaluation of Rotarix, a new rotavirus vaccine.

After my brief introduction, GlaxoSmithKline will talk in regard to their evaluation of the product. And after a break, I will present CBER's evaluation of the license application.

I want to acknowledge my colleague, Paul Kitsutani, who did the primary work for this presentation. He recently became a father, and that is the reason he's not here with us today.

Rotarix is a live attenuated oral human monovalent rotavirus vaccine derived from human 89-12 strain, which belongs to the G1P(8) type. It is prepared as a lyophilized

formulation with an end-of-life shelf potency of greater or equal to 10 to the 6.0 median cell culture infective dose, or CCID 50 for each dose after reconstitution with liquid diluent. The vaccine contains no preservatives.

The proposed indication for Rotarix vaccination is the prevention of rotavirus gastroenteritis, or GE, caused by G1 and non-G1 types, including G2, G3, G4, and G9 types. It is to be orally administered as a two-dose series to infants 6-24 weeks of age, with the first dose beginning at six weeks of age, the second dose given by 24 weeks of age, and an interval of at least four weeks between doses.

Rotarix has been under a U.S. Core since July 2000; however, many non-Core studies have been conducted thereafter outside the U.S., including the pivotal efficacy and safety study submitted to the BLA.

Pre-BLA meetings involving the applicant and FDA were held from July-

September 2006, and based on an FDA applicant agreement during this period, 10 of the completed Phase 2 and Phase 3 studies were to be submitted to the BLA. An additional Phase 3 study conducted in the U.S. Trial Rota-60, which evaluated non-inferiority of immune responses to routine vaccinations when co-administered with Rotarix was to be submitted to the BLA after study completion. The Rotarix BLA was subsequently submitted to FDA on June 1st, 2007.

So the first question we'll be asking the Advisory Committee: Are the available data presented adequate to support the efficacy of Rotarix in preventing rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, and G9, when the first dose of vaccine is administered beginning six weeks of age, followed by a second dose separated by at least four weeks? If not, what additional information should be provided?

Question 2: Are the available data

presented adequate to support the safety of Rotarix when used in a two-dose series beginning with the first dose at six weeks of age, followed by a second dose separated by at least four weeks? If not, what additional information should be provided?

And, lastly: Are there additional issues that should be addressed in post-marketing studies beyond the applicant's proposed U.S. post-licensure safety study?

Thank you for your attention.

DR. MODLIN: Thanks, Dr. Rosenthal. I understand that GSK's presentation will be led by Dr. Leonard Friedland. I'm wrong. Sorry, Dr. Clair Kahn. I beg your pardon, Dr. Kahn.

DR. KAHN: Good morning, Mr. Chairman, Members of the VRBPAC, FDA and guests. I'm Dr. Clair Kahn, as you see, Vice President of Regulatory Affairs for Vaccines North America for GlaxoSmithKline, and it's my pleasure to introduce our candidate rotavirus

vaccine.

Dr. Leonard Friedland will present the Clinical Development Plan and results for efficacy and safety, and Dr. Thomas Verstraeten will discuss the current post-marketing safety experience, and the proposed pharmaco vigilance plan for the post-licensure period. And then I will return for some concluding remarks.

As noted, the generic name for the vaccine is rotavirus Vaccine Live Oral, and the brand name, which we will use throughout these presentations is Rotarix.

Rotarix, as mentioned by Dr. Rosenthal, is a lyophilized vaccine. It's reconstituted with a liquid diluent containing calcium carbonate buffer, and each one ML contains a dose of at least 10 to the 6L culture infective dose 50 of live attenuated human rotavirus strain.

It is administered in two oral doses beginning at six weeks of age, with an

interval of at least four weeks between first and second dose. The two-dose series should be completed by 24 weeks of age.

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 6-24 weeks of age. rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. By the age of five, as you see here, almost 100 percent of children will have an episode of RVGE, rotavirus gastroenteritis, 15-20 percent of whom will require treatment in a clinic, one in 50 will require hospitalizations, as many as one in 205 will die from this disease. In absolute numbers on the left-hand side, this translates into 114 million episodes of gastroenteritis, 24 million clinic visits, 2.4 million hospitalizations, and over 600,000 deaths in children under the age of five each year.

Not only is there a similar incidence of disease in developing countries, and in developed world, severe RV infections are equally common in the developing world, and in the developed world. They usually occur between three months and 35 months of age.

Looking at the impact of the disease in the United States, industrialized living does little to reduce infection rates. Almost all children, four out of five children, will be affected by RV by their fifth birthday. This amounts to 2.7 million episodes of gastroenteritis in a year, and while better supportive care lessens the risk of hospitalization and death, this 2006 report of Glass, et al. cites 600,000 clinic or emergency room visits, up to 70,000 hospitalizations, and 0 to 60 deaths which occur annually in the United States.

rotavirus is the most common cause of nosocomial acquired diarrhea in children,

and an important cause of acute gastroenteritis in children attending daycare. Hospitalizations for rotavirus can account for as many as 2.5 percent of all pediatric hospitalizations, and of these 17 percent are younger than six months of age.

As I noted, the similar incidence of rotavirus disease between developing and developed countries suggests that both treatment and preventive measures have only a limited impact on the disease burden; and, therefore, vaccination against RV represents an important preventive strategy in controlling the morbidity and mortality of what is a very common pediatric disease.

Studies in the U.S. have shown that G1 here shown in the green, G1, G2, G3 and G4, these types represent the majority of the strains each year. The G1 type, as you see, has been the predominant circulating strain in the U.S. for over 30 years, with an average prevalence of over 70 percent. Now depending

on the year, the prevalence of other common types in the U.S. can vary, and it has ranged from 6 to 15 percent for G2, from 1 to 11 percent for G3, and zero to 3 percent for G4. In the 1990s, the G9 type here in blue appeared, emerging as the fifth most common type.

The distribution of the predominant rotavirus types in North America is concordant with other regions, including here Europe and Latin America, the countries where Rotarix pivotal efficacy and safety trials were conducted.

The rotavirus virion is an icosahedral non-envelope particle 17 nanometers in diameter. The genome of 11 segments of double-stranded RNA is encased by three protein capsids, and in a capsid VVP2 is shown in green, a middle VP6 shown in purple, which is common to all RV strains that cause human disease. Then there's an outer capsid with two outer capsid proteins, VP7, shown in

yellow, which is called the G-protein, and the red structures are VP4, and they are referred to as the P-protein. These G and P proteins induce neutralizing antibodies which are thought to be important in protective immunity. And it's, thus, these proteins that were key targets for vaccine development.

Human rotaviruses are classified into 10G and 11P genotypes. However, five GP combinations constitute 90 percent of human rotavirus strains worldwide, and these are G1-P8, G2-P4, G3-P8, G4-P8, and G9-P8, and it's important to note that genotypes P4 and P8 share cross-reactive epitopes.

So rotavirus vaccine is derived from a G1-P8 human rotavirus strain which was isolated from a child in Cincinnati, Ohio. It's my pleasure to acknowledge Dr. David Bernstein, one of the originators of this vaccine, as he is sitting here in the audience today.

The candidate vaccine was acquired

by Virus Research Institute, now Avant Therapeutics, Inc., who further cultivated the vaccine before conducting successful proof of concept studies with the virus at Passage-33, and GSK next acquired this vaccine and subjected it to further cell passages and cloning of the strain resulting in the vaccine known as RIX4414, a live attenuated human rotavirus vaccine.

RIX4144, and the original unpassaged isolate genome differ by 12 nuclear type mutations, which include for 10 amino acid substitutions. RIX4414 is genetically stable from seed to final vaccine.

The basis for vaccination with a human strain comes from studies of natural RV disease. Studies conducted by Velasquez and others show that rotavirus infection induces immunity against subsequent re-infection episodes of gastroenteritis. Here we show one previous infection, various severities, and two infections confer virtually 100 percent

protection against clinically moderate to severe disease regardless of the serotype.

GSK chose to develop a human rotavirus vaccine in order to mimic human infection, and to provide broad cross-reactive protective immunity using a two-dose vaccine. There's a high degree of homology between human rotavirus vaccine proteins and human rotavirus strains.

Clinical research and development of rotavirus vaccines began in the 1970s with strains isolated from bovine and rhesus hosts. However, the efficacy of these animal-derived vaccines was variable, so animal-human reassortant vaccines were developed. The first of such vaccines was RotaShield, licensed in the U.S. in 1998. RotaShield was a rhesus-human reassortant vaccine given in three doses. This vaccine, however, was withdrawn in 1999 due to safety concerns related to an increased risk of intussusception following the immediate

vaccination period.

The second, RotaTeq, is a three-dose bovine-human reassortant vaccine that was licensed in 2006. And Rotarix is a live attenuated vaccine, as mentioned, derived from a human RV strain administered on a two-dose schedule. The experience with RotaShield set a new standard on the size of pre-licensure trials required to demonstrate the acceptable safety of subsequent vaccines.

Several key considerations were taken into account to determine the global strategy for Rotarix development. As previously mentioned, very large studies of at least 60,000 subjects would be necessary to adequately assess the risk of vaccine-induced intussusception following the market withdrawal of RotaShield. And at that time of uncertainty about where such a vaccine might be developed, because there was nothing then to go to the Third World, the WHO called for manufacturers to extend development programs

to countries with the highest medical need where the benefit-risk would be very clear. The majority of deaths resulting from rotavirus gastroenteritis occur in Southeast Asia, Africa, and Latin America.

Other considerations included the availability of good data on the epidemiology of RV disease, and the epidemiology of intussusception, and a health career infrastructure that could handle the conduct of very large trials.

With this in mind, Phase III clinical development was initiated last year in Latin America, shown here in green, and then we moved to the more industrialized North for a second pivotal trial, which was conducted in Europe, shown here. Additional clinical development was conducted in the U.S., Canada, and many other regions here shown in blue, including the pivotal co-administration study, Study 60, in the United States.

A very nice tabulation of the study characteristics and the demographics with respect to gender and ethnicity in the over 75,000 subjects in the file is presented in the FDA's briefing document in Table One.

The US IND was opened in August 2000, and as development progressed overseas, GSK met with CBER to discuss the use of the two pivotal trials to support U.S. licensure. Following year, a pre-BLA meeting was held to agree BLA content, and in July 2006 the U.S. BLA was filed. Sorry, I beg your pardon, June 2007 the BLA was filed.

It's very important to note that the two pivotal clinical trials conducted in Latina and Europe complied with the criteria defined by the FDA for acceptance of foreign clinical data. The epidemiology of circulating serotypes in Latina and Europe is similar to the United States. The epidemiology of intussusception is similar across the Americas.

The assessment of the pivotal endpoints was objective, such that any potential regional differences in clinical practice could be minimized, and these include the identification of intussusception, the case definition for RVGE, and the use of an internationally accepted scoring system for the severity of gastroenteritis. And, furthermore, as mentioned, all studies were well conducted by experienced investigators, and appropriate ethical standards and good clinical practice.

Rotarix is currently licensed in over 100 countries worldwide, shown here. These include Canada, Mexico, Australia, European Union, with the first launch in Mexico in January 2005. And Rotarix is recommended in several national immunization programs across the world.

Rotarix is the first rotavirus vaccine to be awarded WHO pre-qualification, February of 2007. This allows the United

Nations agencies, such as PAHO and UNICEF, to purchase and use Rotarix for massive vaccination programs. To date, more than 12 million doses of Rotarix have been distributed. Actually, I could say that since the BLA was filed, it's close to 20 million, and have these doses distributed worldwide outside the United States since 2005.

So now I'll turn the podium over to Dr. Leonard Friedland. He's the Executive Director of Clinical Research and Development for Vaccines North America.

DR. FRIEDLAND: Thank you, Dr. Kahn. Members of the VRBPAC, FDA, and guests, I am pleased to be here today to present an overview of the clinical development program for the candidate vaccine, and the clinical trial results in support of the biologics licensing application.

As mentioned by Dr. Kahn, GSK undertook a global development program designed to support license requirements for

initial registration in developing countries, areas of the world where rotavirus vaccine is more urgently needed. And, subsequently, to support licensure requirements in developed countries, including the United States.

Shown on this slide is an overview of the 11 clinical studies submitted in support of licensure of Rotarix in the United States. In these clinical trials, more than 40,000 infants received Rotarix, and more than 34,000 received placebo, over 37,000 infants received a formulation of at least 10 to the 6^{th} median CCID, which is currently marketed outside of the United States, and is the formulation intended for U.S. licensure.

There were six Phase II studies. Objectives in these studies included dose ranging evaluations, and assessments of vaccine efficacy, safety, and immunogenicity. Over 35,000 infants received the licensure formulation in five Phase III studies. Objectives in these studies included vaccine

efficacy, safety, including intussusception, manufacturing lot consistency, and immunogenicity of Rotarix in the context of co-administered vaccines.

Ten of the studies were prospective, randomized, blinded, and placebo-controlled. In all 11 studies, infants enrolled were healthy and received their first study vaccine dose between five and seventeen weeks of age. In the Phase III studies, the first dose was administered between six and fourteen weeks of age, and the second dose administered one to two months after the first dose.

Vaccine efficacy was evaluated through two years, or two rotavirus seasons after vaccination. Two Phase III studies, Studies Rota-023, and Rota-036, are pivotal to the proposed efficacy indications. Safety was evaluated in all studies, and one particular study, Rota-023, was specifically designed and powered to assess intussusception as the

primary endpoint.

Immunogenicity was evaluated, and co-administration of routine infant vaccines according to local recommendations were allowed in nine of the eleven studies. One study, Rota-060, conducted in the United States, included all of the vaccine antigens currently administered to U.S. infants.

The clinical data that I will review with you today are the following; efficacy data from the two Phase III studies, Study O-23 conducted in Latin America, and Study O-36 conducted in Europe. I will present immunogenicity data in terms of IGA seroconversion and vaccine take, co-administration data with U.S. licensed vaccines, and data on fecal antigen and live virus shedding.

I will conclude the clinical trial presentation with a review of safety data on intussusception, serious adverse event data from an integrated summary of safety, events

of clinical interest, reactogenicity data from the integrated summary of safety, and conclude with a review of representative reactogenicity data from studies conducted in Europe, and the United States, and Canada.

Prior experience with live oral vaccines, such as oral polio virus and the first licensed rotavirus vaccine, RotaShield, demonstrated variable vaccine efficacy and immunogenicity in developed and developing world countries, generally lower in developing world countries. Participating factors may include diverse populations, socio-economic class differences, interaction with co-administered vaccines, and host factors, such as maternal antibodies, breast feeding, interfering enteric pathogens, and malnutrition. Therefore, GSK conducted vaccine efficacy trials in countries of both the developed and the developing world.

Two Phase III studies, Rota-023 conducted in Latin American, and Rota-036

conducted in Europe, as mentioned, are pivotal to the proposed efficacy indications. I will now review these two Phase III efficacy studies.

The first efficacy study results come from Study Rota-023, a Phase III efficacy and safety study conducted in 11 countries in Latin America, and in Finland. Over 63,000 infants were enrolled and vaccinated in this trial. Please note that vaccine efficacy was only studied in this study in the 11 Latin American countries.

This is a schematic of the 023 Study. I'll walk you through this a bit. Infants six to thirteen weeks of age were randomized one-to-one to receive Rotarix or placebo, and a second dose was given one to two months later. There were no feeding restrictions in this trial. Routine immunizations, except oral polio virus vaccine, were co-administered according to local recommendations. All infants were

followed for 30 to 90 days after receiving their second dose of study vaccine. This cohort was followed for a median of 100 days after dose one.

In the presentation, I will refer to this follow-up period as the safety surveillance period. The safety surveillance period is illustrated on this slide by the green bar. A subset shown by the white bar on the slide, only from the 11 Latin American countries, were followed through one-year of age for vaccine efficacy analysis. And infants from 10 of the 11 Latin American countries, as shown by the red bar, were followed through a second year for vaccine efficacy analysis.

The primary objective of this study was to determine if two doses of Rotarix can prevent severe rotavirus gastroenteritis caused by circulating rotavirus strains starting from two weeks after dose two until one year of age. Secondary objectives

included efficacy against G1 and non-G1 types, efficacy using the Vesikari efficacy scale, and efficacy through two years of age.

The case definition for severe RVGE was diarrhea, three or more loose stools in a 24-hour period with or without vomiting that required hospitalization and/or rehydration therapy in a medical facility. This case definition will subsequently be referred to as the clinical case definition.

rotavirus antigen in stool was detected by ELISA. rotavirus type was determined by reverse transcriptase PCR, followed by reverse hybridization assay or option sequencing, as needed. This methodology allowed for discrimination between G1 vaccine virus and wild-type G1 rotavirus.

Efficacy endpoints included protection against severe rotavirus gastroenteritis as assessed by the clinical case definition, and by the Vesikari scale. The Vesikari scale is an internationally

accepted and widely used 20 point scoring system in which severity of gastroenteritis episodes is assigned according to the intensity and duration of diarrhea and vomiting, fever, dehydration, and type of treatment. This scale has also been used in efficacy trials with the previous licensed RotaShield vaccine. Severe gastroenteritis on the Vesikari scale is defined as a score greater than or equal to 11.

Endpoints also included efficacy against RV hospitalizations, and all-cause severe gastroenteritis, rotavirus type-specific efficacy, and efficacy in the second year after vaccination. Vaccine efficacy in this, and in the other Phase III efficacy study which I will soon speak about, was evaluated through two years after vaccination as the majority of rotavirus in children occurs under the age of two.

I'd like to take a moment to orient you to this slide presentation, which you'll

see again. Efficacy outcomes are shown on X axis. The numbers at the bottom of the efficacy bars represent numbers of cases reported in the Rotarix group. Well, I can't figure out to how it, shown by V. And rates in the placebo group are shown at the bottom of the bars by P. Vaccine efficacy rates with 95 percent confidence intervals are shown at the top. Vaccine efficacy rates with 95 percent confidence intervals are shown at the top of each efficacy bar.

As shown on this slide, Rotarix was highly efficacious. Through the first year of life, vaccine efficacy was 85 percent against severe RVGE using both the clinical case definition and the Vesikari scoring system. Efficacy was 85 percent against rotavirus gastroenteritis hospitalizations, and 40 percent against all-cause severe gastroenteritis regardless of etiology.

This slide shows efficacy rates through two years after vaccination. Efficacy

was sustained at similar high rates through two years of age against all of the outcomes studied.

Type-specific efficacy against severe RVGE through two years of age is shown on this slide. Statistically significant efficacy was demonstrated for common circulating RV-types G1, G3, G4, and G9.

The second Phase III efficacy study was Study Rota-036, conducted in six countries throughout Europe. The majority of the infants enrolled in this study were from Finland. This is a schematic of the 036 study, and I'll walk you through it briefly.

Nearly 4,000 infants six to fourteen weeks of age were randomized two-to-one to receive Rotarix or placebo, and a second dose was given one to two months later. There were no feeding restrictions in this study. All of the infants received concomitant vaccination with DTaP, HepB, IPVHIB combination vaccine, and a subset

received concomitant vaccination with pneumococcal conjugate or meningococcal-C conjugate vaccine. All infants were followed through the first rotavirus season after vaccination, and again through the second rotavirus season after vaccination.

Whereas, in Study O-23 the primary objective was efficacy against severe RVGE, objectives in Study-O36 included efficacy against any severity and severe RVGE during the first rotavirus season after vaccination. Secondary objectives were similar to those in Study O-23 with the addition in Study O-36 of an efficacy assessment against medically attended RVGE. Medically attended RVGE was defined as gastroenteritis that required a contact or a visit with a medical provider, evaluation in an emergency department, or hospitalization.

The case definition for rotavirus gastroenteritis was diarrhea, three or more loose stools in a 24-hour period with or

without vomiting. Severity was assigned using the previously discussed Vesikari severity scale. rotavirus detection and typing methodology was the same as in Study O-23.

