FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL

PRODUCTS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,

DECEMBER 14, 2005

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The meeting was held in the Versailles Ballroom of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, Maryland, at 9:00 a.m., Gary Overturf, Chairman, presiding.

MEMBERS PRESENT:

GARY D. OVERTURF, M.D., Chairman

CHRISTINE WALSH, R.N., Executive Secretary

MONICA M. FARLEY, M.D., Member

MEMBERS PRESENT (Continued):

RUTH A. KARRON, Member

DAVID MARKOVITZ, M.D., Member

WALTER ROYAL, III, M.D., Member

STEVEN SELF, Ph.D., Member

BONNIE M. WORD, M.D., Member

BRUCE GELLIN, M.D., M.P.H., Temp. Voting Member

PAMELA McINNES, D.D.S, Temp. Voting Member

MELINDA WHARTON, M.D., M.P.H., Temp. Voting Member

SAMUEL MALONARDO, M.D., M.P.H., Acting Industry Representative

C O N T E N T S

P R O C E E D I N G S

(9:02 a.m.)

CHAIRMAN OVERTURF: I'd like to call the meeting of the Vaccines and Biological Advisory Committee to order for December 14th.

The first matter of business is presented by Dr. Baylor.

DR. BAYLOR: Good morning. We have two committee members that I want to point out to the committee this morning, and we wanted to present plaques for their service to them.

The first person is Dr. Gary Overturf, our Chair, and his term was from February '02 to the end of January '06. Dr. Overturf also served as a member of two site visits, one for the Laboratory of Bacterial Polysaccharides back in November of 2002, and he also served as a member of the site visit on the Laboratory of DNA Viruses, and that was back in March of '04.

Gary, we really thank you for your contributions. Thank you for all the service, and we're very appreciative of your contributions to the

FDA and VRBPAC.

(Applause.)

DR. BAYLOR: And the second person is Dr. David Markovitz. His term was also from February '02 to the end of January '06, and David served as at the site visits for the Laboratory of Methods Development back in January of '03. He also chaired the scientists for the evaluation of the Laboratory PF Respiratory Viral back in November of 2004 and also the site visit to the Laboratory of Retroviruses and the Laboratory of Mental (phonetic) Regulation back in April of 2005.

David, are you -- oh, she switched that.

(Laughter.)

DR. BAYLOR: We also appreciate your service and your contributions to the FDA.

(Applause.)

DR. BAYLOR: Thanks again to both of you.

CHAIRMAN OVERTURF: It goes to show you that the years of service and good intentions are lined by plaques.

I would like to turn the meeting over to

Christine Walsh who has some administrative matters to address.

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

Both today and tomorrow's session will consist of presentations that are open to the public.

I would like to request that everyone please check your cell phones and pagers to make sure they are off or in the silent mode.

Due to a family emergency Ms. Cindy Provine, our consumer representative, will be unable to attend this meeting.

I would now like to read into the public record the conflict of interest statement for today's meeting.

The Food and Drug Administration is convening today's meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of

1972. With the exception of the industry representatives, all members and consultants of the committee are special government employees 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 21 USC 355(n)(4), is being provided to participants in today's meeting and to the public.

FDA has determined that members of the Advisory Committee and consultants of the committee are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC 208 and 21 USC 355(n)(4).

Under 18 USC 208, applicable to all government agencies, and 21 USC 355(n)(4), applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that

the agency's need for a particular individual services outweighs his or her potential financial conflict of interest, Section 208, and where participation is necessary to afford essential expertise, Section 355.

Members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed at temporary voting members, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child related to the discussions of the safety and efficacy of RotaTeq manufactured by Merck & Company, and the safety and efficacy of Zostravax manufactured by Merck & Company. These interests may include investments, consulting, expert witness testimony, contracts, grants, credos, teaching, speaking writing, patents and royalties and primary employment.

For today's agenda regarding Topic 1, the committee will review and discuss the safety and efficacy of RotaTeq, manufactured by Merck & Company.

For Topic 2, the committee will review and

discuss the safety and efficacy of Zostravax, manufactured by Merck & Company.

In accordance with 18 USC, Section 208(b)(3), waivers have been granted to the following special government employees. Please note that all interests are in firms that could potentially be affected by the committee's discussions.

Dr. Ruth Karron for unrelated consulting with a competitor for which she receives less than $10,000 per year;

Dr. Thomas Fleming for unrelated consulting with a competitor for which he receives less than $10,001 per year.

Dr. Daniel Scharfstein for unrelated consulting with a competitor for which he receives less than $10,001 per year, and ownership of stock in the sponsor currently valued at less than $10,001 per year.

A copy of the written waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, there may be regulated industry and other outside organization speakers making presentation. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they wish to comment upon.

These individuals were not screened by the FDA for conflict of interest.

Dr. Samuel Malonardo is serving as the industry representative for Topic 1, acting on behalf of all related industries and is employed by Johnson & Johnson.

Also, Dr. Seth Hetherington is serving as the industry representative for Topic 2, acting on behalf of all industry and is employed by Inhibitex, Incorporated.

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 remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an 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.

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

CHAIRMAN OVERTURF: Again, I'd like to welcome the members of the committee, and at this time I'd like to have the committee members introduce themselves and tell us where they're from and who they represent.

I'll start with Dr. Self.

DR. SELF: I'm Steve Self, University of Washington and Hutchinson Cancer Research Center in

Seattle.

DR. KARRON: Ruth Karron, Johns Hopkins University.

DR. MALONARDO: Sam Malonardo, Johnson & Johnson.

DR. WORD: Bonnie Word, Baylor College of Medicine, Texas Children's Hospital.

DR. GELLIN: Bruce Gellin, National Vaccine Program Office, Department of Health and Human Services.

DR. WHARTON: Melinda Wharton, National Immunization Program, Centers for Disease Control and Prevention.

DR. McINNES: Pamela McInnes, National Institute of Allergy and Infectious diseases, NIH.

DR. ROYAL: Walter Royal, University of Maryland, School of Medicine.

DR. FARLEY: Monica Farley, Emory University, School of Medicine.

DR. MARKOVITZ: David Markovitz, University of Michigan.

CHAIRMAN OVERTURF: And I'm Dr. Gary

Overturf. I'm from the University of New Mexico, School of Medicine.

I'd like to open the meeting now by a brief introduction by the FDA by Rosemary Tiernan.

DR. TIERNAN: Good morning, everyone, and welcome to the Vaccines and Related Biological Products Advisory Committee meeting, the VRBPAC, where they will consider Merck's Rotavirus vaccine, RotaTeq.

But before we have the staff from Merck begin their presentations, I'd just like to review some of the questions that we're asking the Advisory Committee to consider today, and you can keep them in mind during the presentations this morning.

The first question will be: are the available data adequate to support the efficacy of RotaTeq in preventing Rotavirus gastroenteritis cause by serotypes G1, G2, G3, G4 and G serotypes that contain P1, example G9 when the first dose of vaccine is administered at six to 12 weeks of age followed by two subsequent doses separated by four to ten week intervals? If not, what additional information should be provided?

And the second question: are the available data adequate to support the safety of RotaTeq when used in a three dose series beginning with the first does again at six to 12 weeks of age followed by two additional doses separated by four to ten-week intervals? If not, what additional information should be provided?

And then the third question: please identify any other issues that should be addressed, including post licensure studies. In particular, please address the assessment of intussusception, the applicant's proposed pharmacovigilance plan, concomitant use with other routinely administered vaccines, and the use of the vaccine in immunocompromised children, such as those with HIV, or children taking steroids or other immunosuppressant therapies or other special populations.

So I think we'll let the staff at Merck unless, Dr. Overturf, you have any other comments about the questions.

CHAIRMAN OVERTURF: Any questions from the committee?

(No response.)

DR. BAGARAZZI: Good morning, everyone, members of the committee, members of FDA, and ladies and gentlemen.

My name is Mark Bagarazzi, Director of Regulatory Affairs for Merck Research Laboratories. It's my pleasure to introduce to you today RotaTeq, a vaccine that has the potential to virtually eliminate the morbidity and mortality due to rotavirus gastroenteritis, one of the most significant unaddressed infectious diseases of infancy and childhood.

It's an honor to represent everyone who has played a role in generating the scientific evidence used to support and generate the scientific evidence to establish the safety and efficacy of this live oral intravalent (phonetic) rotavirus vaccine.

With the over 400 clinical investigators and their staffs, we had over 70,000 families that enrolled their children into the study and the hundreds of my colleagues at Merck.

We are proposing for your recommendation

that this oral pentavalent vaccine be authenticated for the prevention of rotavirus gastroenteritis in infants and young children caused by the serotypes G1, G2, G3, G4 and G Serotypes that contain P1, for example, G9, and that RotaTeq be administered as early as six weeks of age.

These G and T serotypes represent the most prevalent types isolated here in the United States.

The Advisory Committee had previously received a briefing document from Merck that goes into more detail than what we have time to present here this morning. The outline for our presentation this morning is as follows. I'll briefly review the disease burden of rotavirus gastroenteritis worldwide, and then I'll introduce the clinical development program of RotaTeq by outlining the major safety, efficacy and immunogenicity objectives of our Phase 3 program.

Then I'll be turning the podium over to Dr. Penny Heaton who will describe the scope of rotavirus disease specifically here in the United States, and she'll spend the majority of her time

sharing with you the actual clinical trial results supporting RotaTeq's safety and efficacy.

Dr. Heaton will conclude by outlining the benefit-risk profile that supports the proposed indication for RotaTeq.

So the wheel-like rotavirus particles you see here in the slide are responsible and the leading cause of severe diarrhea in infants and young children both here in the United States and worldwide as well. The rotavirus infects virtually all children by the time they reach their fifth birthday.

The CDC estimates that worldwide roughly 1,000 children die every day from rotavirus. The dehydration that results from the vomiting and diarrhea leads to over two million hospitalizations worldwide every year, and that's 55,000 to 70,000 hospitals that children are hospitalized every year in the United States alone.

The virus affects all children equally. It doesn't discriminate on the basis of socioeconomic status, environmental conditions or geographic area. Once infected, a child growing up here in the United

States has the same chance of developing severe gastroenteritis characterized by the fever, vomiting and diarrhea as does the child living in the developing world.

Merck's development of RotaTeq began in earnest in 1993 with our proof of concept study when we showed that a quadrivalent version of the vaccine was efficacious. This was followed by a study of different formulations to demonstrate that the vaccines could be stored at refrigerator temperatures and buffered to neutralize stomach acid.

In 1998, we initiated a dose ranging study to determine the dose that we should take into Phase 3. During the course of the dose ranging study, the first reports of an association between Wyatt's rhesus tetravalent rotavirus vaccine and the intestinal obstruction known as intussusception came to light in the summer of 1999.

These reports changed our plans for Phase 3 since we now set out to design a study that would show that this association did not exist for our bovine reassortant vaccine.

We designed a placebo controlled study that would enroll a minimum of 60,000 subjects which was reviewed and ultimately endorsed by this committee and the FDA in May of 2000, and in January 2001, we enrolled the first subjects into the trial that we named the rotavirus efficacy and safety trial, or REST.

So ultimately over 70,000 subjects were enrolled into REST to demonstrate that RotaTeq did not increase the risk of intussecption relative to placebo within 42 days of any dose, thus satisfying the primary safety hypothesis by meeting the prespecified statistical criteria for this study.

There were two other Phase 3 studies that contributed to the overall safety database for RotaTeq. In addition to REST, our Protocol 7, which was a study to confirm the efficacy of our final formulation of RotaTeq, and our Protocol 9, which was a study to establish the consistency of our manufacturing process, enable us to show that RotaTeq is generally well tolerated with regard to all adverse advents and also with regard to adverse events that we

call of special interest. Those are the symptoms of gastroenteritis, the fever, vomiting, diarrhea, and irritability.

The efficacy of RotaTeq was assessed in both our Protocol 7 and in the REST trial. We set out to demonstrate RotaTeq's efficacy against the serotypes contained in the vaccine that are responsible for approximately 90 percent of disease here in the United States.

The integrated analysis showed that RotaTeq prevents over 98 percent of the most severe cases of gastroenteritis as graded by our investigators, and prevents fully three-quarters of all disease of any severity.

The large sample size of the REST trial also enabled us to assess RotaTeq's ability to reduce health care encounters, and we show that RotaTeq reduced the number of hospitalizations and emergency department visits for rotavirus by over 94 percent.