Efficacy endpoints in this study were similar to those in Study-O23 with the addition in Study O-36 of efficacy assessment of any severity of RVGE, of medically attended RVGE, and efficacy from dose one up until dose two.

In this second Phase III study, Rotarix was also highly efficacious. Through the first rotavirus season after vaccination, efficacy was 87 percent against any severity, and 96 percent against severe RVGE. Rotarix was 100 percent effective in preventing RVGE hospitalizations, and 92 percent effective in preventing RVGE which required medical attention.

Vaccination also has the potential to reduce the overall burden of gastroenteritis disease during early childhood

because RV infections are the most important cause of severe gastroenteritis in young children. Reductions in hospitalizations, as shown on this slide, for all-cause gastroenteritis regardless of etiology was 75 percent.

Efficacy in this study was sustained through two rotavirus seasons after vaccination against all outcomes. In this study, 82 percent of the infants received their first dose of study vaccine prior to the rotavirus season, 10 percent of the infants had completed the full two-dose series before the start of rotavirus season. As a result, a small number of rotavirus cases occurred prior to the time the infants received their second dose of vaccine. Thus, vaccine efficacy from dose one up until dose two could be analyzed, and was shown to be 90 percent against any severity, and 100 percent against severe RVGE with wide confidence intervals given the small number of cases.

In contrast to Study O-23, in Study O-36 through two rotavirus seasons there were sufficient number of cases of all serotypes to assess efficacy for all common circulating strains. Statistically significant vaccine efficacy was demonstrated for all circulating rotavirus types, including Type G2.

In summary, Rotarix is highly effective in preventing RV gastroenteritis. Rotarix prevents severe RVGE, any severity RVGE, RV hospitalizations and medically attended visits due to rotavirus, and efficacy was observed as early as after the first dose. As expected, a small difference in vaccine efficacy was observed in the developing world countries in Latin America compared to the developed world countries and Europe.

Serotype-specific data indicate that Rotarix prevents gastroenteritis caused by all common circulating types. Rotarix efficacy persists through at least two years or two rotavirus seasons after vaccination.

I'd like to now switch focus to immunogenicity data. Immunogenicity of Rotarix was assessed by IGA seroconversion and vaccine take. Immunogenicity results from a co-administration study with U.S. licensed infant vaccines will be presented, as will data on fecal antigen and live virus shedding.

A relationship between antibody responses to rotavirus vaccination and protection against RVGE has not been established. However, serum anti-RV IGA antibodies are a commonly used indicator of the immune response to rotavirus. Seroconversion was used as a measure of Immunogenicity in the clinical trials, and was defined as a post-vaccination anti-rotavirus IGA antibody concentration greater than or equal to 20 units per ml in subjects who were negative for rotavirus prior to their first dose.

In the pivotal Phase III safety and efficacy studies after the two-dose regimen,

87 percent of the infants in Study O-36, and 77 percent of the infants in Study O-23 seroconverted. This difference in immunogenicity between Europe and Latin America is consistent with previous observations using other live oral vaccines. Efficacy, especially against severe RVGE paralleled, but was always higher compared to antibody response indicating that the antibody response tends to underestimate the level of protective immunity elicited by the vaccine.

It has been observed that in some cases after vaccination or natural infection there is no detectible serum IGA antibody response, although rotavirus antigen in stools is detected for several days or weeks indicating that virus replication has taken place. Therefore, in addition to seroconversion, in selected studies and subsets of subjects vaccine take was assessed as a combined endpoint of serum IGA antibody seroconversion and/or stool rotavirus antigen

positivity in infants negative for rotavirus prior to their first dose. AS shown on this slide, across the clinical trials, vaccine take rates ranged from 73 percent to 98 percent.

Rotarix was investigated in U.S. infants in a Phase III study when co-administered with the U.S. licensed routine infant vaccinations, Pediarix, Prevnar, and ActHIB. The study design is shown on this slide. Infants in the co-administration group received Rotarix concomitantly with Pediarix, Prevnar, and ActHIB, and infants in the separately administered group received Rotarix one month apart from the routine vaccines.

The objective of this study was to demonstrate that co-administration with Rotarix does not impair the immune response to any of the antigens contained in each of the vaccinations currently included in the ACIP Infant Immunization Schedule.

The pre-specified criteria for

demonstrating non-inferiority of antibody responses at one month after dose three of Pediarix, Prevnar and ActHIB were met for all 17 co-administered antigens, namely, the lower limits of the 95 percent confidence interval for the treatment difference in seroprotection rates or GMC ratios for the respective antigens as listed on this slide exceeded the pre-specified non-inferiority criteria. The results from this study demonstrate that Rotarix does not negatively impact the immune responses to any of these routine vaccine antigens.

Fecal rotavirus antigens excretion is a feature of natural wild-type rotavirus infection. Up to 30 percent of children with rotavirus gastroenteritis continued to excrete antigen for more than 21 days after the onset of symptoms, and antigen shedding has been detected for as long as 57 days after disease onset in immunocompetent infants.

As Rotarix is a live attenuated

human rotavirus vaccine, after oral administration excretion of rotavirus antigen is expected in the absence of GE symptoms, and is an indication of vaccine activity.

Viral shedding following Rotarix administration was evaluated by two methods. The first was the presence in stool of rotavirus antigen demonstrated by ELISA. The ELISA test detects the presence of the highly conserved antigen VP-6 from infectious particles, as well as from non-infectious viral debris. However, it is important to note that detection of antigen does not necessarily imply the presence of infectious rotavirus. Therefore, the presence of live rotavirus particles in stool detected by cell culture was also evaluated.

Fecal rotavirus antigen shedding, as assessed by ELISA, was studied in a subset of subjects in seven of the eleven studies. Shown on this slide is representative data in Study Rota-033, in which antigen shedding

measured by ELISA was assessed at multiple time points after each dose. After the first dose, as shown in blue, the rate of antigen shedding measured by ELISA peaked at 50 percent on day seven, was 20 percent at day 15, and antigen shedding was not detected at day 30. Shedding, as might be expected after the second dose was lower, and is shown by the yellow bar, peaked at 17 percent on day three, and was not detected at day 10.

As mentioned previously, detection of antigen does not necessarily imply the presence of infectious rotavirus. In the two studies shown on this slide, all stool samples collected at day seven after the first vaccine dose that were ELISA-positive for rotavirus antigen and with sufficient quantity of stool remaining were tested for the presence of live rotavirus in cell culture by indirect fluorescence. The percentage of vaccinees with live rotavirus 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 rotavirus. Thus, it was estimated that approximately 26 percent of the infants were shedding live rotavirus at day seven after dose one in these two studies.

In summary, the data presented show that Rotarix is immunogenic. Rotarix can be administered with the routine recommended infant vaccines in the United States without impacting the immune response to antigens present in DTaP, HepB, IPV/Hib, pneumococcal conjugate, and HIB vaccines. Live virus shedding was reported in approximately 26 percent of subjects on day seven after dose one.

The overall clinical trial database, which will be reviewed shortly, shows that Rotarix is not associated with an increase in GE symptoms in vaccine as compared to placebo recipients. Nearly all children will be infected with natural rotavirus by an

early age. The limited potential of transmission of attenuated human rotavirus strain should be weighted against the high likelihood of acquiring and transmitting natural rotavirus.

The last section of the safety data presentation is vaccine safety. I will present data from Study O-23, which was the pivotal study which evaluated intussusception. An integrated summary of safety serious adverse event data, information on events of clinical interest, integrated summary of safety reactogenicity data, and reactogenicity data from studies conducted in Europe, and the United States, and Canada will be reviewed.

This is a schematic of Study O-23, which I showed earlier. As a reminder, all 63,000 infants were followed through the safety surveillance period noted on the slide by the green bar. The safety surveillance period was a median of 100 days after dose one.

The primary endpoint for safety was a case of intussusception diagnosed within 31 days of receiving the first or second dose of vaccine. Intussusception cases were detected by independent complimentary methods. All hospitals and study areas were informed about the study, and relevant hospital departments were advised to contact study personnel regarding each case of intussusception evaluated. Parents of participating infants were informed about symptoms consistent with intussusception, and instructed to seek medical advice at the nearest hospital if symptoms suggestive of intussusception appeared, and to inform the investigator.

At each study visit or contact the investigators queried each subject's parent on whether the infant had been evaluated in a hospital or emergency department for a complaint that led to abdominal surgery, or had an abdominal radiology procedure. Every affirmative answer was followed with a

complete case investigation by the study personnel. All potential intussusception cases were reviewed by an Independent Clinical Events Committee composed of a pediatric gastroenterologist, surgeon, and radiologist who remained blinded to treatment allocation and characterized cases of intussusception as definite, probable, or possible using the Brighton Collaboration Intussusception Criteria.

As an additional layer of safety monitoring, an Independent Data Monitoring Committee was established to monitor the safety of the Rotarix development program. The IDMC had the authority to unblind the data.

Before reviewing the study's primary safety objective, it's important to mention that the criteria for meeting the study's primary objective were revised during the course of the study when the trial remained fully blinded. The reason is the

following; when the study was initially designed, we used available information on age-specific background rates of intussusception. At the time, the most reliable information was available from the United States. During the course of the trial, updated information on estimates of age-specific background rates of intussusception in Latin America were obtained through a concurrent prospective epidemiology study conducted in the same Latin American countries. The study showed that although the overall rates of intussusception in Latin America were comparable to those in the United States, the peak incidence started one month earlier Latin American coincident with the time of the second dose of vaccine administration in Study O-23.

This finding supported by a higher than expected overall incidence of intussusception cases in the clinical trial led to the conclusion that the original

assumption was no longer appropriate. Accordingly, before any analyses were performed, the criteria for meeting the primary objective were revised. This change was discussed with the study's IDMC, and endorsed prior to implementation when the trial remained fully blinded.

After the adjustment to the primary endpoint, the primary safety objective was set as listed on this slide. The primary objective would be met if the upper limit of the two-sided 95 percent confidence interval of the risk difference for intussusception within 31 days after vaccination was below 6 per 10,000, and there was no statistical significant increase in the incidence of intussusception within 31 days after vaccination defined as the lower limit of the two-sided 95 percent confidence interval for the risk difference was below zero.

Considering an incident rate of 3 to 5 definite cases of intussusception for

10,000 infants within 31 days in the placebo group, a sample size of 60,000 had more than 86 percent power to meet the primary objective if the risk difference was truly zero. A secondary safety objective was the occurrence of all serious adverse events during the study. Now on to the intussusception results.

From dose one through the end of the safety surveillance period, among the over 63,000 infants enrolled and vaccinated, there were 27 investigator-diagnosed intussusception cases. The Independent Clinical Events Committee adjudicated one case as probable, and 26 cases as definite. Among the 26 definite cases, 13 were diagnosed within 31 days of a dose of study vaccine, 6 cases in the Rotarix group, and 7 cases in the placebo group, 12 cases were diagnosed between 31 days of a dose of study vaccine, and the end of the safety surveillance period. The next two slides present additional information on the intussusception cases which are reported.

This slide shows the adjudicated definite intussusception cases. Within 31 days of any dose, there were six cases in the Rotarix, and seven in the placebo group. The relative risk was 0.85, and the risk difference was -.32 per 10,000. Within the safety surveillance period, which was a median of 100 days after dose one, there were nine cases in the Rotarix, and sixteen in the placebo group. The relative risk was 0.56, and the risk difference was -2.23 per 10,000.

The safety results from this study demonstrate that Rotarix is not associated with an increased risk of intussusception. In addition, the characteristics of the intussusception cases were reviewed, and they were similar in subjects who received Rotarix or placebo.

Illustrated on this slide are the 13 definite intussusception cases within 31 days of any dose by day range in relation to dose. As you can see, the cases occurred

sporadically. There was no clustering of intussusception cases within seven or fourteen days after any vaccine dose. Specifically, there were no intussusception reported within 14 days of dose one in any group, which was the period of greatest risk of intussusception associated with RotaShield.

In pivotal safety Study O-23, the primary safety hypothesis with regard to intussusception was satisfied. Within 31 days of any vaccine dose, the upper limit of the two-sided 95 percent confidence interval of the risk difference was below 6 per 10,000, and the lower limit of the 95 percent confidence interval of the risk difference was below zero, demonstrating no statistical increase in intussusception incidents.

In Study O-23 within 31 days of any dose, the relative risk was .085 with an upper limit of 2.4, and the risk difference was -.32 with an upper limit of 2.18. There was no clustering of intussusception cases within

seven or fourteen days of any dose.

Cases of intussusception were also captured in all of the eleven clinical trials, which included different formulations of Rotarix. In all clinical trials, within 31 days after vaccination, there were 10 cases of intussusception in Rotarix, and seven in placebo subjects, with a relative risk of 1.3. Among intussusception cases which occurred regardless of time to onset after vaccination, in all placebo-controlled trials there were 18 cases in Rotarix, and 22 in placebo, with a relative risk of 0.72. In summary, the clinical trial database on intussusception provides a high level of confidence that Rotarix is not associated with intussusception.

An integrated summary of safety of all randomized placebo-controlled trials submitted in the licensing application was performed. The Core Integrated Summary of Safety, which I'll call the Core ISS, includes

eight randomized placebo-controlled trials, and compares placebo to Rotarix at potency greater than or equal to 10 to the 6^{th} median CCID 50, the potency licensed for use outside of the United States, and proposed for use in the United States. The ISS includes data on solicited adverse events, unsolicited adverse events, and serious adverse events.

The relative risk accounting for study effect with the exact 95 percent confidence interval of Rotarix versus placebo was estimated for each safety endpoint. Statistical imbalances for each safety endpoint were defined as the 95 percent confidence interval for the relative risk excludes one. Due to the multiple comparisons between the groups without adjustment for multiplicity, imbalances between groups should be interpreted with caution, as it is possible that these findings may have occurred by random chance.

In the Core ISS, including over

36,000 infants receiving Rotarix, and over 34,000 infants receiving placebo, at least one serious adverse event was reported by similar numbers of subjects in both groups. The most common serious adverse events occurring within the 31-day post-vaccination period after any dose reported with a frequency of greater than 0.1 percent in either group were bronchiolitis, pneumonia, and gastroenteritis. Bronchiolitis and pneumonia were reported at similar rates in both groups. As would be expected, given the protective effect of Rotarix against gastroenteritis, gastroenteritis was reported more frequently in the placebo group.

Compared to placebo subjects, Rotarix subjects reported significantly less diarrhea, gastroenteritis, and dehydration in keeping with the protective effect of Rotarix against gastroenteritis. All other serious adverse events reported within the 31-day post-vaccination period, including deaths,

intussusception, nervous system disorders, and as previously mentioned, bronchiolitis and pneumonia, were reported by similar proportions of subjects in both the Rotarix and the placebo groups.

Although the ISS did not show any significant imbalances in favor of the placebo group, the company has identified six events worthy of further exploratory analysis and follow-up. These events were identified either because they were highlighted in the context of another rotavirus vaccine, or because they were found to be occurring at higher rates following Rotarix compared to placebo in single studies.

The first event, bloody stools, was reported as part of the spectrum of gastrointestinal illness related to RotaShield. Hematochezia is also a clinical sign of intussusception, and information on Hematochezia is included in the Rota Teq U.S. package insert. The second and third events,

Kawasaki disease and convulsions, have been discussed in the context of Rota Teq. Convulsions and the remaining events, pneumonia deaths, pneumonia and bronchitis are events of clinical interest because an imbalance was found during exploratory analyses of single Rotarix studies. It should be noted that for each of these events, the imbalance was only noted in a single study, and not in any other study, or in the Core Integrated Summary of Safety.

The pivotal safety results for this licensing application come from the pooled Integrated Summary of Safety. In the Core ISS, there were no hematochezia serious adverse events, or cases of Kawasaki disease within 31 days of vaccination. For the four events of clinical interest where an imbalance was noted in a single study, in the Core ISS within 31 days of vaccination there were no imbalances for convulsions serious adverse events, pneumonia deaths, pneumonia serious

adverse events, or bronchitis serious adverse events. Because of their clinical importance, I will discuss the following events of clinical interest in more detail; Kawasaki disease, convulsion, and pneumonia deaths.

In the completed and ongoing clinical trials, including more than 90,000 subjects, a total of 27 cases of Kawasaki disease have been reported following Rotarix or placebo. Five of these reports occurred in trials that were either not placebo-controlled, or not one-to-one randomized, and their importance is difficult to interpret. The remaining 22 cases occurred in Southeast Asia, where the background rate of Kawasaki disease is known to be higher than in other parts of the world.

This past June, GSK unblinded these 22 cases. The distribution of these cases is 13 in the Rotarix, and 9 in the placebo group. The associated relative risk is 1.4, and the 95 percent confidence interval includes one.

Among all 27 reports, time to onset after vaccination does not suggest any clustering in either group. Only three cases occurred within 31 days after vaccination, two cases in the Rotarix, and one in the placebo group.

The currently available data do not indicate an increased risk of Kawasaki disease associated with Rotarix. GSK will further investigate Kawasaki disease in the post-marketing setting.

Before reviewing data on convulsions and pneumonia deaths, it is important to mention that in Study O-23, the primary safety objective was the occurrence of the serious adverse event intussusception. Multiple comparisons of other serious adverse events were made between the Rotarix and placebo group for exploratory purposes to evaluate potential imbalances. The reported serious adverse events in Study O-23 were coded to 24 different system organ classes, and 265 different preferred terms according to

the MedDRA Classification system. Asymptotic P values were used as an aid to highlight potential imbalances worth further clinical evaluation. Thereafter, the assessment of such imbalances should be based on thorough qualitative clinical evaluation.

GSK has evaluated any potential signal. We reviewed cases coded to similar preferred terms. We've reviewed data from other clinical trials, consulted with the study's IDMC, reviewed the clinical characteristics of each case looking for consistent patterns, and checked for symptom onset in close proximity to vaccination.

In the exploratory analysis of serious adverse events, imbalances in favor of Rotarix were noted for diarrhea, vomiting, gastroenteritis, and dehydration. These observed differences most likely reflect efficacy of Rotarix in preventing gastroenteritis-related symptoms.

In the exploratory analysis of

SAEs, imbalances in favor of placebo were noted for urticaria, convulsion, and pneumonia deaths. A brief mention first about the urticaria serious adverse events. Four of the five infants who developed urticaria developed the urticaria between 15 and 82 days after dose one. All four infants went on to receive a second dose of Rotarix without a recurrence of urticaria or other symptoms. The fifth infant had onset day four after dose two. No cases of anaphylaxis or drug hypersensitivity were reported in any of the Rotarix subjects. These observations, in our opinion, are inconsistent with an increased risk of immediate hypersensitivity to Rotarix.

Now on to discussion of the convulsions serious adverse events. Within the whole safety surveillance period in Study O-23, 16 cases of convulsion were reported in Rotarix, and 6 in placebo subjects. Considering convulsions within 31 days after vaccination, the time window that might be

considered the most relevant for biologic plausibility, there were seven convulsions reported in the Rotarix, and five in the placebo group.

The investigators in this study reported new onset seizures under five different diagnoses. These were convulsion, epilepsy, grand mal convulsion, status epilepticus, and tonic convulsion. To better capture all seizures, reports for all serious adverse events related to these five convulsive disorders were grouped together for an exploratory analysis, which showed that during the whole surveillance period there were 20 convulsion-related cases in the Rotarix, and 12 in the placebo group. Within 31 days after vaccination, there were seven convulsion-related cases in the Rotarix, and nine in the placebo group.

This finding in Study O-23 was further investigated. A review of the individual case histories revealed that many

subjects in both the Rotarix and the placebo groups had pre-existing or concurrent medical conditions as risk factors. A temporal association related to vaccination was not established. Imbalances were not observed when pooled terms related to convulsions were analyzed. In addition, imbalances in convulsion-related SAEs were not observed in the other large Phase III study Rota-036, or in the Core Integrated Summary of Safety.

The currently available data do not suggest a causal relationship between Rotarix and convulsions. Further assessment is planned in the post-marketing setting, and these post-marketing plans will be discussed later in the presentation.

A discussion on the pneumonia deaths now. Study 0-23 was not designed to study the effect of vaccination on fatalities, and the study was not controlled for factors associated with higher post-neonatal fatality, such as prematurity, age of mother, smoking

exposure, and nutritional deficiencies. In this study, when looking at the entire safety surveillance follow-up time, there were 56 deaths in the Rotarix, and 43 deaths in the placebo group, a difference that is not statistically significant.

A blinded Independent Safety Review Committee appointed by the study's IDMC reviewed each death, and assigned a primary cause of death. Among multiple exploratory analyses performed, the only potential imbalances noted was for death coded to the preferred term pneumonia. Several supplementary analyses were performed to assess the relevance of this finding.

First, as pneumonia could be reported under various terms, an additional exploratory analysis was performed combining preferred terms that were related to pneumonia. During the whole surveillance period, there were 16 pneumonia-related deaths in the Rotarix, and six in the placebo group.

Second, we looked at whether this imbalance was replicable in other studies. There are no studies that have been completed to-date in which a comparable number of deaths have occurred.

As a next step, we reviewed the individual cases to look for patterns that may suggest a relationship to vaccine. A review of the cases shows that there were no unique or distinguishing clinical characteristics, consistent patterns, or common chest x-ray findings. Seven of the sixteen cases had symptom onset between day zero and 30 after vaccination. Within 30 days after vaccination, the time window that might be considered the most relevant for biologic plausibility, two of the cases occurred within one week of vaccination, two in the second week after vaccination, two in the third week after vaccination, and one in the fourth week after vaccination. This absence of clustering does not suggest a causal association.

Nine of the sixteen infants had symptom onset beyond 30 days after vaccination occurring between 31 and 199 days after vaccination. Five of the sixteen infants had pre-existing conditions, risk factors, or alternative diagnoses that could have contributed to the pneumonia.

One would expect that a vaccine-associated signal in pneumonia deaths would be part of a clinical spectrum of vaccine-associated pneumonia-related disease, including non-fatal severe pneumonia resulting in hospitalization. Therefore, an additional analysis was performed to evaluate pneumonia-related hospitalizations. In the previous slide, I was speaking of pneumonia deaths. On this slide now we're going to look at pneumonia hospitalizations in Study O-23.

As mentioned, this slide shows the additional exploratory analyses on all hospitalizations coded to the various pneumonia-related preferred terms. Let me

remind you that in Study O-23, the parents and guardians of the infants in the study were contacted by study personnel at least every four days, and emergency department and hospital admission logs were systematically reviewed. There were approximately 275 hospitalizations for pneumonia in both groups, numbers that would have been large enough to detect an imbalance if vaccination was associated with serious adverse respiratory outcomes.

These data show that the observed imbalance in pneumonia-related deaths among Rotarix recipients was not supported by observation of other pneumonia-related serious adverse events.

An Independent Data Monitoring Committee has monitored the safety aspects of the Rotarix development program since 2002. In their report on Study O-23, the IDMC said the following: "Overall, compared to placebo recipients, Rotarix vaccinees had lower rates

of hospitalizations and GE-related SAEs. Hospitalization rates for respiratory diseases and for all infectious causes, excluding diarrheal disease, were comparable in the two groups."

Concerning the observed fatalities, the IDMC stated that "these could be due to chance. The multiple analyses of safety data could have resulted in a spurious finding of statistical significance." The IDMC noted that "there is no known biological explanation for this observation. Natural rotavirus disease is not an established cause of mortality from non-diarrheal causes."

Because of the unclear significance of this finding, and the potential benefit of the vaccine, the IDMC recommended that the current trials should be continued. The IDMC concluded that "further evaluation is warranted." The IDMC continues to monitor the safety of the Rotarix development program.

There are two studies currently

ongoing in Africa which have enrolled nearly 5,000 infants in which, as could be expected, a considerable number of deaths have occurred. In fact, in these two ongoing studies, 135 deaths have occurred, 60 of these deaths were pneumonia-related.

GSK remains blinded to treatment allocation in these two ongoing studies in Africa. GSK has asked the IDMC that oversees these studies to inform us of imbalances in deaths, and specifically pneumonia-related deaths it may observe. The IDMC met recently, and in their last statement said that "there are no safety concerns in these two ongoing studies in Africa, nor in other ongoing studies."

Several sets of criteria to assess causality exist, of which the Bradford Hill may be the best known. In this slide, I summarize our findings as they relate to the criteria that apply to vaccine safety. The first criterion is consistency. The

association between pneumonia deaths and Rotarix was seen only in Study O-23, and not in other studies, including ongoing Phase III studies in Africa, where a large number of deaths, including pneumonia deaths, as mentioned, have occurred. In addition, there was no consistency within Study O-23 in that no imbalances were observed in non-fatal pneumonia hospitalizations.

The next criterion is strength of association. In this particular case, the strength is weak. The P-value in our, as well as in the FDA analyses, is close to, or only slightly below .05. In addition, these P-values do not take into account the multiplicity of the exploratory analyses from which this finding stemmed.

The third criterion looks at specificity. The adverse event of interest, pneumonia deaths, although relatively rare did not occur exclusively in the vaccine group. Lower respiratory tract infection, in general,

occurs quite frequently in the study population. There are multiple alternative etiologies for lower respiratory tract infections, including fatal pneumonia.

The next criterion is relationship in time to vaccination. Less than half of the events in the Rotarix group occurred within the zero to 30-day interval after vaccination, the time window in which one would expect a vaccine-associated reaction. Among the seven cases that occurred within that time frame, again, there was no clustering in time as they were spread equally over the first month after vaccination. Among the additional nine cases, the day of symptom onset ranged from 31 to 199 days after vaccination without temporal clustering.

The final criterion is biological plausibility. Although there are several reports of respiratory symptoms among infants with rotavirus infection, the existence of a rotavirus syndrome leading to lower

respiratory tract infections has not been established.

Based on these observations, our overall assessment is that the currently available data do not suggest a causal relationship between Rotarix and pneumonia deaths. However, GSK follows the conclusion of the IDMC and further assessment is planned. These post-marketing plans will be discussed by my colleague, Dr. Verstraeten, in a few moments.

The last part of the clinical trial data presentation is a review of reactogenicity data. In the Integrated Summary of Safety, in the 8-day period after each of the two vaccinations, similar percentage of infants in the Rotarix group and the placebo group reported any intensity of fever, cough and runny nose, diarrhea, vomiting, irritability, fussiness, and loss of appetite.

Overall, reporting rates of Grade 3

were severe intensity solicited symptoms in all groups was low, mostly below 5 percent. In the 8-day period after each of the two vaccinations, similar percentages of infants in the Rotarix and the placebo groups reported Grade 3 symptoms for all outcomes. When considering individual studies included in the ISS, the incidences of solicited adverse events were comparable between vaccine and placebo groups in each study, irrespective of potency of vaccine tested. As examples, solicited adverse events in studies conducted in Europe, and the United States, and Canada will now be presented.

In the Phase III Study O-36 conducted in Europe, reactogenicity data was evaluated in a subset of approximately 1,400 subjects. Routine pediatric vaccines used in Europe, combination DTAP, HepB, IPV/HIB, pneumococcal conjugate, and meningococcal-C conjugate vaccines were co-administered. The incidences of solicited adverse events of any

intensity, and under the Grade 3 intensity, were similar, and not statistically different in the Rotarix and placebo groups.

Study O-05 was a Phase II dose ranging study conducted in the United States and Canada. Over 500 infants were enrolled in this study, and received either one of two Rotarix formulations which differed in virus titer or placebo, concomitantly with routine recommended infant vaccines used in the U.S. and Canada; specifically, DTaP, IPV/HIB, pneumococcal conjugate, and HepB. In this study, the incidence of solicited adverse events of any intensity and of Grade 3 intensity were comparable among the Rotarix licensure potency group, and the placebo groups.

In summary, the safety data presented show that Rotarix is well-tolerated. There is no increased risk of intussusception among infants vaccinated with Rotarix compared to placebo. In single studies, statistical

differences in convulsions, pneumonia deaths, pneumonia SAEs, and unsolicited bronchitis were observed. In all of the other clinical trials, and in the Core Integrated Summary of Safety, imbalances were not noted for convulsions or acute lower respiratory tract infections.

GSK plans to monitor convulsions and acute lower respiratory tract infections in the post-marketing setting, which will be discussed next in the presentation.

Other serious adverse events, including deaths, intussusception, bronchiolitis, pneumonia, and nervous system disorders were reported by similar proportions of subjects in the Rotarix and placebo groups.

There is no increased reactogenicity following co-administration with routine pediatric vaccines. The overall safety profile of Rotarix is similar to placebo.

Now I'd like to turn the podium

over to my colleague, Dr. Thomas Verstraeten, who's Director and head of Worldwide Safety for Vaccines at GSK.

DR. VERSTRAETEN: Thank you, Dr. Friedland, and good morning, everyone.

Before I joined GSK, I spent two years at the CDC's Vaccine Safety branch, during which time I participated in the assessment of the association between RotaShield and intussusception. I will present to you today the post-licensure safety profile of a rotavirus vaccine manufactured in my own country.

First, I will present a brief summary of the adverse events that have been reported to us in the first two-and-a-half years since launch, with some detailed attention to the reports of intussusception. Following this, I will present to you an overview of the plans GSK has to monitor the safety of Rotarix in the post-marketing setting worldwide, including our plans to

monitor intussusception, the effectiveness of Rotarix, and some other events of interest.

In the first two-and-a-half years since the launch of Rotarix in Mexico, the company has distributed over 12 million doses of the vaccine. The majority of these, 11-1/2 million doses, have been distributed in Latin America, of which most in Brazil. An additional .4 million doses have been distributed in Europe, and the remaining doses in other parts of the world.

In the same period, the company has received a total of 802 reports of events that occurred following the administration of Rotarix. This represents a reporting rate of 6.5 per 100,000 doses distributed. Note that this rate is not unusual for a new vaccine.

Among the 802 reports, 323 referred to events considered to be serious. The distribution by dose is also shown on this slide, suggesting a slightly higher reporting rate for the first dose of the vaccine.

This table lists the three events most frequently reported as occurring after Rotarix administration. It is not surprising to note the two gastrointestinal events, diarrhea and vomiting, as the most frequently reported ones, following this orally administered vaccine. To see intussusception on the list of most frequently reported events is also not surprising, given the large awareness that exists on the event following the RotaShield experience. I will come back to the intussusception reports in more detail later.

A total of seven fatal events have been reported in temporal association with Rotarix. One fatality occurred following a severe thrombocytopenia that was detected within hours of administration of Rotarix, and is, therefore, not likely to be actually related to the vaccine.

Another fatality occurred as a complication of a rotavirus infection in a

child nine months old. The company received conflicting information from the treating pediatrician and a relative on whether the child was actually vaccinated against rotavirus or not.

A third fatality occurred in Kenya as a complication of gastroenteritis caused by adenovirus.

Finally, the company has received four reports of fatalities following intussusception in Brazil. None of these reports reached us from the treating physician directly, but either through the Brazilian Ministry of Health, a consumer, or a sales representative. For two of these, the company, nor the Ministry of Health could confirm that the cases actually occurred. The information on the other two cases is very limited, and does not allow us to make a sound assessment of their potential relationship to Rotarix.

The time to onset was reported in

only one of these four Brazilian cases. In this case, symptoms of intussusception would have started within six days after vaccination.

Let's now look in more detail at the reports of intussusception and temporal relationship to Rotarix. Out of the 131 reports of intussusception made spontaneously to the company between January 2005, and July 2007, 79 could be considered as confirmed when applying the Brighton criteria. Further analysis will focus on these 79 cases.

The corresponding reporting rate is .64 cases per 100,000 doses distributed. The time to onset between vaccination and onset of symptoms varied from zero to 244 days, with a median of 15 days. The age at which the intussusception occurred varied from two to thirteen months, with a median of five months. There were no fatalities among these confirmed cases. As observed for all adverse events, there were slightly more reports

following the first dose compared to the second dose of Rotarix.

To assess whether the number of reports received reflects the natural background rate of intussusception in the countries where the reports originated from, or potentially reflects an increased risk following Rotarix, we conducted an observed expected analysis. In this analysis, the number of confirmed cases occurring within 30 days of Rotarix is compared to the number of cases expected to occur by coincidence taking into account the known background rate in the regions of interest, the expected age distribution of intussusception, and the age at which Rotarix is expected to be administered.

Given that the reporting rates in Latin America where the majority of the vaccine has been distributed, thus far, may be lower than in Europe, we have applied this analysis both on a global level, and on a

Europe-only level.

From this table we can see that the global number of cases we observed through passive reporting to be 58 within 30 days of Rotarix. That's the number on this cell, and 40 within seven days of Rotarix. The number of cases expected to occur according to our most recent estimations is 496, and 116 for the same respective 30 and seven-day intervals.

This comparison suggests that the number of cases that have been reported to the company on a worldwide basis does not exceed the number expected to occur by coincidence after vaccination.

When limiting the analysis now to Europe, we can see that the number of cases we observed through passive reporting to be eight within 30 days after Rotarix administration, and four within the seven-day interval after Rotarix. The number of cases expected to occur for the same respective intervals is 19

and five. We did see that also in Europe the number of cases reported is below the number of cases expected.

Note also that the difference between the numbers observed and those expected is smaller in the Europe-only analysis, suggesting that reporting is probably more complete at the European level, and less complete at the Latin American level.

Now, we have also conducted a sensitivity analysis in which we assumed that the number of doses administered is only 75 percent of dose distributed, and the number of cases reported is only 75 percent of dose that actually occurred. These are the same assumptions that were proposed as the most realistic assumptions in a recent ACIP review of intussusception cases after RotaTeq administration in the United States.

In this sensitivity analysis, we note that the number of cases reported is still below those expected, except for the

Europe-only analysis of the seven-day interval, where the number of cases reported is extrapolated to be six, compared to four cases expected. Corresponding reporting ratio is 1.7 with 95 percent intervals largely overlapping one, suggesting that this difference is not significant.

Besides intussusception, we also pay special attention to any reports of the events of interest that have been previously highlighted in a clinical safety discussion, and are listed again on this table. As can be noted, few, or even no reports have been made for these events, and the estimated reporting rates are, therefore, very low, suggesting no new safety concerns from this data.

I would now like to present the additional plans GSK has put in place to monitor the safety and effectiveness of Rotarix in the post-licensure setting. These plans include various Phase IV clinical trials, several observational studies, as well

as some enhancements to the classic pharmacovigilance activities. I will go through these individually. It should be noted that several of these activities have already started following licensure in Europe or elsewhere.

In addition to the many clinical trials presented to you by Dr. Friedland, GSK is currently conducting a clinical trial to assess the frequency of transmission of the human rotavirus vaccine between twins. For each twin, one brother or sister has been randomized to receive the vaccine, and the other the placebo.

GSK is also conducting a study in South Africa to assess the safety and immunogenicity of Rotarix in infants who are HIV positive. This is the same study that was reviewed by the IDMC, as mentioned by Dr. Friedland, and which, in combination with an efficacy study, showed no imbalance for the pneumonia deaths. Finally, a study is ongoing

in Europe to assess the safety and immunogenicity of Rotarix in infants born prematurely.

In addition to these clinical trials, GSK has put, or is putting in place, a number of observational studies to further monitor the safety and effectiveness of Rotarix in the real-life setting. GSK intends to conduct an observational study in the United States to monitor the safety of Rotarix in relationship to intussusception, Kawasaki disease, hospitalizations for acute lower respiratory tract infections, and convulsions.

This study will be powered to detect an increased risk of intussusception due to the vaccine of 2.5 or greater, with 80 percent probability. All deaths that occur in this study will also be reported in an expedited fashion to the FDA and the CDC.

The design of this study, as well as the site where the study will take place are currently under discussion with the FDA

and the CDC. GSK will assess the feasibility of conducting the study outside the existing vaccine safety datalink network. Sites will be considered that have access to a sufficiently large population, are capable of linking health records with reliable capture of vaccination, and, of course, all outcomes of interest. These sites should have access to medical records for review, and preferably have a track record in performing vaccine safety research.

You will recall that Dr. Friedland showed you that the upper limit of the relative risk of intussusception observed in our large Phase III trial was 2.4; whereas, we and others believe that this is very reassuring, we wanted to evaluate whether we could reassess this relative risk in the real-life setting, and achieve an upper limit of the confidence interval that is even lower. We soon realized that this would only be feasible in a large country that uses our

vaccine on a large scale.

In Mexico, a large study has just started that intends to follow more than one million children vaccinated with Rotarix to evaluate their risk for intussusception in the first month after vaccination. This study is run within one of the country's largest healthcare systems called the Instituto Mexico de la Seguridad Social, or IMSS. This system covers approximately 40 million individuals in birth cohorts of 575,000 children. When combining several birth cohorts we will have over 80 percent power to exclude a relative risk of 2.7 for intussusception following within 30 days of the first dose of Rotarix, and over 80 percent power to exclude a relative risk of 1.6 of intussusception occurring within 30 days of the second dose of Rotarix.

Besides intussusception, this study also has pneumonia deaths as an additional outcome. All deaths that may be related to a

lower respiratory tract infection are actively captured in this study. For each of these, standardized information is being obtained, and then submitted to an adjudication committee for review.

Finally, GSK is currently assessing the feasibility of studying hospitalizations for lower respiratory tract infections as an additional outcome in this study. In addition to these two observational studies, GSK has initiated, or is involved in a number of other observational studies which are listed here by outcome of interest.

Surveillance for intussusception conducted at the request of GSK, and in collaboration with Merck and Sanofi Pasteur has just been concluded in Germany, and is now taking place in the United Kingdom. The objective of this surveillance is primarily to obtain reliable background rates on intussusception in Europe.

Three studies to assess the

effectiveness of Rotarix in preventing severe rotavirus gastroenteritis in the real-life setting are about to start in Panama, in Belgium, and in Singapore.

Finally, GSK has partnered with the European Rotavirus Surveillance Network, and again with Merck and Sanofi Pasteur to monitor the circulating rotavirus strains in Europe, with the objective of identifying any shifts as a consequence of vaccination.

Last, but not least, we are, and we will be very closely following all adverse events reports that are made to us spontaneously. GSK has a worldwide network of safety personnel to receive such reports. All cases of intussusception are actively followed to obtain as much information as possible. We intend to forward all these, and additional reports, in a more expedited fashion than is strictly required to the FDA.

We will also continue to perform the types of cumulative analysis, such as the

observed expected analysis, and engage in regular discussions with the FDA and the CDC on the results of these analyses.

In conclusion, I have illustrated to you how the currently available information from spontaneous reporting systems does not suggest any increased risk for intussusception following Rotarix, nor do these data suggest any new safety signal related to other events of interest. In addition, you've heard how GSK has put in place a comprehensive pharmacovigilance plan to further monitor the safety and the effectiveness of Rotarix. Thank you.

DR. KAHN: I have some very brief concluding remarks. To summarize, Rotarix, GSK's attenuated human rotavirus vaccine induces protective immunity against RVGE, as demonstrated in two pivotal trials conducted in Europe and Latin America. In both studies, robust efficacy against RVGE was consistently demonstrated against severe disease, any

disease, hospitalizations, and medically attended RV disease.

There was broad efficacy against disease caused by all the common circulating human serotypes. And efficacy was demonstrated against severe gastroenteritis, regardless of the etiology, indicating that RV is the leading cause of gastroenteritis worldwide. Efficacy was evident early post-dose one, and was persistent through at least two years.

Importantly, Rotarix may be concomitantly administered with U.S. licensed pediatric vaccines without interference. Rotarix is supported by extensive safety database from clinical trials, and post-marketing experience, which provide a high level of confidence in the safety of the vaccine.