There were also two main immunogenicity objectives in our Phase 3 program. First, the consistency of the RotaTeq manufacturing process was

demonstrated by comparing the immunogenicity of three consecutive lots of vaccine in our Protocol 9.

And finally, in a substudy of the REST trial, the immunogenicity of the currently licensed vaccines of two to six month olds was assessed to demonstrate that RotaTeq can be integrated into the current immunization schedule of infants.

So now before I hand over the podium to Dr. Heaton, I'd like to point out several consultants that are attending today's meeting who will be available as a resource during the committee's deliberations and discussions.

Drs. Fred Clark and Paul Offit from the University of Pennsylvania and Children's Hospital of Philadelphia, who pioneered the work on the human bovine reassortants that are the backbone of this pentavalent vaccine.

Dr. Ken Holmes and Dr. Janet Wittes, who I don't think has arrived yet, but they served as chair and statistician that oversaw the Phase 3 program in their roles on a Data and Safety Monitoring Board.

And Dr. Gary Marshall of the University of Louisville, who was a participant as an investigator in the REST trial.

And Dr. David Matson who served as principal investigator for the almost 200 sites that participated in REST here in the United States.

So now Dr. Heaton will provide the actual details regarding rotavirus disease here in the United States, and the clinical trial results from RotaTeq.

DR. HEATON: Well, thank you, Dr. Bagarazzi, and good morning, everyone.

It was six and a half years ago that I stood here and presented to this committee Merck's plan for moving forward with development of the pentavalent human bovine reassortant rotavirus vaccine in the face of safety concerns about intussecption with the rhesus vaccine. So I'm happy to tell you that that plan has now come to fruition, and it's my honor today to present to you the safety, efficacy, and immunogenicity data to support the licensure of RotaTeq.

I'm going to begin my presentation with a

brief review of the epidemiology of rotavirus and the basis for developing a multivalent vaccine. I'll provide you with a description of the characteristics of the vaccine, and I will give you an overview of the Phase 3 clinical trials, including some detail about the large scale rotavirus efficacy and safety trial to evaluate intussecption.

But I want to spend the bulk of my time sharing with you the results of the efficacy, safety, and immunogenicity endpoints of the Phase 3 studies.

As Dr. Bagarazzi mentioned, rotavirus is the leading cause of diarrheal related deaths worldwide and a major cause of morbidity among children in the United States. CDC estimates that rotavirus accounts for four to six percent of all pediatric hospitalizations, and that the risk of developing severe rotavirus gastroenteritis and being hospitalized does not vary by geographic region.

CDC has recently updated their estimates of the burden of rotavirus disease in anticipation of licensure of this vaccine, and they've showed that the disease burden estimates have remained the same over

the last decade. The same number of hospitalizations, the same number of emergency department visits are occurring now that occurred in the mid-'90s.

This pyramid shows the outcome of rotavirus infections in the United States each year. All children are infected early in life. By the time a child reaches their fifth birthday, two out of three will have had a symptomatic infection with rotavirus. One out of ten will have visited their physician for rotavirus. One out of 17 babies will have been to the emergency room with rotavirus gastroenteritis, and one out of 65 will be hospitalized for rotavirus gastroenteritis.

Although uncommon, deaths still do occur in the United States. CDC estimates that there are about 20 to 60 deaths every year from rotavirus.

There are five strains that cause the majority of rotavirus disease here in the United States and worldwide. Before I discuss those strains, I want to go over the structure of the virus and how the virus is classified into serotypes.

So this is a picture of the virion. It's

a non-enveloped virus that contains 11 segments of double stranded RNA, and each of those segments codes for one or two proteins.

The two most important proteins with respect to immunity are the outer surface glycoproteins shown here in yellow, and we call that the G protein for short, and then this attachment protein which is protease sensitive, which we call the P protein. These two proteins induce neutralizing antibodies and they are used to classify rotaviruses into their G and P serotypes. So each virus is classified according to their G and P type.

Now, the serotypes that account for over 90 percent of rotavirus disease in the United States are G1, G2, G3, and G4, and the P type that is most commonly associated with these G types is serotype P1a, which you may have also seen referred to as P genotype 8.

The clinical manifestations of rotavirus gastroenteritis are fever, vomiting, and watery diarrhea, and the features that distinguish rotavirus gastroenteritis and non-rotavirus gastroenteritis are

twofold. One is that rotavirus causes vomiting.

In this study by Rodriguez, et al., that was published in the late '70s, 96 percent of children that has rotavirus positive gastroenteritis had vomiting compared with only 58 percent of rotavirus negative gastroenteritis.

And, of course, when a child is vomiting five to ten times a day, then oral rehydration becomes impractical.

The second feature of this disease that distinguished it from other forms of rotavirus gastroenteritis is the duration of the illness. Rotavirus lasts on average six days, and that extended duration of the illness with the vomiting together can clearly lead to dehydration which may require hospitalization and death if supportive care is not available.

The basis for preventing rotavirus gastroenteritis through vaccination comes from studies of wild type disease. Dr. Velasquez and his colleagues in the 1990s published a study where they had followed a cohort of children near Mexico City

from birth through two years of age. They followed them weekly collecting stools and then collected sera about every four months.

And what they found in that study is that rotavirus infection induced immunity against subsequent episodes of rotavirus gastroenteritis, and that immunity was greatest against severe disease, but there was also substantial protection against mild gastroenteritis.

The other significant finding from that study is that the immunity induced by rotavirus is strain specific. So particularly with the first infection. So, therefore, we developed a multivalent rotavirus vaccine containing the most prevalent serotypes to provide the most comprehensive protection possible.

This slide shows the characteristics of RotaTeq. It is an oral vaccine, and the formulation consists of a buffer and stabilizer. The buffer protects the vaccine strains from gastric acid so that it may be administered orally, and the stabilizer provides for stabilization at refrigerated

temperatures and for 24 months.

The vaccine can be administered directly from the tube. The tubes are shown here. They're a plastic dosing tube with a twist off cap, and it's easy to administer. You just twist the cap to the right to break the seal, then unscrew the cap, and you can administer the vaccine directly to the infant from the tube.

It is a three-dose regimen that will easily be integrated into the routine immunization schedules. The first does is given at age six to 12 weeks, and then subsequent doses can follow at one to two-months intervals.

And it contains five human bovine reassortants. The human serotypes that are represented in the vaccine are G1, G2, G3, G4, and P1, and the bovine strains that are represented are G6 and P7.

This is a schematic of how the vaccine was developed, and here we have the parent strain of the vaccine, the bovine WC3 rotavirus. This virus was isolated from a calf at the Wistar Institute. That's

Wistar Calf 3, or WC3, in 1981, and it was purified and actually evaluated in several vaccine trials over the 1980s.

The hope was that this heterologous animal virus would induce immunity against human disease, but it's naturally attenuated for humans. So it wouldn't be pathogenic or cause side effects.

Well, what they found in those early trials of the WC3 vaccine is that, indeed, it was well tolerated. It did not induce side effects, but the efficacy was inconsistent across studies. So, therefore, we developed human bovine reassortants that consist of the bovine backbone with human outer surface proteins.

Rotaviruses naturally reassort their genetic segments in cell culture. So we took advantage of that natural property, coinfected in cell culture with the bovine WC3 strain and the human rotavirus strains of interest, so G1, G2, G3, and G4, and then we selected out the reassortants that we wanted to include in the vaccine.

So we have here a bovine backbone with a

human outer surface G1, and this is the bovine backbone with the human outer surface G2 and P1 and then G2, G3, and G4, and these five strains are suspended in the formulation that make up the vaccine.

Now I'd like to move into an overview of the development program for RotaTeq. As Dr. Bagarazzi shared with you earlier, we licensed the technology for the vaccine from Children's Hospital of Philadelphia in the early 1990s. We did a proof of concept study in 1993 to 1994 that showed that the vaccine was well tolerated, and it was 100 percent efficacious against severe disease.

We then went on to develop the liquid buffered formulation so that we could give the vaccine orally without preadministration of an antacid and so that it would be stable in the refrigerator, and that study showed that the vaccine was well tolerated, and the immunogenicity of the buffered formulation was similar to that of an unbuffered formulation.

We went on then to do a study to establish the dose and serotype composition of the vaccine, and when that study had just started in 1998, the rhesus

rotavirus tetravalent vaccine, or RotaShield, which I'm just going to refer to as "the rhesus vaccine" for the rest of this presentation, was licensed and a universal recommendation was given by the ACIP.

Then approximately a year later is when the reports of intussecption came about with the rhesus vaccine.

So let's talk a little bit about what intussecption is. Intussecption is a naturally occurring illness where the bowel telescopes in on itself, and it can get clogged, and you can have compromise of the vascular supply of the bowel wall. There can be necrosis and even perforation of the bowel wall.

The etiology is not well defined. Adenovirus has been consistently associated with intussecption in several studies. It is an uncommon illness occurring in about one out of 2,000 infants per year.

The peak incidence is between five and nine months of age, and it occurs more commonly in males than females, and we're not certain why. The

treatment is typically with an enema or surgery, and the morbidity and mortality is low if the diagnosis is made early. However, if the diagnosis is delayed, it can be fatal.

Now, the cases of intussecption that were reported with the rhesus vaccine clustered during the two weeks after the first dose and the week after the second dose. This slide was adapted from the New England Journal of Medicine article with the CDC studies of the rhesus vaccine and intussecption, and as you can see here, the highest risk of intussecption with this vaccine was during this first two-weeks after the first does, and there was also an increase during the first week after the second dose.

So we had to decide if we were going to move forward with our vaccine program, and we made that decision based on these factors.

First of all, as I've already shared with you, there is a public health need for a safe and effective rotavirus vaccine.

Second, by the time these studies were available we already had data from the Phase 2 trials

that said that our vaccine was 100 percent efficacious against severe disease and 75 percent efficacious against any severity of rotavirus gastroenteritis, and at that point we had only seen a single case of intussecption in the Phase 2 trials in over 2,400 infants that had been vaccinated.

The other reason we decided to move forward is we had evidence to suggest that the intussecption seen with the rhesus vaccine may be specific to that strain. First of all, there are studies to indicate that wild type rotavirus is not a major contributing cause of intussecption. So there was reason to think this would not be a class effect.

Secondly, there are several preclinical and clinical differences between the two vaccines, as I outlined in the background document for you. For example, we looked at the two vaccines in mice. You get systemic spread with the rhesus vaccine seeding at distal sites with hepatitis and death in SCID mice, and we did not see that with the RotaTeq vaccine.

And there are also differences in the clinic with respect to reactogenicity, with high

fevers in some of the trials the rhesus vaccine during the week after the dose, which we've not seen with our RotaTeq vaccine.

So based on all of these reasons, we developed a plan to move forward to evaluate the safety of RotaTeq with respect to intussecption. We presented that plan to the FDA Advisory Committee in May of 2000 and received approval to move forward.

This slide shows the studies that make up the Phase 3 program. So we moved forward with the large scale rotavirus efficacy and safety trial that I'll refer to as REST.

We also had two other smaller Phase 3 studies, the dose confirmation efficacy study which was done to confirm the efficacy of the final dose of the vaccine, and then the consistency lot study to demonstrate the consistency of the manufacturing process.

So I'm going to begin sharing results with you now, and I want to start with the intussecption since that was a concern with another rotavirus vaccine. So I'd like to share with you the highlights

of the study design of REST.

The same size of REST called for a minimum of 60,000 subjects randomized one to one to receive either vaccine or placebo. After 60,000 subjects were enrolled, if the primary safety hypothesis was not met, we were to enroll additional groups of 10,000 subjects until either the primary safety hypothesis was met or until we reached a maximum of 100,000 subjects.

The age at first dose was six to 12 weeks, and we gave three oral doses at four to ten week intervals. The areas where we did the study were areas with good standard of care for intussecption. We began the study in January of 2001, and the last patient completed 42 days of safety follow-up in April of 2005.

The REST primary safety hypothesis was that RotaTeq would not increase the risk of intussecption relative to placebo within the 42-day period after any dose, and to satisfy that primary safety hypothesis, two criteria had to be met.

The first criteria was for interim

monitoring, that during interim monitoring we would not see an increase in the risk of intussecption among vaccinees. In other words, we wouldn't see a lower bound than the 95 percent confidence interval for the relative risk of intussecption greater than one and two time intervals following vaccination.

We monitored kids for the one to seven day period after vaccination and the one to 42 day period after vaccination to encompass the time of highest risk of intussecption with the rhesus vaccine.