Rotarix was well-tolerated in clinical trials with no increased reactogenicity following co-administration

with routine pediatric vaccines. The safety profile was clinically acceptable with no safety signal related to intussusception according to the pre-specified criteria. There will be active monitoring of adverse events of special interest in the post-marketing plans.

Post-marketing experience is already substantial with relicensure already in over 100 countries, and over 12 million doses distributed, so GSK is able to use the worldwide availability to study outcomes of interest. And, to date, there's been no pattern or frequency of reporting to suggest an increased risk of intussusception, and no new safety signal determined.

Extensive global and U.S. post-marketing activities are ongoing or planned, and they include prospective clinical trials, observational studies, and enhanced pharmacovigilance. These approaches will address not only intussusception and other potential outcomes, but also vaccine

effectiveness, vaccine transmission, and use in immunocompromised and pre-term infants.

Rotavirus is a significant cause of childhood morbidity in the United States. The data on disease burden worldwide demonstrates the importance of vaccination as the only effective preventive strategy. Rotarix confers broad and robust protection against RVGE during the first two years of life, and offers an acceptable safety and reactogenicity profile; thus, the risk-benefit ratio for Rotarix is favorable for the intended population. And that concludes GSK's presentation. Thanks.

DR. MODLIN: Thank you, Dr. Kahn. I'd like to thank both you and your colleagues for presenting an awful lot of information, and staying on time. I think we've earned a break. We will have an opportunity for questions from members of the Committee and from the floor, ample opportunity, a little bit later on. But, for now, why don't we go

ahead and take our break, and we'll see everybody back promptly at a quarter of 11.

(Whereupon, the proceedings went off the record at 10:19:24 a.m., and went back on the record at 10:46:05 a.m.)

DR. MODLIN: The next portion of the meeting will be the FDA presentation. And, Dr. Rosenthal, it looks like you're the man for the entire presentation.

DR. ROSENTHAL: Okay. Thank you, Dr. Modlin. Welcome back, everyone.

I will now discuss findings of FDA's clinical review of Rotarix. For this talk, I will first present the clinical overview of the Rotarix BLA, and overviews of efficacy of the two pivotal Phase III studies, safety in terms of serious adverse events, and co-administration of Rotarix with routine childhood vaccines. I will conclude the talk with an overview of the applicant's post-marketing commitments, and after lunch present again FDA's questions to the Committee.

Complete results of 11 clinical studies were submitted to the BLA. These included the two pivotal Phase III efficacy studies, Rota O-23 and Rota O-36, two supportive Phase II efficacy studies, Rota O-04 and Rota O-06, one Phase III concomitant childhood vaccination study, Rota O-60, and one Phase III lot-to-lot consistency study, Rota O-33. Safety and anti-RV IGA immunogenicity were evaluated in all studies, with Study Rota O-23 also considered a pivotal safety study for intussusception. All studies were designed and conducted in a randomized double blind and placebo-controlled manner.

Please refer to your handout for a better view of this slide. This slide provides a tabular summary of the 11 BLA studies. Most of the studies were conducted in Latin America, Europe, and Asia. Two of the studies, Rota O-05 and Rota O-60, were conducted in the U.S. Rota O-23 and Rota O-36, the two pivotal studies, enrolled and

vaccinated the largest numbers of subjects.

In nine of the studies, including all Phase III studies, Rotarix vaccination at the proposed licensure potency of greater than and equal to 10 to the 6^{th} CCID 50 was evaluated. The mean age at first dose was similar across studies, 8.3 to 8.7 weeks, with the exception of Rota O-07, Rota O-14, and Rota O-36, in which the mean ages were three to five weeks older.

Vaccine doses were separated by one month, two months, or either one or two months. Significant imbalances in male-to-female ratios were not observed. Ethnicity in each study reflected the expected ethnic composition of the participating countries.

Finally, co-administration of routine infant vaccines was allowed in nine of the studies. Of note, only one study, Rota O-14, allowed concomitant administration of OPV with Rotarix.

From the BLA studies, over 40,000

Rotarix, and over 34,000 placebo recipients received at least one study dose with over 78,000 Rotarix, and 67,000 placebo doses given. Over 37,000 infants received Rotarix at the potency formulation in storage conditions intended for commercial use, namely, greater than or equal to 10 to the 6.0 CCID 50 per dose lyophilized buffered and stored at 2 to 8 degrees Celsius.

Across all studies, between 90.4 to 99 percent of Rotarix and between 90.3 and 100 percent of placebo recipients received two doses.

I would now like to discuss the efficacy of Rotarix based on the pivotal studies. Vaccine efficacy was measured in two pivotal Phase III studies, Rota O-23, conducted in Latin America, and Rota O-36, conducted in Europe. Year one, according to protocol or ATP efficacy cohort was used for the primary efficacy analysis in each study.

Criteria for inclusion in the ATP cohort included vaccination with two doses of

Rotarix, or placebo, no rotavirus other than the vaccine strain in GE stool samples between dose one and two weeks post dose two, and entry into the year one efficacy follow-up period.

This slide summarizes the total number of subjects included in the year one ATP efficacy cohort for each study. A total of 17,867 and 3,874 subjects were included in Rota O-23, and Rota O-36, respectively. Demographic data from the year one ATP cohort of each study are summarized in this slide.

Rota O-23 was conducted in 11 Latin American countries, while Rota O-36 was conducted in six European countries. The mean and median ages at dose one and dose two were lower in Rota O-23, compared to Rota O-36. The mean and median duration of follow-up was eight months in Rota O-23, compared to six months in Rota O-36. Male-to-female ratios were similar in both studies. Most of the study subjects in Rota O-23 were Hispanic,

compared to white Caucasian in Rota O-36.

For inclusion into either study, subjects needed to be free of obvious health problems, and their parents or guardians needed to be able to comply with study procedures. The age range at dose one was similar between studies. In Rota O-036, an additional criterion required that the birth weight of subjects be greater than 2,000 grams.

Exclusion criteria common to both studies included a history of chronic gastrointestinal disease, or another serious medical condition, an immunocompromised condition, including HIV infection, and being treated for greater than 14 days with immuno-suppressive therapy.

In addition, there were no feeding restrictions in either study. Co-administration of infant vaccines was allowed in Rota-23, except OPV, which was administered two weeks apart from study vaccination. The

choice of vaccines was determined according to national recommendations in each country, and included whole cell DTP, DTaP, Hepatitis B, IPV, OPV, and MMR vaccines. Co-administration of infant vaccines was also allowed in Rota O-36. Infanrix HexaA, DTaP, Hib, HepB, IPV combination vaccine was given in the Czech Republic, Finland, Germany, Italy, and Spain. Infanrix Hexa, and Infanrix polio Hib, DTaP, Hib, IPV combination vaccine was given in France. In addition, MeningaTeq, Meninge C conjugate vaccine was given in Spain, while Prevnar and pneumococcal seven-valent conjugate vaccine was administered in France and Germany.

In Rota O-23, the primary efficacy objective was to determine if two doses of Rotarix could prevent severe wild-type rotavirus gastroenteritis during the year one efficacy period, defined as the period from two weeks post-dose two, until one year of age. Secondary efficacy objectives were to

determine year one efficacy of Rotarix against severe G1 wild-type rotavirus gastroenteritis, severe non-G1 wild-type GE, both pooled and by individual type, and severe rotavirus GE using the Vesikari scale case definition, which I'll explain shortly.

In Rota O-36, the primary efficacy objective was to determine the efficacy of two doses of Rotarix given with childhood vaccines against any wild-type rotavirus GE during the year one efficacy period defined as the period from two weeks post-dose two until the end of the first rotavirus season. Secondary efficacy objectives were to determine year one efficacy of Rotarix against severe wild-type rotavirus GE, and any severe G1 wild-type rotavirus GE, any and severe non-G1 wild-type rotavirus GE, hospitalization for rotavirus GE, and any medical attention for rotavirus GE.

Following case definitions for diarrhea, vomiting, and GE were applied to

both studies. Diarrhea was defined as greater than or equal to three looser than normal stools within a day. Vomiting was defined as greater or equal to one episode of forceful emptying of partially digested stomach contents greater than or equal to one hour after feeding within a day. GE was defined as diarrhea with or without vomiting. A definition of medical attention used in Rota O-36 was any medical provider contact, advice, or visit, or any emergency room contact or visit, or hospitalization.

Rotavirus GE was defined as an episode of GE in which rotavirus, other than the vaccine strain, was identified in a stool sample collected no later than seven days after GE symptom onset. In Rota O-23, the main definition of severe rotavirus GE was an episode of rotavirus GE requiring hospitalization, and/or rehydration therapy equivalent to WHO Plan B or C in a medical facility. In Rota O-36, the main definition

of severe rotavirus GE was defined as an episode of rotavirus GE with a Vesikari score of greater than or equal to 11 points. This Vesikari scale case definition was also used for one secondary endpoint in Rota O-23, mentioned previously.

The Vesikari scale is based on seven parameters, duration of diarrhea, maximum number of diarrheal stools for 24 hours, duration of vomiting, maximum episodes of vomiting for 24 hours, maximum temperature, degree of dehydration, and treatment. Points are assigned based on the severity in each parameter. A maximum of 20 points can be scored per GE episode.

In both studies, rotavirus GE cases were ascertained through active surveillance. In Rota O-23, hospitals and other medical facilities in the study areas were contacted at least twice a week. Subjects were also contacted or visited at least every four days to identify severe cases not picked up by

routine medical facility surveillance. In Rota O-36, subjects were contacted weekly by telephone from week one post-dose one until the end of the first rotavirus season, which was the end of May 2005.

Diary cards were distributed to parents to collect temperature, stool, NMSS data. Parents were instructed to collect, label, store, and submit stool samples for each GE episode. All collected stools were tested for rotavirus antigen by ELISA at the applicant's laboratory in Belgium. Rotavirus antigen positive stools were further analyzed for G and P type by RTPCR followed by reverse hybridization assay, or optional sequencing at the Delft Diagnostic Laboratory in the Netherlands.

Vaccine efficacy was calculated using the formulation shown in this slide; that is, one minus the relative risk, or one minus the ratio of the attack rate in the Rotarix group over the attack rate in the

placebo group. The attack rate in each group was calculated by dividing the number of subjects reporting at least one episode of the rotavirus GE endpoint of interest, divided by the total number of subjects in that group.

This slide summarizes year one vaccine efficacy results against any rotavirus GE, and against severe rotavirus GE for the ATP cohort in Rota O-36. Efficacy against any rotavirus GE was 87.1 percent with a 94 percent confidence interval of 79.6 to 92.1 percent. Against severe rotavirus GE, efficacy was 95.8 percent with a 95 confidence interval of 89.6 to 98.7 percent.

Vaccine efficacy results against any rotavirus GE by G type are summarized in this slide. Rotarix demonstrated statistically significant efficacy against G1, G3, G4, and G9 types. Of note, these types were associated with the P8 type. Although efficacy against G2 was 62 percent, the 95 percent confidence interval was very wide and

included zero.

Among the G2 cases, the P type of one case, a placebo subject, could not be characterized, while the rest were associated with the P4 type. While all non-G1 types were pooled, efficacy was 79.3 percent with a 95 percent confidence interval of 64.6 to 88.4 percent.

Efficacy results against severe rotavirus GE by G type are summarized in this slide. Similar to results from the previous slide, Rotarix demonstrated statistically significant efficacy against severe G1, G3, G4, G9 gastroenteritis and non-G1 gastroenteritis when pooled. However, the efficacy estimate against severe G2 gastroenteritis did not reach statistical significance, as can be seen by the wide 95 percent confidence interval. All efficacy estimates against severe GE were higher than against any GE that was shown in the previous slide. Rotarix also demonstrated an efficacy

of 100 percent against hospitalization for rotavirus GE, and 91.8 percent against any medical attention for rotavirus GE is shown here.

Year one efficacy results against severe rotavirus GE for the ATP cohort in Rota O-23 are presented here. Efficacy against severe rotavirus GE using the main case definition was 84.7 percent, with a 95 percent confidence interval of 71.7 to 92.4 percent. When the case definition based on the Vesikari scale was used, efficacy was nearly identical at 84.8 percent with similar 95 percent confidence interval.

Vaccine efficacy results against severe rotavirus GE by G type are summarized on this slide. Rotarix demonstrated statistically significant efficacy against G1, G3, and G9 types. The efficacy estimate against severe G2 gastroenteritis was 41 percent with a wide 95 percent confidence interval that included zero. Efficacy against

severe G4 GE was not calculated due to the limited number of cases. When all non-G1 types were pooled, efficacy was 75.4 percent with a 95 percent confidence interval of 50, then 89 percent. All G1, G3, G4, and G9 types were associated with the P8 type, while all G2 types were associated with the P4 types.

In calculating efficacy, FDA considers it more appropriate to use the time to first episode analysis than using attack rates in each group. This is because the time to event approach accounts for differential follow-up of subjects, while the latter approach does not. FDA is, therefore, inclined to place more importance on efficacy results based on the Cox Proportional Hazards Model.

Using this model, the applicant calculated efficacy estimates of 84.8 percent against severe rotavirus GE in Rota O-23, and 87.4 percent against any rotavirus GE in Rota O-36. These estimates, along with their 95

confidence intervals, were similar to corresponding estimates using attack rates that were previously mentioned.

Next, I will present safety findings of Rotarix, first by discussing the intussusception study in Rota O-23. The primary safety objective in Rota O-23 was to determine the safety of Rotarix with respect to intussusception, abbreviated as IS, within 31 days, that is day zero to 30 after each dose. The primary safety endpoint was the occurrence of definite IS within 31 days after each dose. The Brighton Collaboration IS Working Group case definition for definite IS was used.

This slide summarizes the Brighton IS Working Group case definition. A case of IS was classified as definite if demonstration of intestinal invagination surgically and/or radiologically could be achieved. Definite IS could also be defined by demonstration of intra abdominal mass by ultrasound with

specific characteristic features, such as target or donut sign that could be reduced by hydrostatic enema, or by demonstration of intestinal invagination on autopsy.

To capture all IS events, IS cases were reported irrespective of whether they met the Brighton case definition for definite IS. A Clinical Events Review Committee, or CEC performed blinded objective reviews of all IS cases occurring from dose one to visit three. Visit three was approximately one to two months post-dose two, or two to four months post-dose one. The CEC was made up of physicians acting as consultants who were not study investigators, or medical care providers to the study subjects.

Rota O-23 was specifically designed and powered to assess the risk of IS following Rotarix vaccination, with over 31,000 subjects in both the Rotarix and placebo groups receiving at least one study dose. The original criterion for meeting the primary

safety objective was an upper limit of the 90 percent confidence interval of the IS risk difference, Rotarix minus placebo, less than two cases for 10,000 subjects. This criterion was based on the consensus estimate of the RotaShield attributable risk of one case for 10,000 vaccinees.

RotaShield was the first U.S. licensed rotavirus vaccine that was subsequently withdrawn from the market due to the development of an unexpected association with IS.

Nine months after study initiation, the blinded overall IS incident rate 31 days post-vaccination was calculated as two to four cases per 10,000. This rate exceeded the anticipated rate of 0.3 per 10,000 in the placebo group, and, therefore, the upper limit of the 90 percent confidence interval exceeded two per 10,000.

In addition, a background IS incident rate of 5 per 10,000 was calculated

from a separate concurrent prospective multi-center epidemiologic study in the same countries involving children less than two years of age who were not vaccinated with Rotarix.

The higher than expected IS incidence rate led to criteria for meeting the primary safety objective being revised to the following. One, the upper limit of the 95 percent confidence interval of the risk difference for definite IS to be less than 6 per 10,000. This was based on an IS incident of 3 to 5 per 10,000 in the placebo group, and 30,000 subjects in each group. And, two, the lower limit to be less than zero. The study had greater than 86 percent power to meet the primary objective if the risk difference was truly zero.

This table summarizes the analysis of definite IS diagnosed within 31 days post vaccination. After any dose, six cases occurred in the Rotarix group, compared to

seven in the placebo group. The risk difference was negative 0.32 per 10,000, with the upper and lower limits of the 95 percent confidence interval being 2.18, and negative 2.91 respectively. The relative risk was 0.85, with a 95 percent confidence interval that included one.

The risk differences after dose one or dose two also favored the Rotarix group, as demonstrated by the negative values, with the upper limits being less than 6 per 10,000, and the lower limits being less than zero. Based on this data, the primary safety objective was met.

The applicant noted that when the original criterion for meeting the primary safety objective was used, the objective was still met as the upper limit of the 90 percent confidence interval was 1.71 per 10,000, less than the required two per 10,000. In addition, 25 definite IS cases were diagnosed from dose one until visit three, nine in the

Rotarix group, and 16 in the placebo group. The risk difference was negative 2.23 per 10,000, with a 95 percent confidence interval that included zero. The relative risk was 0.56, with a 95 percent confidence interval that included one.

Data just presented for definite IS within 31 days post vaccination was based on the date of IS diagnosis. However, one definite IS case in the Rotarix group had onset on day 29, but was diagnosed on day 31. From FDA's analysis of IS risk within 31 days after any dose using onset, rather than diagnostic date, there were seven cases in each group. The risk difference was very small with the upper and lower limits of the 95 percent confidence interval still meeting the primary safety objective. The relative risk was close to 1.0.

Numbers of definite IS cases by onset interval after each dose are tabulated in this table. These figures do not indicate

an apparent pattern of IS occurrence during day zero to 30, or beyond day 30 after either dose one, or dose two.

Numbers of definite IS cases during days three to seven, and days three to fourteen after each dose are tabulated in this table. These intervals were chosen because the risk of IS appeared to be increased among RotaShield vaccine recipients during days three to fourteen post-dose one, and days three to seven post-dose two. Of note, no cases occurred during either interval after dose one. Numbers of cases in each group after dose two were also small; therefore, one cannot rule out that they occurred during these intervals by chance alone.

As mentioned previously, criteria to meet this primary safety objective in Rota O-23 was revised during the conduct of the study. Such changes while the trial is ongoing could potentially compromise the integrity of the study. Because the study

wasn't performed under US IND, the FDA wasn't discussing this with the applicant at the time that this happened. The Agency asked for more detailed information on whether or not proper procedure was followed, and the applicant responded, and FDA was satisfied with that response. So I'll now present safety data on serious adverse events.

For safety analysis, integrated safety summary, or ISS analysis, were conducted. These analyses were based on total vaccinated cohort data from 10 studies, the exception being Rota O-60, and involved pooling of subjects into Core ISS and Supplementary ISS groups. The Core ISS group was composed of pooled subjects who received Rotarix at a potency of greater than or equal to 10 to the 6 CCID 50 per dose, or placebo, while the Supplementary ISS group was made up of pooled subjects who received Rotarix at a potency of less than 10 to the 6 CCID 50 per dose or placebo.

In the Core ISS analysis group, over 36,755 Rotarix, and 34,454 placebo subjects were pooled from eight studies. In the Supplementary ISS analysis group, 3,076 Rotarix, and 1,613 placebo subjects were combined from five studies. For studies included in both ISS analysis groups, the same numbers of placebo subjects were used.

ISS analysis endpoints included both fatal and non-fatal SAEs that occurred from day zero to 30 post vaccination, and during the entire length of the studies. SAEs were coded using the Medical Dictionary for Regulatory Activities, or MedDRA. For each MedDRA preferred term, or PT, the relative risk defined as the rate in the Rotarix group divided by the rate in the placebo group along with a 95 percent confidence interval were calculated. Relative risk estimates were adjusted for study effect, and a multiplicity adjustment was not performed.

SAE analysis for pivotal studies

Rota O-23 and Rota O-36 will be presented. In both studies, SAEs were recorded throughout the study periods, approximately two years each in duration, and risk differences, Rotarix minus placebo, and 95 percent confidence intervals were calculated for each MedDRA PT. For Rota O-23, over 31,000 Rotarix and placebo subjects were included in the safety analysis, while for Rota O-36, 2,646 Rotarix, and 1,348 placebo subjects were included.

A total of 128 post-vaccination deaths were reported from 10 studies included in the ISS analysis. In addition, there were no deaths in Rota O-60. In the Core ISS group, 68 deaths were reported, with 62 of them occurring in Rota O-23. Five deaths were reported in the Supplementary ISS group, and 55 deaths were reported in the placebo group. Similar to the Core ISS group, most of the deaths in the placebo group occurred in Rota O-23.

In the Core ISS group, 53 deaths were reported from day zero to 30 post-dose, 33 were in the Rotarix group, and 20 were in the placebo group. The relative risk was 1.64 with a 95 percent confidence interval of 0.92 to 3.02. Notable imbalances were not observed for each MedDRA PT. The PT pneumonia was the most common death code, with seven deaths in the Rotarix group, compared to five in the placebo group. The relative risk was not statistically significant.

In the Core ISS group, 118 deaths were reported throughout the study periods, 68 and 50 in the Rotarix and placebo groups respectively. Again, PT pneumonia was the most common death code with 19 in the Rotarix, and 10 in the placebo groups. Relative risk estimates were not statistically significant.

In the Supplementary ISS group, seven deaths were reported from days zero to 30 post dose, three in the Rotarix group, and four in the placebo group. The relative risk

was 0.38. Eleven deaths were reported throughout the study periods, five in the Rotarix group, and six in the placebo group. The relative risk was 0.42.

During Rota O-23, 111 post-vaccination deaths were reported, 62 or .2 percent were in the Rotarix group, and 49 or .16 percent were in the placebo group. Ninety-nine of the 111 deaths were reported from dose one to visit three, 56 in the Rotarix group, compared to 43 in the placebo group. The risk difference was 4.05 per 10,000, with a 95 percent confidence interval including zero.

When looking at the deaths within 31 days post-dose, 22 Rotarix versus 11 placebo deaths occurred post-dose one, with a risk difference o 3.46 per 10,000. Post-dose two, there were two Rotarix, compared to five placebo deaths for a risk difference of negative 1.02 per 10,000, 95 percent confidence intervals, for both risk difference

estimates included zero.

Among the 99 deaths reported from dose one to visit three, PT pneumonia was reported significantly more in the Rotarix group than the placebo group, 14 versus 5, risk difference of 2.84 per 10,000, P value of 0.04. Seven of these pneumonia deaths had symptom onset within 31 days post dose, five in the Rotarix group, versus two in the placebo group. Because the etiologic pathogen was not recovered in all pneumonia-related deaths, the applicant conducted an ad hoc analysis by combining PTs, pneumonia, bronchopneumonia, and CMV pneumonia.

After combining, the number of deaths remained higher in the Rotarix, with a risk difference of 3.15 per 10,000. However, the P value was 0.054. Within 31 days post-dose, there were seven Rotarix, compared to three placebo deaths. There appeared to be no clear temporal association of pneumonia-related deaths by week of onset.

For the ad hoc pneumonia deaths analysis mentioned in the previous slide, the exact P value of the risk difference calculated by FDA differed from that calculated by the applicant. To reiterate, 16 combined pneumonia-related deaths occurred in the Rotarix group, compared to six in the placebo group from dose one to visit three, with a risk difference of 3.15 per 10,000, and the applicant's P value of 0.054. However, FDA calculated P values of 0.0345 and 0.0354 using two different statistical methodologies.

In the Core ISS group, a total of 1,286 subjects reported at least one SAE, fatal or non-fatal, from day zero to 30 post-dose, 1.71 percent of subjects in the Rotarix group, compared to 1.91 percent in the placebo group for a relative risk of 0.90. Rates of PTs, diarrhea, gastroenteritis, and dehydration were significantly less in the Rotarix group, while rates of PTs, pneumonia and convulsions, were the same or very similar

between groups. Throughout the study periods, 4,519 subjects reported at least one SAE, with significantly less subjects in the Rotarix group, compared to the placebo group, as reflected by the relative risk of 0.89, and 95 percent confidence interval of 0.84 to 0.94. Results of MedDRA PT analysis were similar to those observed from day zero to 30.

When looking at intussusception in the Core ISS group, among cases of IS with onsets from days zero to 30 post-dose, nine occurred in the Rotarix group, compared to seven in the placebo group. The relative risk was 1.23, but not statistically significant. These figures included definite IS cases in the Rota O-23 IS study previously discussed. Of note, no cases had onsets from day zero to 14 post-dose one. Of the IS cases with onset throughout the study periods, 16 were reported in the Rotarix group, compared to 22 in the placebo group, for a relative risk of 0.69.

In the Supplementary ISS group,

only one IS case occurred from day zero to 30 post-dose. That in the Rotarix subjects, six days post-dose one. Throughout the study periods, IS was reported in two Rotarix subjects versus one placebo subject.

In Rota O-23, significantly less Rotarix than placebo recipients reported at least one SAE from dose to visit three, 2.93 percent versus 3.32 percent, with a risk difference of negative 38.8 per 10,000, and a P value of 0.005. PTs diarrhea, vomiting, gastroenteritis, and dehydration were also reported significantly less in the Rotarix group. No notable imbalances between groups for pooled pneumonia-related PTs were observed from dose one to visit three, or for hospitalizations for pneumonia-related PTs during this period. In Rota O-23, the PT convulsions was reported significantly more in the Rotarix group than the placebo group, 16 versus 6, risk difference of 3.15 per 10,000, P value of 0.034.

The applicant performed an ad hoc analysis by combining PTs convulsions, epilepsy, grand mal seizures, tonic convulsions, and status epilepticus. After pooling, the number of SAEs remained higher in the Rotarix group, with a risk difference of 2.51 per 10,000, but a P value that was no longer statistically significant.

Within 31 days post-dose, there were seven Rotarix compared to nine placebo convulsion-related SAEs, with no notable imbalances either post-dose one, or post-dose two.

In Rota O-36, less Rotarix than placebo recipients, 11 percent versus 13 percent reported at least one SAE from dose one to visit seven, visit seven being the end of the second rotavirus season. During this interval, PTs gastroenteritis and gastroenteritis rotavirus were reported significantly less in the Rotarix group. From dose one to visit seven, PT pneumonia was

reported significantly more in the Rotarix group, .9 percent versus .3 percent, with a risk difference of 61 per 10,000, and a P value of 0.029. However, over half of the cases occurred after visit five, the end of the first rotavirus season. From day zero to thirty post-dose, only one case in a Rotarix subject was reported.

To determine whether an imbalance in non-febrile convulsion-related PTs was present, FDA performed an analysis by combining subjects in each group who were coded for the PTs convulsions, epilepsy, infantile spasms, myoclonus, and partial seizures. When combined, the frequency of convulsion-related PTs from day zero to 30 post-vaccination was similar between groups.

Similarly, to determine whether an imbalance in pneumonia-related PTs was present, FDA performed an analysis by combining subjects in each group who were coded for the PTs pneumonia, bronchopneumonia,

low bar pneumonia, and pneumonia viral. When pooled, the frequency of pneumonia-related PTs from dose one to visit seven was higher in the Rotarix group, 1.2 percent versus 0.5 percent. However, from day zero to thirty post-dose, only two Rotarix subjects reported a pneumonia-related PT compared to zero placebo subjects.

Now I would like to briefly discuss Kawasaki disease. At the ACIP meeting on June 28th, 2007, FDA presented data on the occurrence of Kawasaki disease, or KD, within 30 days after RotaTeq vaccination during Phase III clinical trials. Five out of 36,150 RotaTeq subjects developed KD, compared to one out of 35,536 placebo subjects. The unadjusted relative risk was 4.9, with a 95 percent confidence interval of 0.6 to 239.1. The causal relationship between RotaTeq and KD was not established, although post-licensure studies are ongoing.

Upon request by FDA, the applicant

submitted an analysis report of KD following Rotarix on July 20th, 2007. This report included all cases of KD from completed and ongoing clinical trials. An information amendment in response to FDA comments was submitted on February 1st, 2008. A total of 27 unblinded cases of KD were reported in Rotarix clinical trials. In Rota O-23, KD was reported in a two-year old Hispanic female Rotarix subject from Mexico, with onset 19 months post-dose two of Rotarix, seventeen months post wholesale DTP, HepB, Hib and OPV vaccinations, and seven months post-Hepatitis A vaccination.

This case lacked clinical information to assess whether criteria for either KD or incomplete KD were met. In Rota O-06, KD was reported in a 13-month male Rotarix subject of mixed ancestry from Brazil with onset seven months post-dose two of Rotarix, and five months post routine vaccinations with wholesale DTP, Hepatitis B,

and Hib. In Rota O-61, not one of the eleven studies submitted in the original BLA, KD was reported in a three-month white male Rotarix subject from Finland with onset 12 days after dose two of Rotarix dose two, DTAP, IPV, HepB and Hib.

The remaining 24 cases were reported from four Asian studies, Rota O-07 and Rota O-28 in Singapore, Rota O-29 in Hong Kong, and Rota O-30 in Taiwan. Fifteen or .21 percent Rotarix subjects developed KD, compared to nine, or 0.15 percent of placebo recipients. The male-to-female ratio was 15-19, and all subjects were of Asian ethnicity. The median onset interval after Rotarix or placebo was 5.5 months, with a range of three days to 19 months. The median onset after routine vaccinations was 3.5 months, with a range of three days to 18 months. From day zero to 30 post-dose with Rotarix or placebo, one case each was reported in both groups. In addition, one case, a Rotarix subject who

developed KD 55 days post-dose two lacked clinical information to assess whether criteria for either KD or incomplete KD were met.

I'll now present immunogenicity results from Rota O-60, a study that evaluated the co-administration of Rotarix with other childhood vaccines.

As previously mentioned, co-administration of other routine childhood vaccines with Rotarix was allowed in nine of the eleven BLA studies. However, only Rota O-60 was specifically designed to evaluate non-inferiority of immune responses to routine U.S. childhood vaccine antigens, when these vaccines were co-administered with Rotarix.

All subjects were given three doses each of PEDIARIX, the DTAP, Hep B, IPV combination vaccine, Prevnar, the pneumococcal seven-valent conjugate vaccine, and ActHIB, Haemophilus B conjugate vaccine on a zero, two, and four month schedule. Subjects were

randomized to one of two groups, the co-ad group where Rotarix was administered with the first two sets of routine vaccine doses, and the sep-ad group where Rotarix was given one month after dose two, and one month after dose two of routine vaccines.

One hundred and eighty co-ad and 137 sep-ad subjects were included in the ATP immunogenicity cohort. Antibody responses to Diphtheria, Tetanus, Pertussis, Hepatitis B surface, Poliovirus, Hib and pneumococcal antigens were measured at one month post-dose three of routine vaccinations. Geometric mean concentrations, or GMCs, or geometric mean titers, or GMTs were measured for all antigens. Definitions of seroprotection for anti-PRP, anti-HBS, anti-polio, anti-diphtheria, and anti-tetanus responses are shown in this table.

Demonstration of non-inferiority of the immune response to routine vaccine antigens in the co-ad group required meeting

the following criteria. The lower limit of the 95 percent confidence interval for the difference in seroprotection rate with difference being defined as the rate in the co-ad group minus the rate in the sep-ad group needed to be greater than or equal to negative 10 percent to the anti-PRP, anti-HBS, anti-polio, anti-diphtheria, and anti-tetanus responses.

In addition, the lower limits of the 95 percent confidence interval for the GMC ratio defined as the GMC in the co-ad group divided by the GMC in the sep-ad group needed to be greater than or equal to 0.67 for the anti-pertussis response to each of the three antigens, greater than or equal to 0.5 for the anti-pneumococcal response to the seven serotypes.

Non-inferiority of seroprotection rates in the co-ad group compared to the sep-ad group was demonstrated for anti-PRP, anti-HBs, anti-polio, anti-diphtheria, anti-tetanus

responses based on the lower limits of the 95 percent confidence intervals on the difference in the seroprotection rates all being greater than or equal to negative 10 percent. Non-inferiority of GMCs in the co-ad group compared to the sep-ad group was also demonstrated for the anti-pertussis responses to the three antigens, and anti-pneumococcal responses to the seven serotypes based on the lower limits of the 95 percent confidence intervals for the GMC ratios, all being greater than or equal to 0.67.

FDA also looked at non-inferiority of the anti-polio response when the lower limit of the 95 percent confidence interval for the difference was increased from greater than or equal to 10 percent, to greater than or equal to negative 5 percent. Despite this increase, non-inferiority criterion for each polio virus type was still met.

So, in summary, Rotarix was effective in preventing any rotavirus

gastroenteritis and severe rotavirus gastroenteritis during the first year of life. Protection was also demonstrated against wild-type G1, G3, G4, and G9 types individually, and non-G1 types when pooled together.

Rotarix did not increase the post-vaccination risk of intussusception. However, increased rates of pneumonia-related deaths, and convulsion-related SAEs were observed in the Rotarix group from dose one to visit three in Study Rota O-23.

Finally, co-administration of Rotarix with other routine vaccines in the U.S. did not interfere with immune responses to each of these vaccine antigens.

As part of the pre-BLA agreement, the applicant will conduct a U.S. post-licensure observational study, safety study in which a cohort of infants will be vaccinated in a routine pediatric healthcare setting. Safety data will be collected prospectively,

and the total number of vaccinated infants will be calculated in order to provide 80 percent power to detect a relative risk of intussusception greater than or equal to 2.5 at a 5 percent significance level.

Other measured outcomes in the study will include deaths from all causes, hospitalizations due to acute lower respiratory tract infections, including pneumonia, convulsions, and Kawasaki disease.

I'd like to acknowledge all the members of the FDA review team listed in this slide, as well as other CBER members who assisted with preparations for this Advisory Committee meeting. Thank you very much.

DR. MODLIN: Thank you, Dr. Rosenthal. We do have a few minutes. I thought maybe I might first give Bruce Gellin an opportunity to ask any questions or make any comments, since you're not going to be here this afternoon. And I know it's premature, but we do have some time, Bruce. I

didn't know if there's anything that you wanted to --

DR. GELLIN: Thank you for the opportunity, John. I think that we're going to have a discussion about some more of the details of the post-marketing studies, and I'll be interested in some of those. But that's the place I'd like to focus. Thanks.

DR. MODLIN: All right. If not, I think what we'll do, given the time, again, let's take the opportunity to take an early lunch break. We will start back up at 1 p.m. sharp, and I think we will, again, have ample opportunity for questions, and for discussion. So thank you, everyone.

(Whereupon, the proceedings went off the record at 11:37:03 p.m., and went back on the record at 1:01:29 p.m.)

DR. MODLIN: At this point on the agenda, we have allotted time for the open public hearing. I'm going to turn things over to Christine.

EXEC. SECRETARY WALSH: Thank you, Dr. Modlin. As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda, and would like to make a statement concerning matters pending before the Committee. I have received two written comments. One comment has been received from B. Sachau, and the other is from Dr. Leonard P. Ruiz. Copies of their statements have been given to the Committee members, will be made part of the meeting record, and are available for review in the viewing notebook at the registration desk.

Is there anyone in the audience who would like to make a statement during this open public hearing before the Committee?

DR. MODLIN: Thank you. Dr. Rosenthal, do you want to go ahead and present the questions before the Advisory Committee?

DR. ROSENTHAL: Thank you. I'd

just like to restate the questions that were presented earlier in the day. Question One: Are the available data presented adequate to support the efficacy of Rotarix in preventing rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, and G9 when the first dose of vaccine is administered beginning six weeks of age, followed by a second dose separated by at least four weeks? If not, what additional information should be provided?

Question Two: Are the available data presented adequate to support the safety of Rotarix when used in a two-dose series beginning with the first dose at six weeks of age, followed by a second dose separated by at least four weeks? If not, what additional information should be provided?

And Question Three: Are there additional issues that should be addressed in post-marketing studies beyond the applicant's proposed U.S. post-licensure safety study? Thank you very much.

DR. MODLIN: Why don't we leave those up? Before we start, I'm going to ask if there are any questions about the questions. We sometimes do have them, believe it or not, from the Committee.

Seeing none, what I would like to do would be to give the members of the Committee and others opportunities to address questions to both the Sponsor and to the Division, before we actually begin to focus specifically on each of those questions. Now is the time to do so. I assume a number of people will have questions. We can take them in any particular order, but maybe starting with Dr. Jackson, if you have them.

DR. JACKSON: I had some questions that were then addressed by the FDA presentation. What I have left is pretty minor, so I think I'll pass.

DR. MODLIN: Pablo, Dr. Self. Dr. McInnes.

DR. McINNES: I have a question

about data to support the timing. So the issue on the table is that the first dose beginning at six weeks of age, two doses to be completed by 24 weeks of age with four weeks between dose one and dose two. So if you back down from 24 weeks, you could actually get your first dose at 20 weeks of age, get your second dose and be completed at 24. And I have a question about what data are available, both efficacy and safety data, to support this first dose being given as late as 20 weeks, and yet still meet the time parameters. And in O-23, I know the mean age at dose one was 8.4 weeks, and in O-36 it was 11.5, but I didn't see data that would address dose one really being given as late as 20 weeks.

DR. MODLIN: That's a great question, and I think others have it in the same -- Dr. Friedland?

DR. FRIEDLAND: Yes. Thank you for that question. We would not propose to give the first dose as late as 20 weeks. We would

propose to give the first dose, as studied in the clinical trials. In Study O-23, the first dose was per protocol given between six and 13 weeks of age, and in that study 10 percent of the infants enrolled in the total vaccinated cohort, so both safety data, including efficacy there, were given the dose at 12 weeks of age, and 3 percent of those enrolled were given a dose at 13 weeks of age.

In Study O-36, the per protocol criteria for dosing of dose one is between six and 14 weeks of age, and in that study, 13 percent of those enrolled received their first dose -- I'm sorry, 21 percent of those enrolled received their first dose at age week 13, 7 percent received their first dose at age week 14, and .3 percent were out of protocol and received their first dose in the 15th week of age, so we would not propose to give a dose as late as you were back-calculating.

DR. McINNES: So could you then maybe define more specifically what your

window would be for those ones, because the way it's phrased right now, one doesn't get an indication of that.

DR. MODLIN: Perhaps this is the best time to maybe look specifically at the language that's intended to be in the label. And, Dr. Rosenthal, do you want to address that? It would seem this is an appropriate time to do.

DR. ROSENTHAL: If -- we haven't started our negotiations yet with labeling language with the applicant. I mean, I guess you could present your draft of the label that you've presented to us already. Where it stated that the first dose should begin at six weeks of age following a second dose four weeks apart. That's sort of where we are now.

DR. MODLIN: But it sounds like Dr. McInnes' question, if I understand it, is the concern about both safety and efficacy for the upper limit for the first dose. And the data that we've just heard, the information that

we've just heard from Dr. Friedland is that the numbers of individuals in these trials that have received their doses beyond 13 weeks is exceedingly small, probably not large enough to support either safety or efficacy in that age group. Is that fair?

DR. FRIEDLAND: As mentioned, the data after 13 or 14 weeks of age based on two studies is very limited. And as mentioned by Dr. Rosenthal, we have yet to begin negotiations over the label, and will settle on an appropriate age range for the first -- recommendations for the first dose.

DR. MODLIN: Thanks, Pam, for bringing that up. Did you have any other questions, Pamela, before -- Dr. Self?

DR. SELF: Related to this, have you looked at trends in either safety or efficacy outcomes by age of administration? This was a related question and some of the other materials. And if you've done those analyses, could you describe them?

DR. FRIEDLAND: We haven't done any specific analyses based on age of administration; although, we have looked at the children who had intussusception at the age in which they were vaccinated. And I can provide you those data, as I pull them up here.