Secondly, at the end of the study the upper bound on the 95 percent confidence interval for the relative risk of intussecption had to be less than or equal to two, and that translates into point estimates of relative risk -- less than or equal to ten; sorry -- and that translates into point estimates of relative risk of less than or equal to two, which would be based on the number of subjects that we would expect given -- the number of cases of intussecption expected given the size of the enrollment.

This is a diagram of our comprehensive safety monitoring system that we put in place to make

sure that we knew the outcome of the infants in the study. So we set up a system of active surveillance at the study sites where we contacted them on days seven, 14, and 42 after each dose, and then up to one year after dose one.

So the parents were called, and they were asked specifically about any hospitalizations, any GI illnesses, including gastroenteritis and intussecption.

If there was a potential case of intussecption, then that case was reported to an independent safety endpoint adjudication committee that consisted of a pediatric surgeon, a pediatric radiologist, and a pediatric emergency department specialist.

They collect the medical records, the radiographic films. They were given to that committee, and they would decide, yes, this is a case or, no, this isn't a case.

Then positively adjudicated intussecption cases or confirmed cases were referred to an independent data and safety monitoring board. They

would unblind each case as it was reported and make recommendations for continuing the study, and they also reviewed all of the serious adverse event data approximately every six months.

I'd now like to just provide a few comments on the statistical properties of the REST study design. The goals of the study design and the extensive safety monitoring system that we had put in place were twofold.

First of all, we wanted to design a study that would have a high probability of stopping early if there were to have been an increase in intussecption risk, but secondly, we also wanted to balance that with a study design that would have a high probability, and if we did have a safe vaccine, that we would satisfy the safety criteria at the end of the study.

So we estimated the probabilities that the study with each of these endpoints using Monte Carlo simulation. With 10,000 different simulations or possible outcomes, these are the results. So here we have the outcome for different risk scenarios and

here's the probability of stopping early because of an unsafe vaccine. This is the probability of meeting the end of study safety criteria.

So for a vaccine with a safe profile of relative risk of one, this study design left us with a six percent chance of erroneously stopping early because of an unsafe vaccine and a 94 percent chance of meeting the end of study safety criteria. If the vaccine were to have had a risk profile similar to that of the rhesus vaccine, as reported by Murphy, et al., in 2001, the probability of stopping early because we were unsafe was approximately 90 percent, and the probability of meeting the end of study criteria was only ten percent.

So now I'd like to share the results of the Phase 3 studies with you. Overall we enrolled and vaccinated over 71,000 subjects in 11 countries with over 36,000 receiving RotaTeq and over 35,000 receiving placebo. Fifty percent of the enrollment took place in the United States, about 30 percent in Finland, and then the remaining 20 percent were distributed among countries in the rest of Europe,

Asia, and Latin America.

This is a diagram showing the safety follow-up of the subjects in the study. So the 71,799 vaccinated subjects came from the three Phase 3 studies with 36,000 in the vaccine group, 35,000 in the placebo group. Over 99 percent of children in each group completed follow-up for the 42 days after their last dose, and of course, that's the time period upon which the primary safety hypothesis was based.

Over 91 percent of children in each group received all three doses and 42 days of safety follow-up after the last dose. And a slightly higher number, over 93 percent, received complete follow-up for one year after the first dose.

The reason why that number is a little higher is what parents, when it's a dropout of the dosing phase of the study, we would continue safety follow-up with their consent.

So we had a very small number of children that were absolutely lost to follow-up, .2 percent in the vaccine group and .3 percent in the placebo group.

We looked at detailed safety in a subset

of about 11,000 subjects, and I'm going to talk about these subjects a little bit later.

These are the intussecption results from REST. In total, we had 35 investigator diagnosed cases of intussecption. Of these, there was one case that could not be adjudicated because of a malfunction in the radiographic equipment, and that child was in the placebo group.

There were two cases that were negatively adjudicated, and they were also both in the placebo group. We had 32 positively adjudicated cases. There were 11 within the 42-day period of a dose, the time period upon which our primary safety hypothesis was based; six in the vaccine group and five in the placebo group.

There were 17 cases that occurred between the time period of 42 days after a dose and within the one year period after the first dose. Seven of those were in the vaccine group and ten in the placebo group. So I'm going to go into these cases in a little bit more detail on the next two slides.

And then we had four cases that were

reported to us after the child had actually completed the study, and all of those cases occurred in the placebo group.

We did not have any intussecption cases reported in the other two Phase 3 studies, Protocol 7 and Protocol 9.

This graph shows the confirmed intussecption cases in REST within the one year period after the dose. We had a total of 28 cases, 13 in the vaccine group, 15 in the placebo group, with a relative risk of .9 and a 95 percent confidence interval of 0.4 to 1.9.

This slide shows the confirmed intussecption cases in REST within 42 days of each dose, and this is, of course, the time period upon which the primary safety hypothesis was based. So this is dose one, dose two, and dose three, and you have your line here representing the 42 day mark.

During this time period there were 11 cases, six in the vaccine group and five in the placebo group for an unadjusted relative risk of 1.2 with a 95 percent confidence interval of .3 to five,

which is well below the upper bound of ten that was required in order to meet the primary safety hypothesis.

The cases occurred sporadically. There was no clustering of vaccine cases alone at any time after a dose, and what's remarkable is there were no vaccine cases during this first two-week period after dose one, which was the time period of greatest risk of intussecption with the rhesus vaccine.

We looked at the characteristics of all of the cases of intussecption carefully, and they were similar to naturally occurring intussecption. The incidence in infant years was one in 2,253 overall and one in 2,101 in the placebo group, which is very similar to the assumed rate of one in 2,000 that we used when designing the study.

There was a male predominance of cases with 19 males and 13 females overall, and the peak age at diagnosis was five to nine months with no shift of cases to younger infants age two to three months.

So in summary, the REST data provide a high level of confidence in the safety of RotaTeq with

respect to intussecption. The primary safety hypothesis was satisfied. The relative risk of intussecption met the prespecified statistical criteria for clinical susceptibility. After we adjusted the relative risk for multiplicity with enrollment of 70,000 subjects, the relative risk was 1.6, with a 95 percent confidence interval of 0.4 to 6.4, again, well below the upper bound of ten that was required to meet the primary safety hypothesis.

The intussecption cases occurred sporadically. There was no clinical evidence of an increased intussecption risk among vaccine as compared with placebo recipients during the one to two week period after a dose, and the overall characteristics of the case of intussecption in REST were similar to those of naturally occurring intussecption.

So now I want to shift gears and share with you some of the other additional safety data from the Phase 3 studies. So just to give you a reminder, the way we evaluated safety in the Phase 3 studies, in the large scale cohort, as we call them, the group of over 71,000 subjects, we looked at all serious adverse

experiences including intussecption within the 42 day period after a dose, and then we evaluated them for vaccine related serious adverse events and deaths until the end of the study.

Now, in a subset of children, over 11,000 children, we looked at all adverse events serious and non-serious. So upper respiratory infection, eat infection, we looked at all adverse events. And we specifically focus on other adverse events of clinical interest for this vaccine. So fever, vomiting, diarrhea, irritability, and also hematochezia since that had been reported with the rhesus vaccine.

The other safety evaluation that we did was that we looked at fecal vaccine strain shedding. This is a life oral rotavirus vaccine. So we looked for vaccine strains in the stool, and we did that in two ways.

The first way was that we looked at in a prespecified group of subjects as a specific time interval, and then the second way we did it is any child who had an episode of acute gastroenteritis that was rotavirus positive, we looked for vaccine strains.

This slide shows a summary of the serious adverse events that were reported within 42 days of any dose in the large scale cohort of over 71,000 subjects, and as you can see, the incidence of serious adverse events was similar in the vaccine and placebo groups, 2.4 percent in the vaccine group as compared to 2.6 percent in the placebo group.

The incidence of dose related serious adverse events was also similar in the two groups, .1 percent in the vaccine group as compared with .2 percent in the placebo group.

There were a total of 28 deaths during the 42-day period after a dose, 15 in the vaccine group and 13 in the placebo group, and the most common cause of death was sudden infant death syndrome. Over the course of the trial we had 17 cases, eight in the vaccine group and nine in the placebo group. And discontinuations due to serious adverse event was also similar in both groups.

This slide shows the most frequently reported serious adverse events within a 42 day period after a dose, and it's exactly what we would expect

based on the age of infants enrolled in the study. The two most frequent serious adverse events that were reported overall were bronchiolitis and gastroenteritis. Both had similar incidences in the vaccine and placebo group.

And the most frequent dose related serious adverse events were gastroenteritis, fever, and dehydration, again, which had very similar incidences in both the vaccine and placebo groups.

Now, shifting to the subgroup of 11,000 subjects where we evaluated all AEs, first I want to share with you the data on fever. This slide shows the percent of infants with fever within the week after a dose by vaccination group and dose number. So on the Y axis we have the percent of subjects. On the X axis we have dose one, dose two, and dose three. The yellow bars represent RotaTeq recipients, The white bars represent placebo recipients.

And as you can see, the incidence of fever, which we defined as a temperature greater than or equal to 100.5 rectal equivalent was similar in vaccine and placebo recipients after each dose. None

of these differences were statistically significant.

This slide shows the percent of infants with vomiting, diarrhea and irritability within the week after the first dose by vaccination group. And the slide is set up the same way with the yellow bars representing vaccine recipients and the white bars representing placebo recipients.

There was an increased incidence of vomiting in vaccine as compared with placebo recipients after the first dose, and also an increase in the incidence of diarrhea in vaccine as compared with placebo recipients after the first dose. This difference was 1.3 percent for each of these AEs, and it was statistically significant.

However, these differences were not unexpected, given that this is a live oral rotavirus vaccine.

This slide shows the percent of infants with hematochezia, which we defined as bloody stools or Melena or procedures for hematochezia, within the six weeks of a dose by vaccination group and dose number.

And as you can see here, the overall incidence of hematochezia that was reported was low. After dose one, we had .5 percent of subjects in the vaccine group as compared with .3 percent of subjects in the placebo group with hematochezia. After dose two it was .2 percent to .3 percent, and after dose three, it was .01 percent in both groups, and none of these differences were statistically significant.

For the evaluation of fecal shedding and vaccine strains, I'd like to provide just a little bit of history about what we saw in our Phase 2 programs before I present the results. Our Phase 2 studies, what we found there was that a very low proportion of subjects shed vaccine strains, less than ten percent. It was shed in low quantities, and almost exclusively after dose one.

The bovine human reassortants don't replicate vigorously in humans, and you typically get a board of replication and then they die off quickly.

So what we also found in the Phase 2 study is that the vaccine virus strain shedding peaked during the four to six day period after a dose. We

did one study where we looked at several different time periods after the dose and found that the peak of vaccine shedding almost exclusively occurred during that first week after the first dose.

So in REST and in Protocol 7, we evaluated fecal shedding of vaccine strains in two ways. We prospectively identified a subset of 300 subjects where we collected stools during days four to six after vaccination, and then again in all cases of acute gastroenteritis that were rotavirus positive we looked for vaccine strains.

And these are the results of the Phase 3 studies for fecal shedding. We saw a very similar pattern as to what we saw with -- in our Phase 2 studies. Eight, point, nine percent of vaccine recipients had fecal shedding of vaccine virus after dose one. We know that the majority of this was during the week after the dose. The latest shedding that we saw was 15 days from dose one.

We had no subjects that shed after dose two, and only one subject shed after dose three. He shed four days from dose three.

The quantities were low, similar to what we saw in the Phase 2 studies as well.

We also had two placebo recipients that shed, and of course, this raised a red flag for us. Could this have been transmission of vaccine virus from vaccine recipients to placebo recipients?

We did a very thorough investigation looking for opportunities for a vaccine transmission to occur and did not find anything. These children were not siblings of a vaccine recipient. They didn't attend day care with vaccine recipients. They didn't have a common caretaker with the vaccine recipient, and in the office and clinic in which they were vaccinated, they were not exposed to vaccine recipients.

So going on then to summarize general safety, RotaTeq was well tolerated. With respect to the adverse experiences of special clinical interests that I shared with you, fever, vomiting, diarrhea, irritability, and hematochezia, there was an increase in mild diarrhea and vomiting after vaccination being 1.3 percent greater in the vaccine as compared with

the placebo groups.

Our vaccine strain shedding studies look very similar to the Phase 2 studies. Vaccine strain shedding occurred infrequently and almost exclusively during the week after the first dose, which suggests that the risk of transmission of vaccine virus strains is low.