So, specifically, in the 13 definite intussusception cases that occurred within 30 days of vaccination, in the total vaccinated cohort at-large, the mean age of the first dose given in that study was 8.2 weeks, and the mean age in the children who had intussusception who received Rotarix was similarly 8 weeks. The range were that three of the six infants were dosed at first dose at ages 6, 7, and 7 weeks, and three were dosed at 11, 11, and 12 weeks. In the placebo group, there was a similar mean age. As mentioned, in the placebo subjects, of the seven, the time of age when they received their first dose, and those who had

intussusception was 6 weeks, 6 weeks, 7 weeks, 7 weeks, 9 weeks, 10 weeks, and 12 weeks, so we don't see an increased risk of intussusception in infants who are vaccinated at an older age.

DR. MODLIN: Thank you.

DR. VERSTRAETEN: Dr. Modlin?

DR. MODLIN: Yes.

DR. VERSTRAETEN: Can I add something?

DR. MODLIN: Yes, certainly.

DR. VERSTRAETEN: Few more data on that. Because the issue of the association between the risk of intussusception and age has come up related to another vaccine, we've done some analysis to look into that. So I'd like to show you a graph we did. Basically, what we did is we looked at the relative risks as they relate to the age at the first dose of vaccination.

Now, within the clinical trials, we stopped vaccinating. There were few children

that were vaccinated beyond 90 days of age. Can you project the slide, please? So this is a smoothed curve of the relative risk of intussusception in the vaccinated group compared to the placebo group, as it relates to age at the first dose. And, as you can see, the red line is actually the relative risk, and the pink lines are the 95 confidence intervals around it, so this certainly doesn't suggest that there's any increase in risk with age.

In addition, and since the label in Europe allows vaccination of the first dose up to 20 weeks, we've also looked at our spontaneous reports to see if there's any indication that there's an increased risk with age. Can I have the next slide, please?

Now this becomes a little bit complex, because we were thinking how are we going to evaluate spontaneous reports where we don't have denominators? And what we wanted to see is what's the age distribution of the

cases that's being reported to us. Now there's three different parameters that can influence that age distribution. The first one, of course, is the age distribution of intussusception and the background, the natural age distribution. The second one is the age at vaccination, and the third one is the probability of a report being made to us in function of age.

Now, the second and the third parameter we've combined. Basically, we've had it represented by the distribution of the age of other reports that are being made to us, non-intussusception reports related to Rotarix. For the first parameter, we took data from a recently completed study in Switzerland. Can I have the next slide?

So this is the age at which reports are being made to us spontaneously following Rotarix, excluding intussusception reports. The next slide, please. This represents the age distribution of intussusception in Europe.

Next slide. So this is what, when we combine the two previous curves, this would be the age at which we expect cases of intussusception to be reported to us, assuming there is no association at all between the age and the risk of intussusception. So what we figured is if there is a true association with higher risk, that curve should be shifted to the right when we look at the reports we received in reality. So can I have the next slide?

So the green curve now shows you the actual age distribution of reports of intussusception made to us, which very nicely fits the actually expected age distribution. Now this is for all doses. Can I have the next slide? This is the distribution of the two different doses that we have for Rotarix. And then the next slide, this is what we see for the first dose. Again, the green curve, which is the real age distribution, fits very well on the red curve, which is the expected age distribution. So at least the spontaneous

reports do not insinuate that there's any association between the age at vaccination and the risk of intussusception.

DR. MODLIN: Very helpful. Thanks, Dr. Verstraeten.

DR. FRIEDLAND: Dr. Modlin, may I add one more thing?

DR. MODLIN: Certainly.

DR. FRIEDLAND: Ken mentioned that there's a study that was presented by the FDA this morning when we talked about the Kawasaki cases, a study ongoing that's recently finished in Asia. And in that study, there are a number of infants who are vaccinated ages 17, 18, and 19 weeks of age. And if the Agency is interested, we can submit those data for your review.

DR. MODLIN: Thank you. We'll continue on. Dr. Romero, do you have questions?

DR. ROMERO: I do, and tentatively, since this is my first meeting. So the safety

data has focused on the issue of convulsions or seizures. Is there any data that you looked at with regard to encephalopathy not associated with convulsions; that is, rotavirus, natural rotavirus infection is associated with encephalopathic conditions, not associated with seizures. Any comment on that?

DR. MODLIN: So you're asking something that's a little bit more general than just presence of seizures, but something that might include seizures, may or may not include seizures, but may be something even more general than that.

DR. ROMERO: Correct.

DR. MODLIN: Okay.

DR. FRIEDLAND: Yes. When we look at the Core Integrated Summary of Safety, I took a look to see if there were reports of encephalopathy, encephalitis, et cetera, and there are very limited numbers of reports, one, two cases, sometimes in Rotarix,

sometimes in placebo, no signal there for those types of adverse events.

DR. ROMERO: And in your post-marketing, will you specifically look for these events, other than just seizure?

DR. VERSTRAETEN: We're just checking, but we do look at all neurological serious adverse events, of course. As far as I recall, we have not seen any such events, but I will check with my colleague who's dealing with the vaccine, specifically. And as soon as we have the information, we'll give you that answer.

DR. MODLIN: All right. I know that Roger Glass and colleagues have recently published a review of rotavirus-related CNS events, including actually demonstration of the presence of rotavirus antigen in CSF in patients that apparently had disease following natural rotavirus infection, so that question has come up in our clinic around RotaTeq, so that's a terrific question to ask. Do you

have further ---- Jose?

DR. ROMERO: Yes, just one other question. I don't know if it's germane to this, John, so guide me. But one of the questions I was going to ask is, have you at all looked at viremia associated with your vaccine, or is that not germane or relevant to this?

DR. MODLIN: Viremia as measured by anigenemia, or PCR, or whatever?

DR. ROMERO: Well, I would be interested to hear whether they did either/or.

DR. FRIEDLAND: There are limited data on antigenemia and viremia with natural rotavirus infection, and also with vaccine. We have limited data with our vaccine. There was a Phase II study called Study O-03, which was not part of the BLA. It was a study with early formulations of Rotarix, and in this study, Dr. Vesikari from Finland, and colleagues, presented data on RNAemia from the study at the Second European rotavirus meeting

this past summer. And I can tell you briefly the results from the study.

Approximately 6 percent of infants who were given Rotarix had evidence of RNA in their serum. At the same time, 20 children with rotavirus who were admitted to the hospital in Finland were also evaluated in Dr. Vesikari's lab. And testing there showed that 11 of the 20 samples tested were RNAemia positive from wild-type rotavirus testing. So RNAemia does occur after vaccination at significantly lower rates than in wild-type natural infection.

DR. MODLIN: Any further questions?

DR. ROMERO: Thank you, John.

DR. MODLIN: Seth?

DR. HETHERINGTON: Getting back to the question of immunogenicity and the intervals of vaccination, is there any information available as to the magnitude of the duration of antibody response based on the intervals between the two doses? In other

words, does interval between the doses impact either magnitude or durability of the immune response?

DR. MODLIN: Did you get the question, Dr. Friedland?

DR. FRIEDLAND: I don't believe we have such data to answer that question. Most of the clinical trials, the first and second dose was given either one to two months after the first dose. What we do have data on is an effect of time to testing antibody levels after vaccination. And we know that antibody levels are sensitive to time with IGA levels, and that the further from the last dose that the sample is tested, in general, the lower the antibody level.

DR. MODLIN: Dr. Debold?

DR. DEBOLD: Okay. This is my first meeting, so bear with me. I have a lot of questions, some of them are just general, because I'm new to the subject. But I was curious as to why the OPV was avoided in some

of the clinical trials. And, also, why administration of Hepatitis B vaccine was a criteria for non-eligibility for the one -- Hepatitis B vaccine at birth or within four weeks of getting the rotavirus vaccine was a criteria for not being included in the one U.S. co-administration study, Rota O-60, I believe?

DR. FRIEDLAND: Yes, I'm happy to address those in the order that you asked regarding OPV. OPV is an Oral Poliovirus Vaccine. There would be a question if two oral vaccines given at the same time might have some interference. We did do one study in the BLA, Study O-14 conducted in South Africa where OP was given at the same time as Rotarix, and in that study poliovirus seroconversion levels were adequate. There was no evidence of interference, and the antibody response to Rotarix, itself, was adequate.

Subsequent to that, we have

completed a study that is not part of the BLA. It's finished after the BLA was submitted in Latin America where Rotarix was given with OPV on an EPI schedule, versus a placebo plus OPV on an EPI schedule. That was a safety and efficacy study, and in that study it was demonstrated that Rotarix is efficacious, as previously seen in Latin America, and there was no interference on the OPV, or the Rotarix responses.

The second question you asked had to do with Hepatitis B. In the United States, Hepatitis B vaccine is recommended to be given at birth, and then subsequent doses, two subsequent doses, so we wanted to make sure in the Rota O-60 study, if a child was vaccinated with Hepatitis B, that it was given at birth, and that we knew about that so we wouldn't give them additional doses of Hepatitis B in the study. So they were completely vaccinated appropriately with Hepatitis B in that study.

DR. VERSTRAETEN: Just one

additional comment, because your question was also why did we avoid co-administration with OPV at the beginning? As you may or may not recall, when the whole RotaShield and intussusception concern was raised, there was also a certain concern at a certain point in time that OPV could be linked to intussusception, and we wanted to make sure that our data would only refer to our vaccine, and not to another vaccine that would have been co-administered at the same time. However, as Dr. Friedland said, in a later stage we then did studies where we co-administered the two.

DR. DEBOLD: Should I go ahead?

DR. MODLIN: Please, do.

DR. DEBOLD: I have a question, too, about the horizontal transmission issue. In the materials that were provided to us, there were seven documented cases of vaccine strain rotavirus in placebos. I'm just wondering if the manufacturer could talk a

little bit about what effect that might have on some of the results that were observed? And I also, while I'm at it, would like to know -- because it sounds like what was provided was that the placebos that tested positive for the vaccine strain were asymptomatic. How frequently does asymptomatic infection with wild-strain or wild-strain rotavirus vaccine occur? And to what extent could that have affected the results that you observed?

DR. FRIEDLAND: Yes, if I could have this slide up, please. In the clinical trials, stool samples were obtained at pre-determined time points, and among the 421 stool samples that were collected on placebo subjects, seven were positive for rotavirus vaccine strain. Shown on the slide, too, the samples came from Study O-05 in the United States, a Phase II study, one sample from a study in Latin America, three samples from a study in Singapore, and the last sample from a

study in Taiwan. Two of the seven placebo subjects shed vaccine virus at two time points, as mentioned, as you've just said. We reported that none of these symptoms reported fever or gastrointestinal symptoms at or around the time of vaccination. Four of the seven subjects seroconverted, had an antibody response, and two of the subjects both from Study 5, had a twin in the same study at the same time.

Your question regarding how often does rotavirus infection occur without gastrointestinal symptoms; it certainly has been reported, but the classic presentation for rotavirus is vomiting, diarrhea, and fever. We'd like to say that if shedding is occurring, it's not occurring with associated gastrointestinal symptoms.

It's important to point out that nearly all children in the United States will be exposed to natural rotavirus at an early age, certainly under the age of five, and

probably by the time they're two years of age. This is an attenuated human rotavirus strain, and one needs to weigh the high likelihood of acquiring natural rotavirus to the potential likelihood of transmission from an attenuated human rotavirus strain.

DR. MODLIN: But your question, also, was how it might affect the results of the study, presumably, the efficacy results. And to the degree to which your placebo patients are being immunized with vaccine strains, presumably, they also are being protected, and that would actually have the effect of reducing the observed efficacy when you think about it.

DR. FRIEDLAND: Yes. Thank you, Dr. Modlin.

DR. MODLIN: If that were an important effect. Do you have other questions, Dr. Debold? Okay. Would you like to pass, and we can come around again?

DR. DEBOLD: I'll pass.

DR. MODLIN: Dr. Belay.

DR. BELAY: I also had a question about the convulsion or the seizure in the patients. I was curious about the investigator's conclusion as to what might be causing the convulsions in some of those patients. Did they, for example, look at each one of the cases and see or come up with another potential explanation for them? I was just curious about that.

DR. FRIEDLAND: Yes. The question is regarding the seizures and the investigators, and how did they reach that diagnosis, what type of evaluations were done? All of the cases were reviewed, and of the cases of convulsions, of the 20 cases that occurred during the whole surveillance period in the Rotarix group, and the 12 that occurred in the placebo group, almost exclusively these diagnoses were made clinically. Very few of the patients had an EEG, and in all cases when an EEG was done, it was normal. Very few had

further evaluations, including imaging or other testing. And almost exclusively, these cases were clinically diagnosed.

DR. BELAY: Any evidence that the seizure actually continued and they became epileptic, for example?

DR. FRIEDLAND: I can look at my notes, and I can tell you that in rare cases, patients were reported to have seizures at a second time during the study.

DR. MODLIN: Any further questions? Dr. Davis.

DR. FRIEDLAND: I can just answer that.

DR. MODLIN: I'm sorry.

DR. FRIEDLAND: Two of the 20 subjects had a repeat seizure. I should also mention that many of the subjects had pre-existing or concurrent medical conditions that could have accounted for the seizures, such as hypocalcemia, or hyponatremia, severe neonatal hypoxia, et cetera.

DR. DAVIS: Thank you. I have three questions, one actually from a safety standpoint, one from an efficacy or effectiveness from a parent viewpoint, and one from a statistical viewpoint. So the first question is, both Bruce Gellin and I were talking about sort of the one thing that is a little bit concerning, which is the pneumonia-related deaths, or the pneumonia deaths. And we both wanted to know if it was possible, or maybe if you had a slide that shows in a bit more granularity the time line of the pneumonia-related deaths. You sort of have them divided into, I think before 30, and after 30 days, and we both were interested in just seeing a more sort of in-depth view of that.

And related to that is, are there pneumonia-related deaths in any other rotavirus vaccine studies, including this vaccine, or the other two previous vaccines that have been developed, and about to market?

Has this ever been seen before?

DR. FRIEDLAND: Okay. Thank you. I'll first start with your question about --

DR. DAVIS: So that's the first question, and then I'll get to the other two in a second.

DR. FRIEDLAND: Right. The first part of the first question.

DR. DAVIS: Yes.

DR. FRIEDLAND: If I could have this slide up, please. This is the time of onset of the pneumonia deaths. There were, as mentioned, when we look at the pneumonia-related, 16 deaths in the Rotarix group, and 6 in the placebo group. The light blue color are the children who received Rotarix, and the dark red color are those who received placebo. And as you can see, there is no clustering after vaccination close to either dose one or dose two.

If I could have -- in addition, you were asking about other pneumonia deaths. If

I could have Slide Y. H-19 I think is what I'd like. So the deaths that we mentioned this morning were deaths that occurred in Study O-23. Yes, thank you. There were additional studies included in the BLA, which I'll show on this slide, if I can have this slide up, please. So if we look at the additional studies within the licensing application that were submitted, there were four additional pneumonia-related deaths in the other studies submitted to the BLA in the Rotarix group, and there were five pneumonia-related deaths reported in placebo subjects in the other studies submitted to the BLA.

One of these four subjects had pneumonia-related death onset within 30 days of a vaccine dose. Three of the placebo subjects had pneumonia-related death within 30 days of receiving the placebo.

I should mention that there are additional studies that have been completed since the licensing application was submitted.

One of them was a study known as 24, which I mentioned was a study where Rotarix was given OPV on an EPI schedule, and then the other study we talked about briefly earlier related to Kawasaki disease, a large study conducted in Asia, Study 28, 29, 30. The FDA has not received these data to review, but they were aware that we might be interested in presenting these data anticipating such a question. They have given us permission to show you these data, but they have not had time to fully review it on their own.

Within those two studies, 24 in Latin America, and 28, 29, 30 in Asia, over 9,700 children received Rotarix, and over 7,500 received placebo. And there were three pneumonia-related deaths in the Rotarix group, .03 percent, one in the placebo group, none of these deaths occurred within 30 days of vaccination.

I did mention earlier that there are two ongoing studies in Africa, where one

is a safety and efficacy study, and one is a study of HIV-infected infants. And as might be expected, deaths are occurring with increased frequency compared to other studies in that study, including pneumonia-related deaths. If I could have the next slide, please.

Again, the FDA is allowing us to show you these data, but they've not received these data for review. But they are aware that we wanted to show you these data. I should mention that both of these studies are ongoing. They've completed enrollment, but they are ongoing.

GSK remains blinded to treatment allocation. The IDMC has been reviewing these data, and they are unblinded to treatment allocation. In these two studies involving over 5,000 infants, 135 deaths have been reported, 60 of the deaths are said to be pneumonia-related. The IDMC, as I mentioned, met recently and said to GSK that they have no

safety concerns based on these studies. So that's the additional information we have related to additional pneumonia deaths.

I'd like to introduce Thomas Breuer from GSK.

DR. BREUER: Good afternoon. I'm the head of Clinical and Achievement Legal Office of GSK Biologicals. The second part of your question was whether that has been observed with other rotavirus vaccines, RotaShield and RotaTeq. I just want to point out that death in a post-neonatal period due to infectious diseases happen quite often in areas where we have performed a study; namely, Latin America, and in some Asian studies, and then again in Africa. However, the other programs were predominantly studied in the U.S. and in Europe, where you have almost no infectious disease-related death in the post-neonatal period, so you would not expect to see such signals in these programs. So I think it's important to point that out, that

these three programs, two were predominantly run in Western World kind of area, and the other one were run in Latin America, Africa, and Asia.

DR. DAVIS: Great. Thank you. So the second is, as I mentioned, from a parental viewpoint, which is you showed the protective effect of the rotavirus vaccine against gastroenteritis. When the vaccine-associated gastroenteritis was excluded, and when gastroenteritis in the first two weeks after vaccination was excluded, and as a parent getting vaccinated, you don't really care about those exclusions. You want to know what's the effectiveness of the vaccine against everything from this moment on. And I'm sure you've anticipated this question, and I was wondering if you wouldn't mind sharing data towards that. What the protective effect of all gastroenteritis is from the moment of vaccination?

DR. FRIEDLAND: Yes, I can show

you. If I can have Slide E-8. So this would be a total vaccinated cohort efficacy analysis.

DR. DAVIS: Right.

DR. FRIEDLAND: If I could have this slide up. So this is efficacy in the study in Europe, Study O-36, but the same data are available if you'd like for O-23. Looking at efficacy from beginning, from the time the infants received their first dose of vaccine, and if you were to look back into your binder, you would see that the efficacy results in the total vaccinated cohort are that the first season to the second season are very, very similar to the results seen in the according to protocol analysis. We have the same type of data for Study O-23.

DR. DAVIS: Okay. Good. Thank you. I assumed such, I just wanted to -- okay. So then the third question is, in the safety analysis, there was a statement made. And I apologize, Tom, this was adjusted for

study effect. And I have no idea what that means, or how it was done, or why it was done. And I'm wondering if you could just clarify what you mean by "adjusted for study effect." I think I have a clue, but I've never seen it done before.

DR. VERSTRAETEN: Okay. Thanks for that question, Bob. You know, when you pool this data, you always have to be very careful, because you might have difference between the studies. Now in this particular case, most of our studies are one-to-one randomized, so it may not make such a lot of difference. If you start mixing studies with different randomization ratios, this becomes really crucial. So the adjustment for study effect is basically taking the difference that may exist between the different studies into account. It's like you would calculate a relative risk across different studies, and then average those out. That's what it means.

DR. MODLIN: No questions, Dr.

DeStefano?

DR. DeSTEFANO: I have three questions. The first one is for Dr. Friedland. I think you mentioned, or maybe I missed it, that in the pneumonia-related deaths, that you took out deaths that had some underlying cause, or attributable cause for the pneumonia, that you reduced the number. I wonder if you have similar data for the placebo pneumonia-related deaths that didn't have any other attributable cause?

DR. FRIEDLAND: Yes, I do, and I'm going to find those. There were -- of the six pneumonia-related deaths in the placebo group, two of the infants had some pre-existing conditions. One was a questionable infant. This was a child who 46 days after receiving dose one of placebo developed cough, fever, dysmia, infultates, cardiomegaly, and died three days later. The chest x-ray was read as having upper lobe infiltrates and cardiomegaly. And the clinical diagnosis from

the clinicians was a suspected patent ductus arteriosus.