So now that I've shared with you the safety results, I'd like to move on and talk about our efficacy results and the potential of the vaccine in preventing rotavirus gastroenteritis.

So we did an efficacy evaluation in two ways. We looked at efficacy in REST and Protocol 7. So in the large scale cohort in REST in over 68,000 subjects, we looked at the efficacy of the vaccine to prevent hospitalizations and emergency department visits for rotavirus gastroenteritis.

Then in a sub study in REST and in Protocol 7, in almost 7,000 subjects, we looked at the efficacy of the vaccine against all rotavirus gastroenteritis, and we looked at the efficacy of the vaccine to prevent office visits for rotavirus

gastroenteritis.

The primary efficacy hypotheses were identical for both studies, and that is that oral RotaTeq will be efficacious against rotavirus disease caused by Serotypes G1, 2, 3, and 4 that occurs after a three-dose regimen.

Other efficacy objectives that we looked at, we looked at efficacy against moderate and severe rotavirus disease. We looked at efficacy against rotavirus gastroenteritis caused by the individual serotypes in the vaccine and not in the vaccine, for example, G9, and then we looked at the persistence of efficacy through a second rotavirus season post vaccination.

The case definition that we use for rotavirus gastroenteritis was identical for both studies. The clinical case definition called for forceful vomiting and/or at least three watery or looser than normal stools within a 24 hour period.

The severity of cases was assigned using a clinical scoring system. We looked at the intensity and duration of the symptoms of gastroenteritis,

fever, vomiting, diarrhea, and behavioral changes, and we attributed a score to each of those symptoms.

If the score was less than or equal to eight, the disease was considered to be mild. If it was between eight but less than or equal to 16, it was moderate, and greater than 16, it was severe.

The laboratory case definition called for rotavirus detection by EIA with serotype identification by PCR, and then we looked for vaccine strains by plaque and electropherotyping.

And a child had to meet both the clinical and laboratory case definitions in order to be considered a case for the analysis.

So now I'm going to go through the results for each of these efficacy endpoints. So we're going to first talk about the primary efficacy analysis, then efficacy against hospitalizations, emergency department visits, and office visits for rotavirus gastroenteritis, and then the intent to treat efficacy analysis, the serotype specific efficacy, and the second season efficacy.

And I wanted to just point out that all of

the analyses that I'm going to show you are based on the protocol population in children receiving all three doses of vaccine except for the intention to treat efficacy analysis, which would start counting cases from the day of vaccination, the first day of vaccination.

So the primary efficacy hypotheses for both studies were met. RotaTeq was efficacious against G1 to 4 rotavirus gastroenteritis, and this slide shows the efficacy by disease severity. Efficacy against any severity of disease was 74 percent, the lower bound of 67 percent. Efficacy against severe disease was 98 percent. We had one breakthrough case in the vaccine group.

RotaTeq was also efficacious in preventing hospitalizations, emergency department visits, and office visits for rotavirus gastroenteritis. The vaccine reduced hospitalizations by 96 percent as compared with placebo, with a lower bound on the confidence interval of 90.5.

The reduction in emergency department visits was 93 percent, and the reduction in office

visits was 86 percent.

This is the intention to treat analysis looking at the primary endpoint efficacy against G1 to 4 rotavirus gastroenteritis of any severity or severe disease, and what we did here is we included all the protocol violators in the analysis, and what this shows the efficacy against any severity of disease was 59.7 percent, and efficacy against severe disease was 96.8 percent.

This is a similar intent to treat analysis looking at efficacy against hospitalizations, emergency department visits and office visits, and as you can see, these results are very similar to our protocol results, with efficacy against hospitalizations of 95 percent, against emergency department visits of 90 percent, and reduction in office visits of over 84 percent.

This slide shows the efficacy of RotaTeq against each of the individual serotypes that were circulating at the time of the study in that subgroup of 7,000 children, and the serotypes that we saw were what we would expect based on what we know about the

epidemiology of rotavirus.

We saw mostly G1, smaller numbers of G2, G3, G4, and G9.

The efficacy against G1 in this group was against any severity of disease, was 75 percent. Efficacy against G2 was 63 percent. For G3 it was 56 percent. For G4, it was 48 percent, and for G9 we only had five cases, but it was 74 percent.

So in order to get a look at a greater number of cases and do further evaluation of the serotype specific efficacy, we looked at this in the large scale cohort as well that we're following for hospitalizations and emergency department visits. And I have those results for you here on this slide.

The efficacy against hospitalizations and emergency department visits caused by G1 rotavirus gastroenteritis was 95 percent. Efficacy against G2 was 88 percent. For G3 it was 93, G4 89 percent, and for G9 it was 100 percent with 13 cases occurring all in the placebo group.

So these results taken together, the smaller efficacy cohort and the large scale study

demonstrate that RotaTeq was efficacious against all the strains that were circulating during the study.

Then we looked at the efficacy of RotaTeq through the second rotavirus season post vaccination. So this slide shows efficacy here on the Y axis. This is the first season here in the left-hand side of the screen. The second season efficacy here on the right-hand side of the screen, and the blue boxes represent efficacy against severity of disease. The orange diamonds represent efficacy against severe disease.

So the efficacy in the first season, as I shared with you on the earlier slide, was 74 percent against any severity of rotavirus gastroenteritis, and 98 percent against severe disease.

Then we looked at efficacy just during the second rotavirus season, and the efficacy during the second season was 63 percent against any severity of rotavirus gastroenteritis and 88 percent against severe disease.

So in summary, RotaTeq prevented G1 to 4 rotavirus gastroenteritis of any severity and severe disease and significantly reduced hospitalizations,

emergency department visits, and office visits for rotavirus gastroenteritis.

The serotype specific efficacy data indicate that RotaTeq is efficacious against the serotypes in the vaccine and against G9 strains. We did P typing on the G9 strains that were circulating at the time of the study, and they were P1.

Efficacy also persisted during the second rotavirus season.

So I'm going to wrap up the presentation with an overview of the immunogenicity objectives and results from the Phase 3 studies. We evaluated immunogenicity in two ways. We looked at the immunogenicity of RotaTeq. Then we also did a concomitant use study looking at immunogenicity of other vaccines when given concomitantly with RotaTeq.