The last case, or the second of the placebo subjects was an 83-day old who had a history of a communicating hydrocephalus. And this patient had emesis after receiving sedation for a CT scan, and subsequently developed pneumonia.

DR. DeSTEFANO: Thank you. I have a couple of questions for Dr. Verstraeten. First of all, it looked like in your post-marketing surveillance, as I understand it, had about 12 million doses distributed worldwide, and almost 9 million were from Brazil. I wonder if you could describe the post-marketing or pharmaco vigilances in Brazil, and if you have any data on sort of completeness of reporting?

DR. VERSTRAETEN: Yes and no. So, I mean, I'm certainly not an expert on the whole pharmaco vigilance system in Brazil. But what I can tell you is that what we have

seen is that overall, the reports that we receive from Brazil have come in the lower frequency than what we receive in the rest of the world. However, when we look specifically at serious adverse events, they approach must closer what we see from the rest of the world. And then the best news is, when we look at intussusception, the rates that they report are not very much lower to what we see in the rest of the world.

Now to go back a couple of years, when I was working with you at the CDC, you will remember the whole Yellow Fever investigations that were going on. And at a certain moment, Dr. Chen and I went down to Brazil to help them set up some surveillance. And I have to say, we also took advantage to look at their Brazilian VRS, and I was pretty positively impressed, I have to say, with what they collect as data, so they do have a system in place. However, the reporting rates are lower than what we see in the rest of the

world. I have to acknowledge that.

DR. DeSTEFANO: And one other question for you. I guess in this study that you have planned in Mexico with the one million birth cohort, it seemed like you have questions about whether you're going to include Kawasaki disease and pneumonia deaths, and I was just wondering what kind of -- what would the reasoning be, or what it would take to include those, because it seems like this is a tremendous opportunity to really get good data.

DR. VERSTRAETEN: Can you repeat? I'm not sure I understood.

DR. DeSTEFANO: I think in Mexico you said that, whether you include Kawasaki disease, and perhaps pneumococcal deaths. You're not sure whether you're going to include that as part of your outcomes that you're evaluating.

DR. VERSTRAETEN: Okay. So pneumonia deaths, that's one of the outcomes

of the study, actually, intussusception and pneumonia deaths, those are the two main outcomes of the study. The question was posed to us whether we should look at Kawasaki disease in the study.

There's a number of concerns we have there. First of all, Kawasaki disease is not very -- is not so common in Latin America, and Mexico, we're closer to U.S. It might not be that rare, but we'd be mostly concerned about the ascertainment rates of Kawasaki disease.

DR. DeSTEFANO: You mean, they may not diagnose it there?

DR. VERSTRAETEN: They may not diagnose it, and then the other question is will we actually capture it, even if we look for it? So the way we've set up the study is, we go through -- I'm looking at Camille -- I think it's 224 hospitals throughout Mexico. We go and actively look for cases of intussusception and for cases of deaths that

may be related to low respiratory tract infection. To add Kawasaki onto that would be a huge undertaking, and I'm not sure we actually could get much out of it, so we're more comfortable looking at that in the U.S. setting where I think we'll have better data.

DR. DeSTEFANO: So this is very sort of manual-type system. It's not all computerized data systems that --

DR. VERSTRAETEN: Well, it's a mix of the two. So it's active surveillance, where we go and look, and find the data. In addition, they do have a database, and it's a huge database. It's 40 million people that are in the database, so we use the database as a backup. Basically, we'll search for these cases, and after that, we'll search through the database to see if there's anything we may have missed. So we'll then match the two, and anything we find in the database that we didn't find in the surveillance, we'll go back to the hospitals and see if those are true

cases or not.

DR. DeSTEFANO: All right. Thank you.

DR. FRIEDLAND: I'd like to just add with regards to Kawasaki, post-marketing studies that are planned in Latin America or North America are in areas of the world where the incident rate of Kawasaki is lower than in Southeast Asia, and we just happened to have been doing the study in Southeast Asia, Study 28, 29, 30, which I mentioned had over 10,000 infants. So we have fairly robust data on Kawasaki, even though we hadn't planned to do the study for that reason that we have presented, and so I think we have a good handle, thus far, on Kawaski incidence in clinical trials of children who received Rotarix.

DR. DAVIS: John, could I just ask --

DR. MODLIN: Of course. Please, do.

DR. DAVIS: The study in Mexico.

What's not clear to me, it sounds like you're doing fairly intensive active surveillance, but what you haven't described is what you're going to use as the comparison group.

DR. VERSTRAETEN: Thank you for that question, again. So the method used is a self-controlled case serious analysis, so it's basically what Trudy has also done in the RotaShield study, where she did the case control and the self-controlled, so we won't really be needing controls, since we have a predefined exposure or risk period after vaccination. We'll use that one.

DR. MODLIN: John?

DR. ROMERO: May I offer a comment about the Kawasaki issue in Mexico?

DR. MODLIN: Yes, sure.

DR. ROMERO: As somebody who was born and raised, and trained in Mexico, and did his internship in Mexico --

DR. MODLIN: Jose, could you bring the microphone a little closer to you?

DR. ROMERO: I'm sorry. And is familiar with the Mexican health system; although, I did not train in the IMSS, the IMSS system. I'm not certain that this type of a diagnosis would be a diagnosis that would be readily evaluatable under that system. And it's not to be demeaning or pejorative to the system. I think that the way we evaluate Kawasaki in this country is fairly extensive. I mean, the amount of serologic data, the exclusionary tests that we use may not be accessible to all of the systems in IMMS, so I'm not sure that you're going to get a lot of "bang" for your buck on this particular aspect. I think that the issue of pneumonia, though, is clearly something that could be evaluated in that country under that system.

DR. MODLIN: Thanks, Jose. Melinda.

DR. WHARTON: Yes. I have two questions about seasonality. In the large Phase III efficacy trials, although I don't

remember reading this, I would guess that there was an effort to deliver vaccine, both doses, the complete vaccine series prior to the expected onset of the Rotavirus transmission season in the countries in which the trials were being performed, rather than vaccination being ongoing throughout the year, but I don't know that. What was the seasonality of vaccine distribution relative to the Rotavirus transmission season?

DR. FRIEDLAND: Yes, I can address that question. In Study-036, the study in Europe where Rotavirus is anticipated to have a seasonal exposure, the Rotavirus season was defined as December-May, so there was an attempt to vaccinate before the Rotavirus season. Although, as I mentioned, not everybody had received both doses before Rotavirus season started.

In the study in Latin America, where it's felt that Rotavirus is not necessarily seasonal, but year-round, there

was no defined season in Latin America.

DR. WHARTON: Okay. And that's -- thank you. And that's a prelude to my second question, which has to do with seasonality of Rotavirus disease compared to respiratory disease in tropical countries, and temperate climates like the United States, Rotavirus season, and what we usually think of as the respiratory disease season coincide. And what about in tropical countries, where seasonality may differ? You already mentioned the Rotavirus disease, so I guess there isn't seasonality of Rotavirus in tropical settings?

DR. FRIEDLAND: My colleague, Eduardo Ortega, who is a physician from Latin America, and works for GlaxoSmithKline would like to address that question.

DR. ORTEGA: Thank you very much. I am from Panama. I am currently the Vice President for Clinical R&D for Latin America. Before that, I was a principal investigator for Rota O-23 in Panama, and for one year I

was responsible of Carica Modena, the area in which 50 percent of the children were recruited. Basically, Latin America will depend on the hemisphere in which you are. You're in the northern hemisphere, in Mexico, for example, you will have a very varied pattern of respiratory diseases, and it will coincide a little bit with the North American season. And you will see respiratory diseases starting October, November, December, and January. If you are in the southern hemisphere, Brazil and other countries, then you have the reverse, and it will depend of the hemisphere in which you are.

In Rota O-23, we have subjects in northern hemisphere, and the southern hemisphere, and also in the middle of the Central American countries.

DR. WHARTON: Thank you.

DR. MODLIN: I have just a couple, myself, if you don't mind. We haven't really heard any information about the particular

sensitivity, but also the specificity of the ELISA assays that have been used in all these trials to detect Rotavirus disease. And I guess I have a corollary question to that, and that is, we saw impressive reduction in gastroenteritis due to all causes. What do you see when you look at the effect of vaccination on ELISA negative gastroenteritis?

DR. FRIEDLAND: Well, to start with, I can say the Rotaclone assay was the assay used in the Phase III programs for the ELISA. There is no reference, recognized reference standard which the assay is based. It's a commercially available assay for use in the United States and elsewhere.

We did look at the Rotaclone assay and compare it to the ELISA assay developed by Drs. Bernstein and Ward, which was used in our Phase II program. And compared to the Bernstein and Ward ELISA assay, the Rotaclone assay sensitivity is 85 percent, and the specificity is 100 percent.

With regards to your comment about reduction for all-cause gastroenteritis, I don't have an answer to your question about ELISA negative. I can say that, for example, in Study O-36 where there was a 75 percent reduction in all-cause gastroenteritis, if we look at -- this was gastroenteritis causing hospitalizations. If we look at the percentage of placebo subjects who had gastroenteritis who are hospitalized in that study, 55 percent of those infants had Rotavirus. And the reduction was 75 percent.

DR. MODLIN: David, did you want to say anything more about the sensitivity of the assay, David Bernstein? The ELISA assay, because my understanding is it may be a little less sensitive than, say, PCR and others. It's important because the question is are you -- how does it affect -- would affect the results of the trial.

DR. BERNSTEIN: Yes. Dick Ward actually does most of this, and his home-grown

ELISA, uses home-grown reagents. But in the studies that compare the commercial assays, Rotaclone compares very favorably with any other commercial assays. It is less sensitive than PCR. In fact, we have a paper that was just accepted where we compared PCR to both Dick's ELISA and to Rotaclone, and the problem was that when we collected healthy infants as a control group, I think it's something like 20 percent of those were positive, so you actually can't predict that an illness is due to that Rotavirus if they use PCR.

If you Rotaclone or Dick's assay, there was actually zero in the negative control group, because once you get so sensitive, either these kids had an infection a month ago, and still had enough virus to be positive by PCR, or they had a sub-clinical infection, so it actually was not useful doing that. So I think Rotaclone is about as good as we can do.

DR. MODLIN: Thank you. One other

question. The seroconversion rates in developing countries across the board was somewhat less than it is in industrialized countries. And I guess, I just wonder if you have any information that would give us a little bit more information about the basis for that. Is that a higher titer of passive acquired maternal antibody in these infants, the time they're immunized, or are we looking at the possibility of increased risk of interfering gastrointestinal pathogens in this population, or a combination of the two? Do we have any sense of what the reason for the lower seroconversion rates happen to be?

DR. FRIEDLAND: I have my sense of what I've read in the literature, and there might be others who can contribute to this conversation. But lower immunogenicity and lower efficacy has been seen with live oral vaccines, with poliovirus vaccines, with cholera vaccines, and also with Rotavirus vaccines, including RotaShield, and also

Rotavirus vaccines that were in development in which development had stopped. Speculation as to why this may be includes interference of enteric pathogens, presence of maternal antibodies, are two of the etiologies that are given. There might be others in the room who have more information about this, but this was not an unexpected finding.

I think it's important to point out that while vaccine efficacy in the Latin American study, O-23, was somewhat lower than that in O-36, vaccine efficacy was still quite robust in Study O-23; 85 percent protection against severe Rotavirus gastroenteritis.

DR. MODLIN: Okay. Dr. Debold, do you have further questions?

DR. DEBOLD: Yes, actually I do. I'm still concerned about the pneumonia-related deaths, and the convulsions. And I'm concerned partly because I notice that a primary inclusion criteria for the study was that the child be healthy. So part of the

explanation for why some of this may have happened was because we had children who are hyponetrimic, or had some other underlying problem. So now what happens when this vaccine is given to children in the real world, what happens when it's given to preemies, what happens when it's given to children who have feeding difficulties, gastrointestinal problems? Do we have any evidence of not only efficacy, but safety, in giving this in vulnerable infant populations, particularly those who may be immuno suppressed?

DR. FRIEDLAND: Good question.

DR. VERSTRAETEN: So as I mentioned in my presentation, there is a number of additional, what we call Phase IV studies, which are ongoing right now. So one of them looks specifically at the question of prematures. In that study, there's two group of premature children. There's a group of severe premature, less than 30 weeks of age,

and then the other group is, I believe, between 30 and 36 weeks of age, so we're specifically testing the immunogenicity and safety of Rotarix in that group. So we will have that answer shortly.

Another study, which is ongoing in South Africa is looking specifically at HIV-infected children. Now these children, some may be or some are not immuno compromised depending on their status. So, again, it's a very difficult study. It's not easy to find those children, and there's a lot of deaths, unfortunately, occurring in that study, but we will have that answer, also, shortly.

So, in general, when we develop our clinical development program, there's always a balance to make between enrolling healthy children, because you're worried about natural effects and making sure we have as pure data as possible. And, therefore, usually, we will set up these Phase IV studies trying to answer these questions.

Of course, in addition to that, we have our pharmaco vigilance program in which we will try to see if there's any undue effects in populations that were in studies in the clinical trials.

DR. FRIEDLAND: I'd like to add, as mentioned in the briefing materials, in the study in Latin America, Study O-23, we know that there were 254 infants enrolled in that study, small numbers, but still 254 infants enrolled who were gestational age less than 36 weeks; 134 of those infants received Rotarix, and 120 had received placebo. And the adverse event profile between those two groups was comparable, so there was no evidence of any increased adverse events in premature infants in Study O-23.

DR. MODLIN: Thank you. Yes, Dr. Belay?

DR. BELAY: How many, again on the pneumonia cases, if I remember correctly, cases of pneumonia were also observed in Study

36, which is the one that was conducted in Europe. In two of the countries, France and another country, if I remember correctly, used Prevnar as part of the routine childhood immunization program. In your analysis, did you separate out the two countries that use Prevnar and the countries that do not, and look at the pneumonia issue?

DR. FRIEDLAND: You can start, and then I can look up the answer.

DR. VERSTRAETEN: Okay. That's a very good question, thank you. And, actually, it's one of the considerations we made. We also noted, this one country where Prevnar was given, could there have been an interference with Prevnar? So we tried to tease that out. However, we did not see a specific effect limited to France, or to the countries where Prevnar was not given, so as far as the data allowed us, we couldn't tease that out. It didn't look like that was what was happening.

DR. FRIEDLAND: All right. And I

do remember now, there was no country effect seen when we looked at countries in the pneumonia deaths, either.

DR. MODLIN: Yes, Pablo?

DR. SANCHEZ: Getting back to the vulnerable population and premature babies, do you have any -- in the premature studies that you will be conducting, will you be evaluating its use in short gut infants, or full-term babies who've had short gut secondary to gastro --

DR. FRIEDLAND: The question is in the premature study, or I would say even in other studies, are we specifically enrolling children with short gut or other gastrointestinal malformations? The answer is no, that is not a specific population that is being specifically studied at this moment.

DR. MODLIN: I think Dr. Sanchez's question is an important one, and it raises the issue of -- it's a very practical one when it comes to making -- when you make a

universal recommendation for use of a vaccine, and then you need to understand how it's going to be applied to all different types of populations, and what the risk-benefit ratio may be. And I know that the past working groups at the ACIP, for both RotaShield and for Rota Teq have struggled with these issues. In some respects, they're a little bit different from the labeling issue, because the label, necessarily, needs to be based on the data that are brought to bear on safety and efficacy, and doesn't often go beyond that.

It largely comes down to ultimately being an issue for the ACIP until such data are generated that specifically address safety and efficacy in these specific populations, Pablo. And those often take a fair amount of time, and almost always occur as they're occurring in this case, after licensure, as part of a Phase IV program. So it's difficult for us, as this Committee, to weigh-in a lot on those issues, even though they're

critically important. But they're a little bit tangential to what our primary role is here today, if that's a fair way to put it.

I don't know if Norm or Dr. Rosenthal want to speculate as to what the label may say on these issues, or whether or not it will be any different than the Rota Teq label. I'm not forcing your hand, but I'm not going to get very far.

DR. BAYLOR: No, you're not. It's too early to make that speculation, John.

DR. MODLIN: Are there other questions? Pablo, did you have other questions? Dr. Hetherington?

DR. HETHERINGTON: One basic question, maybe too simple, and that is, just to make sure we understand how pneumonia-related death cases were identified. Were these cases where the investigator needed to state the pneumonia was either related to the death, caused primarily or secondary as a cause, or were they deaths that occurred when

pneumonia was a concurrent adverse event that was active, or were they deaths that occurred in patients that had had pneumonia at any time during their participation in the studies, or some other method?

DR. FRIEDLAND: Yes, thank you. It's important to mention that when Study O-23 was conducted, there was no reason to be specifically looking at fatalities in that study, and the study was not designed to look at fatalities. So all fatalities that were reported in that study were as per our standard instructions to investigators; and that is, when a serious adverse event occurs, which fatality being part of that group, investigators are instructed to report the diagnosis of the serious adverse event. So these cases that -- these were cases where the children died, and the serious adverse event diagnosis given by the investigator to the company included pneumonia as a preferred term.

In that study, the Independent Data Monitoring Committee appointed a special Safety Review Committee to review all of the fatalities, and assign a primary cause of death after their assessment. And the cases that I presented to you today, the 16 pneumonia-related cases in the Rotarix group, and the 6 in the placebo group, were with a primary cause of death assigned as pneumonia by the Safety Review Committee.

DR. HETHERINGTON: But just as a follow-up, usually, when you record an SAE, you record an outcome. And one of the outcomes you can record is death, so is it true, then, that all cases that this subsequent Endpoint Committee declared as related to pneumonia, had they all been reported as an SAE by the investigator with an outcome of death?

DR. FRIEDLAND: Yes, that is true.

DR. MODLIN: Jose?

DR. ROMERO: John, one more

question, if I may. So I'm sorry if I missed this when you presented it, but given the wide confidence intervals for efficacy that were shown on the O-23 study for G2-P4 Rotavirus, how many cases were there? I mean, how many actual cases were in that, and in the O-36 case?

DR. FRIEDLAND: Yes. So if I could bring back up from the Core presentation Slide A-38. If you could put it up on the screen. Thank you. In this study, G2-P4 was reported by two vaccine recipients and seven placebo recipients, so small numbers of cases.

DR. MODLIN: Does that answer your question?

DR. ROMERO: Yes. Sorry.

DR. MODLIN: I think it does.

DR. ROMERO: Thanks.

DR. MODLIN: Are there any further questions for either the Sponsor, or for the Agency from members of the Committee? Yes, Dr. Debold?

DR. DEBOLD: Okay. Sorry to keep after this, but the death statistics are still upsetting. And I'm not comfortable with the explanation so far, in the sense that we've talked about a portion of the deaths being related to pneumonia. That's only a fraction of the deaths that were reported. The FDA said they identified 128, there were, as I'm looking at the graph, it says there were 73 in the vaccine group, and 55 in the placebo group. And while I realize the confidence interval includes one, the confidence interval was basically .9 something to -- it was .92 to 3.02. The point estimate being at 1.64, which means that the vaccine group was 64 percent more likely to experience death than was the control group.

Can you please explain what these other causes of deaths were? Pneumonia was only what, 16 of them? What are the other 100 due to?

DR. FRIEDLAND: Yes, I certainly

can. The list is quite extensive, as you can imagine, with so many fatalities. If you'd like, I can go through each one with you. What I can say is an exploratory analysis, we looked at each cause of death comparing the Rotarix group compared to the placebo group to see if there was an imbalance. And the only imbalance that there was when looking at the preferred terms was for pneumonia death.

DR. DEBOLD: I guess I don't know what to -- I'm not that familiar with MEDRA terms. I'm sorry to have my back to you, but I think I'm supposed to talk in the mic. I'm not sure what to make of the coding issue, because it seems like even with the convulsions, I'm not sure that I would have put epilepsy and coded some of these other terms into -- with the convulsion terms the way that you did. But was there any sort of pattern? I mean, what was on the list? I just know that this is going to be come up in parent groups, so it would be better to

discuss it here.

DR. FRIEDLAND: Right. I don't have the list in front of me, so I'm going to go through my memory. But there were cases of accidents, for example, sudden death. I'd have to pull out the list. I'm sorry I don't remember off-hand, but there's a wide variety of list of fatalities. And if there's a break, I can come back and share the list with you. I'm sorry, I just don't remember.

DR. MODLIN: Probably not a bad idea.

DR. FRIEDLAND: Oh, I have -- well, I do have the list in front of me. So within 30 days after vaccination, I can read down the list of these. Thank you whoever put this up for me. I can read down the list of those in the Rotarix group; Leukemia, gunshot wound, congenital patent ductus ateriosus, septicemia, renal tubular acidosis, appendimoma, suffocation, death due to unknown cause. It's that sort of list.

DR. MODLIN: Do you have further questions, Dr. Debold? I'm sure we can provide more specificity on a piece of paper for you; although it's probably not wise use of the time right now to get into great detail. Yes?

DR. BREUER: Maybe making one more comment. I mean, death is, obviously, of high concern to any country. I just want to reiterate that these studies were performed in countries where infant mortality is much, much higher than, fortunately, in the U.S., so you expect to see hundreds of death in, for example, the studies in Africa. The main point is that except for pneumonia, all these were balanced, so the same proportion happened in the placebo group, and a similar proportion happened in the group which received Rotarix. So this should comfort you, and that comfort us that you don't have any imbalance.

The other question you had was around the P-value, and maybe -- I want to

make a general comment. When you have a primary endpoint, obviously, you apply statistics up front, and these statistics mean something when you evaluate these results. However, when you then go into a data mining exercise in your safety data based on hundreds of analysis, they're two schools of thought; one is that you simply report the proportions and eye them by yourself, and decide this is something which looks cautious, and I want to go deeper into it, and you look at it. You look at the clinical cases, and you try to make an assessment.

The other school of thought says, and this was followed in this study. However, there is no consensus, we do it sometimes this way, sometimes that way, depending on who is the statistician on the team, that we say okay, we define what is defined as an imbalance. And to do that, we apply a statistical test.

However, the P-values and the

confidence interval in that setting do mean something totally different than a P-value or a confidence interval as a primary endpoint. And I just wanted to make that point, that we don't get mixed up on these things. This was just a tool to highlight potential issues, and then we dig further into it, so thank you.

DR. MODLIN: If there are no further questions, I think what we'll do is go on and move towards consideration of the questions that have been put before us. Why don't we put the first question back up on the screen again, if we could. And keeping in mind that it's not just our individual votes as members that's important, but the basis for our votes. We are trying to provide as much detail to our opinions for our purpose of giving advice to the Agency.

I think I will go ahead and - while we're getting the question up, go ahead and open up the discussion, which has to do with are the data sufficiently convincing regarding

efficacy of the human Rotavirus vaccine to recommend to the Agency that it be licensed. Here we go. And I'm also assuming that this will include use of the vaccine with the first dose being given no later than 13 weeks of age.

Thoughts, questions? How about the CDC side here, are there any further specific thoughts about this, concerns? Melinda?

DR. WHARTON: Well, of course, we got less data on the G2 type than we do for the other serotypes, so that and the constraint around when vaccine is administered I think are the two issues I would raise related to effectiveness. But, certainly, the data seem quite robust other than the G2 serotype issue.

DR. FRIEDLAND: Dr. Modlin, is it possible that I could add something to that?

DR. MODLIN: Certainly.

DR. FRIEDLAND: If I could go back to Slide A-28 in the Core set. I just wanted

to show again the data on G2-P4 in O-36, just trying to point out to you that the confidence interval that was seen was 86 percent, with a confidence interval of 24-99. But, in addition, we have a integrated analysis of G2-P4 in the first year from a series of the clinical studies where we pooled the numbers just to get larger cases. So if I could bring up that slide. So just an additional analysis to show you additional cases of G2-P4. And that would be Slide E-6. There it is. Thank you.

So what we've done here is following standard procedures for integrated analyses, we've looked at our vaccine efficacy studies, Studies 4 and 6, where two Phase II vaccine efficacy studies, and you've already heard about Study O-23 and O-36. And this is within the first year after vaccination. And when we pooled the G2-P4 cases across these four studies in an integrated analysis, the vaccine efficacy for G2-P4 is 71.4 percent

with statistical significance. So just additional data on G2-P4.

DR. MODLIN: It may very well be that the concern is in the larger study you have the lowest efficacy, if that's a concern. I understand what Melinda is saying. It actually comes down to the actual numbers of cases of G2 illness and in two groups it's important on how much confidence we have around that. Dr. Jackson?

DR. JACKSON: Do you have a similar slide for all Rotavirus GE?

DR. FRIEDLAND: No, I don't have a similar slide for all Rotavirus gastroenteritis. You mean pooling all the types?

DR. JACKSON: Looking for G2 for the outcome of Rotavirus GE not severe. I believe the FDA --

DR. FRIEDLAND: Oh, yes.

DR. JACKSON: Yes.

DR. FRIEDLAND: I'm sorry, I don't

have that slide, but that analysis has been done, and it also is statistically significant.

DR. JACKSON: But lower?

DR. FRIEDLAND: My statistician is here. I don't know. Bridgette, if you know the number off-hand?

(Off microphone comment.)

DR. MODLIN: Please use the microphone. And introduce yourself, if you would, please.

MR. DEBRUS: So I'm Sergio Debrus from GlaxoSmithKline. I was working in R&D developing this vaccine before. Just what I can tell you by heart is the fact that the data we have for the meta analysis is pooling for any gastroenteritis. We have pretty similar number that what we have seen for the severe diseases, and we have a good confidence interval, so it's pretty the same number for any and severe disease for the meta analysis in G2-P4.

DR. KOU: Excuse me. Can I --

DR. MODLIN: Yes.

DR. KOU: My name is Jingyee Kou. I'm a FDA statistician, and I'm a statistical reviewer for this product. And we have looked at each individual serotypes, and to us, the -- we wanted to see is clear evidence on the control, well-controlled study. And the G2, in this case they're combining all of the studies, and they're not all -- have the same condition when they enrolled the subject, and so we don't consider this is enough evidence to support G2.

DR. MODLIN: Thank you.

DR. FRIEDLAND: And if I could just, we could bring back up again, in an individual study, as a reminder, in Study O-36, statistical significant efficacy is seen is an isolated single study through the two years.

DR. MODLIN: Fair enough. It sounds like this is going to be an issue

between the Sponsor and the Agency with respect to labeling. I don't think it's likely to have a major effect on how we feel about its efficacy against the other types, if that's a fair summary. Lisa?

DR. JACKSON: Potentially, it could influence the post-licensure considerations, however.

DR. MODLIN: It could, if you can find enough cases some place. Any other thoughts? Is there anyone on the Committee who feels that -- who have -- let me say, is not disposed to being positive towards this question? And if so, why? Jose, you've got your finger up.

DR. ROMERO: I guess I need a little bit of clarification here, because, again, I hate to use this first meeting as a crutch excuse. I mean, I agree with everything except the G2. And the question that you're asking is, is it approved -- are you going to vote yes for everything but one

of those, or how does that work, John?

DR. MODLIN: I don't think that we ----- I'll just take the prerogative, the Chair's prerogative of saying I think we don't have to settle that issue. Is that fair, Norm? I don't -- it's thrown in there, but that's going to be an issue between the Agency and GSK in terms of what the final label actually says.

DR. ROMERO: Right. And that's what my question about the G2 was early on.

DR. MODLIN: Right. I think they would like to know our general enthusiasm for including it, but I think they've heard it.

Well, is there any further discussion on this question at all? If not, I'll entertain a motion to call the question.

DR. ROMERO: So moved.

DR. MODLIN: So moved.

DR. DAVIS: Second.

DR. MODLIN: Seconded. Any further discussion?

Okay. We are under a new procedure, and that is rather than going around and asking each member's vote, voting member in the past, we will be voting all simultaneously. So I'm going to ask those who would be voting yes on Question One, if you would raise your hand, and keep it raised. And Dr. Wharton, DeStefano, Dr. Stapleton, Dr. Davis, Dr. Belay, Dr. Modlin, Dr. Debold, Dr. Romero. Everybody around to me, Dr. Debold, Dr. Romero, Dr. McInnes, Dr. Self, Dr. Sanchez, and Dr. Jackson. I believe there are no nos, or no abstentions, because everyone voted yes on this question.

Let's move on to Question Two, if we might. And, again, I'm assuming that -- for the safety purposes that we're assuming that this means that the first dose will be given by 13 weeks of age. Let me open this up to questions, or not to questions, questions or discussion. Why don't we start over on this side of the table, if anyone has any

specific issues, questions, discussion regarding safety? We've heard an awful lot about it today. This side. Melinda?

DR. WHARTON: Well, I am not highly concerned about the pneumonia issue, but it is a little concerning seeing a respiratory disease signal in multiple studies. And in thinking about, is there any biological mechanism that one can possibly come up with? What the studies suggest is that Rotavirus disease as developed in the placebo group, may protect from respiratory infection, which I think might be biologically plausible if, in fact, the immune system tends to only get one viral infection at a time. And this is why I was asking the earlier questions about seasonality.

If, in fact, the vaccinated group got Rotavirus vaccine outside of respiratory disease season, and the unvaccinated group got Rotavirus disease during respiratory disease season, perhaps they had a slightly decreased

risk of getting a viral respiratory infection, which then might predispose them to serious viral or bacterial outcomes. And I don't know if this makes any sense from the immunological point of view, but it's the only thing I could come up with in thinking about this.

DR. MODLIN: It does, and I was thinking about the same thing, and whether or not there might be yet ways to probe whether there's actually a statistical interaction between protection against Rotavirus disease; in other words, less disease, and risk of pneumonia. But we're really not looking at risk of pneumonia, we're looking at risk of pneumonia deaths, when you think about it, which is a different animal here. But I would agree with Melinda. I would think that any efforts to try to understand this better, whatever way we can, given the existing database, and it may be possible to do that.

Where those kids -- well, see whether actually there's a statistical

interaction between protection and subsequent pulmonary disease with death would be very interesting. Yes, sir?

DR. IZURIETA: My name is Hector Izurieta. I'm a reviewer for FDA. I had a question which might be interesting, if GSK would address it. When we read the list of deaths on Rota O-23, which is the main one implicated in the pneumonia deaths issue, if you just run the numbers for aspiration deaths, deaths that include the phenomenon of aspiration by the child, you might find an imbalance probably, around 7-2. The intervals may be very far away, there could be some that are very near to the vaccination date, but I'd like to see you comment on that.

DR. MODLIN: There is a specific cause of pneumonia death, which is aspiration. Can you tease that out between the two groups?

DR. IZURIETA: Not necessarily coded as pneumonia, any death that is coded as

aspiration, either pneumonitis, pneumonia, chest aspiration, gastric fluids aspiration, any of those phenomenon, because this is an oral vaccine. I just want the clarification.

DR. FRIEDLAND: There were deaths that were coded as aspiration. Of course, for each preferred term there was no imbalance between the groups. I think it's an excellent suggestion, and we can certainly go and do those analyses, pooling those preferred terms to see if there's an imbalance.

DR. MODLIN: Any other concerns about safety information that has been presented today? Dr. Self?

DR. SELF: Not so much a concern, but a comment about adequate safety -- data being adequate, support safety. And while the signals are important, and should be attended to, we should probably just point out that the attributable risk associated with these safety terms is one or two orders of magnitude below the risk associated with the primary efficacy

endpoint. And there are issues about comparing how severe the different endpoints are, and all of that, but that should be the context, I think, that we use to answer this question. It wasn't quite brought out maybe as well as it could be in the presentations, but that information is there, and we should attend to it.

DR. MODLIN: That's an excellent point.

DR. DAVIS: Can I follow-up on that, because I was wondering about the same thing. Because if you think that the protection against death overall from the primary endpoint is immediate, if the protection is immediate, you should actually see a reduction in death within the very confined time points we're looking at, and for various reasons.

But I'm wondering whether they've actually extended their analyses -- this is unfair, because as an ad hoc on an ad hoc, but

whether you can actually -- whether there is any data that looks at this over a longer term to see whether there is reduction of death due to natural Rotavirus, any overall reduction of death which one would presume would be primary driven by the reduction of natural disease. I think I got that out right. That's actually a question. I mean, feel free to --

DR. MODLIN: I hear your question. Would the company like to respond with data that you don't have?

DR. VERSTRAETEN: Could you clarify, Bob? We're not sure we understood.

DR. DAVIS: Well, Steve was making a point that overall, even though -- let's assume that the data is, in fact, real, that there might be a small blip increase in pneumonia-related deaths, and I don't think any of us are willing to go that far quite yet, but let's -- for the purpose of argument, let's assume that's real. Over time, it will be compensated for many times over by the

reduction in death due to natural Rotavirus disease. And I was just wondering, do you have any evidence that, in fact, demonstrates that?

DR. VERSTRAETEN: As far as I know, we don't have additional follow-up data that would help us in that. Of course, mortality rates go down quickly as these kids age, so the highest mortality, of course, is in the earlier age group.

DR. BREUER: So as we have pointed out in our initial presentation, death due to Rotavirus is still very common in countries, even in countries where we have performed the studies, so since it seems we all agree, including the Committee, that this is a highly efficacious vaccine, so it will have a major impact on Rotavirus death.

However, in clinical studies you will never find this, because these are settings which are sort of artificial. We are taking good care of our placebo group, and we

take good care of our variant group, so this kind of effects you will not find in clinical studies. However, with a high efficacious vaccine, you can fully expect that in a setting where children die from Rotavirus disease, that you will have a major impact on Rotavirus death.

DR. MODLIN: Yes?

DR. BELAY: From the dates that you've already identified, you could potentially compare deaths associated with diarrhea, or dehydration. You can see there are differences in the two groups.

DR. MODLIN: Thank you. Any other discussion? If not, I assume that the Committee is ready to vote on this question. I will ask for a vote -- ask you if you would raise your hand if your vote on this question is yes, the available data are adequate to support the safety of Rotarix when used as described on the slide. Those who vote yes?

DR. BELAY: A question.

DR. MODLIN: Yes?

DR. BELAY: Are we allowed to qualify our answers, or a show of hands?

DR. MODLIN: Yes, you are, but why don't we go ahead and take the vote, and then I'll come back. You're certainly permitted to qualify your vote. Okay. Those voting yes are Dr. Wharton, Dr. DeStefano, Dr. Stapleton, Dr. Davis, Dr. Belay, Dr. Modlin, Dr. Romero, Dr. McInnes, Dr. Self, Dr. Sanchez, and Dr. Jackson. Those voting no, Dr. Debold, and I believe that's everyone, that no one is abstaining. And yes, we are permitted to go back afterwards and explain your vote, if you would like to.

DR. BELAY: My qualification is there would be continued post-marketing surveillance for some of the safety issues that were raised, including the safety concerns associated with previous Rota vaccines, such as intussusception, Kawasaki, and the others. And, also, the new situation

that unrolls during the studies which would include the pneumonia death and the convulsions.

DR. MODLIN: Okay. Should we move on to question three, please? Are there additional issues that should be addressed in the post-marketing studies beyond the applicant's proposed study? And, specifically, Dr. Belay's last comment gets right at this. We've already had a fair amount of discussion about this, already. Is there further discussion?

Dr. Jackson?

DR. JACKSON: Well, I wonder if Tom might want to comment on the methodology, because I'm struggling with how you could possibly use a self-controlled method. I mean, the difference between this and the previous experience that Trudy Murphy analyzed was that you're going to have very little heterogeneity in the timing of your exposure, meaning that you're only to give the first

dose during a certain age, pretty narrow window, and consequently the second dose.

And then I assume there's going to be some risk window, 90 days, or 30 days. So, unavoidably, you're going to be comparing older age with younger age, and since this outcome, or many of the outcomes are age-dependent, and there's a huge difference between a two-month old and a five-month old, I just don't know how you can do it. And I'm sure you've thought about this a lot more than I have, Tom.

DR. VERSTRAETEN: Yes. Thanks, Lisa. Yes, we have thought quite a bit about it. We actually talked to Paddy Farrington, who's the guy who pretty much invented, or at least applied it to vaccine safety, and has been a little bit the godfather of this method. And he was a little bit puzzled at first, as well, because this is obviously a non-recurring event, both intussusception, and certainly deaths. So the only way we could do

it is actually do it by dose, and we cannot combine the two doses, because once you've had one of the events, you will not have another dose.

We were concerned about whether we would have enough heterogeneity. However, the risk period is one month, and there is heterogeneity at the age of vaccination. We see that. We see that in Europe, we see that in Latin America, sufficient that we can actually adjust for age even within that method. So I think that will be okay.

We will not have a control period before vaccination, so that will be the limitation here, the control period will be after the risk period. So the only concern we actually have is, if by any chance our vaccine protects against any of the outcomes, then we will have to take care of that, as well. But as for the age effect, we're confident that we will be taking care of it.

DR. MODLIN: Further questions or

comments? I might just say for myself -- go ahead, Frank.

DR. DeSTEFANO: I guess, just following up on this self-control methodology. So you're going to say, let's say, intussusception cases. You restrict this to vaccinated intussusception cases? I mean, because of this age --

DR. VERSTRAETEN: Yes.

DR. DeSTEFANO: -- issue, and needing to control finely for age, you might be well-served to include all cases, or non-vaccinated cases to get a better distribution by age, or other factors.

DR. VERSTRAETEN: You're right. Theoretically, you don't need them, but if you have them, they help you to take care of the background, to better define the impact of age. Yes. We will use them, but we don't necessarily need them.

DR. MODLIN: I have to admit that I have a fairly high degree of confidence in the

data that I've seen with respect to intussusception. I think the data are very robust. I know that we can never prove the null hypothesis and say that the vaccine never causes intussusception.

But, on the other hand, we have a whole lot more data here than we have over many, many other adverse events that we're concerned about, for good reason. But that's just a comment. I'm not actually looking to see a whole lot more. I don't know how others feel about that. I do think that some of these other signals are very, very important to follow-up on, that we've already discussed, but I'm fairly confident in this.

Dr. Davis?

DR. DAVIS: I can't help myself. Lisa got me thinking, which is that if you do a self-control group, a self-control analysis for death, I'm just sort of harping on that, we've already sort of expressed the fact that the concern may be one of a biologic

phenomenon that extends way passed 30 days, so the exposed group is really almost forever after the exposure -- the time window could go out for three, four, five, six months after the exposure starts.

So I'm not really sure that -- I guess I'm quite concerned that whether a self-control group study is actually possible to examine death.

DR. VERSTRAETEN: We've thought about that, as well. To go beyond one month would be very difficult in a self-controlled. I mean, theoretically it's possible, and Farrington claims that you can actually check for autism after MMR using this method, following up for even longer periods. I think we do have to go back to what we believe is really plausibly possible, so to say, and it brings us back to the question in biological plausibility.

It really doesn't make sense that there would be an effect later, much later

than the actual infection, and any symptoms that have been described, respiratory symptoms around Rotavirus infection have always been around the time of the infection, or even before, having some people suggest that may be a respiratory transmission of Rotavirus.

So we're pretty sure if there is anything, it should be really around the time of vaccination. So that will be a limitation, I agree, but I think it's the most sensible period to be looking at.

DR. MODLIN: Any other questions or comments?

Norm, maybe I could ask either you, or Dr. Leventhal if you felt that there's other issues or items that you'd like the Committee to touch upon that we haven't? If not, I think we can consider this meeting adjourned. Thank you, everyone.

(Whereupon, the proceedings went off the record at 2:37:58 p.m.)