As you all know, no definitive immunologic surrogate of efficacy with RotaTeq has been identified. Studies of wild type rotavirus suggest that serum and fecal anti-rotavirus IgA and also G1 serum newts correlate with protection.

However, we've not found this in our

studies, but we do know that the immunogenicity of RotaTeq, the responses that we see do indicate vaccine activity because they correlate with potency, with the potency or dose of the vaccine. They just don't correlate with efficacy.

So what we've done in the Phase 3 studies is we've utilized our immunogenicity data basically for two purposes: to demonstrate the consistency of the manufacturing process and also in our concomitant use studies.

And the pattern of antibody responses that we've seen to RotaTeq has been consistent across populations as I outlined in your backgrounder. A high proportion of children have over 90 percent -- a high proportion, over 90 percent, of children have a significant rise in anti-rotavirus IgA after three doses, and the magnitude of serum neutralizing antibody responses to the GMP types vary, typically being high for G1 and P1 and G4, and lower for G2 and G3.

I want to now move on to present to you the evaluation of the immunogenicity of licensed

vaccines when given concomitantly with RotaTeq. And this was done in a study of 1,358 subjects with over 600 in the vaccine group and over 600 in the placebo group.

We evaluated antibody responses to DtaP, IPV, hib, Hep B and pneumococcal conjugate vaccines, and we compared the antibody responses to those vaccines when given concomitantly with RotaTeq as compared with antibody responses to those vaccines when given concomitantly with placebo.

The statistical criteria for demonstrating noninferiority of these responses in the two groups for diphtheria, tetanus, IPV, hib, and Hep B was that there would be 95 percent confidence that there was no more than a ten percentage point decrease among vaccinees compared with placebo recipients for the proportion who achieved the established seroconversion or seroprotection criteria.

For pertussis and pneumococcus, since there is no definitive seroprotection criteria that we could look at, we said that there was 95 percent confidence that there would be no more than a twofold

decrease in the GMT of antibody responses to these two vaccines among vaccine recipients, RotaTeq recipients, as compared with placebo recipients.

The concomitant vaccination schedule that we used called for three doses of DTAP and pneumococcal conjugate vaccine, and we measured the antibody responses after the third dose so that the children were approximately seven to eight months of age.

We also gave two doses of COMVAX and IPV, and we measured antibody responses after the second dose of these vaccines. So the children were approximately five to six months of age, and children in this group were also required to get a neonatal dose of Hepatitis B.

And as you can see here, we've outlined this seroprotection criteria that we use when planning the study and that we use for measuring these responses.

This slide shows the antibody responses to diphtheria, tetanus, Hep B, hib, and polio, and they were similar in children who got RotaTeq with these

vaccines and children who got placebo with these vaccines. We have the percent seroprotection here on the Y axis. These are the responses to diphtheria, to tetanus, to Hepatitis B, to hib, to polio virus 1, Type 2, and Type 3.

There are the antibody responses to the pneumococcal conjugate vaccine, and they were also similar in RotaTeq and placebo recipients. We have the GMT here and the different serotypes along the X axis here, and as you can see, the responses were similar for each of the serotypes that we evaluated.

We met our statistical criteria for demonstrating non-inferiority for these responses also.

These are the responses to pertussis toxoid, FHA and Pertactin in RotaTeq as compared with placebo recipients. Again, we have the GMT here on the Y axis, the responses to the toxoid FHA and Pertactin here.

We met our statistical criteria for demonstrating noninferiority for the PT and FHA responses. We did not meet the statistical criteria

for the Pertactin response. We just marginally exceeded the statistical criteria required.

However, children did have evidence of quantifiable Pertactin activity, and that was similar in both the vaccine and placebo groups. Ninety-five percent of RotaTeq recipients and 96 percent of placebo recipients having quantifiable Pertactin activity.

So based on the overall profile with the noninferior responses with toxoid and FHA and the activity that we saw with Pertactin, we feel that children who get RotaTeq with a DTP vaccine would have similar immunity to pertussis as other children.

So in summary, RotaTeq was generally immunogenic. We have not identified yet a definitive immunologic surrogate for efficacy, and in administration of RotaTeq with licensed pediatric vaccines induced acceptable antibody responses to those concomitant vaccines.

So before I close, I want to share just a couple of slides about the post licensure plan to monitor the safety of RotaTeq. Certainly post

licensure surveillance is planned to monitor the safety of the vaccine with respect to intussecption. As you can see here on this graph, from data from New York State with the number of hospitalizations for intussecption here on the Y axis and the age and months in the X axis that the peak of intussecption occurs between five to nine months of age. RotaTeq is going to be given on a two, four, six month schedule. That schedule overlaps with the peak of naturally occurring intussecption. So we will see cases of intussecption among children who get RotaTeq.

So we'll be monitoring that closely post licensure.

And I have here on this slide our post licensure plan for monitoring intussecption and other adverse events. First of all, we have a huge volume of data from our Phase 3 clinical trials. REST was one of the largest clinical trials that's ever been done prelicensure with over 36,000 children getting active vaccine.

We also have other pharmacovigilance activities that are planned, and we're going to be

doing active surveillance in a population based study to assess intussecption and general safety, and that study has been designed to allow for essentially real time assessments of intussecption events.

We're also going to be doing enhanced passive surveillance. For intussecption, if we get passive reports we'll be following those up with a telephone call and be promptly reporting those to FDA, and then for all adverse events we're going to be reporting to FDA on a monthly versus quarterly basis.

And we're continuing to coordinate with public health agencies, including the FDA and CDC on our plans.

So now I would like to conclude. As I've shared with you, rotavirus is a significant cause of childhood morbidity in the United States, responsible for over 55,000 to 70,000 hospitalizations each year.

The only available therapy for rotavirus in the United States is supportive care. There is no preventive treatments available.

The results of REST and the other Phase 3 studies provide a high level of confidence in the

safety of the vaccine. RotaTeq was well tolerated with respect to all adverse events, and there was no signal of a safety concern with regard to intussecption.

The efficacy data show the tremendous potential benefit of the vaccine. RotaTeq prevented 74 percent of any severity of rotavirus gastroenteritis and 98 percent of severe disease, and that clinical efficacy resulted in significant reductions in health care encounters for rotavirus gastroenteritis, a 96 percent reduction in hospitalizations, a 93 percent reduction in emergency department visits, and an 86 percent reduction in physician office visits.

Our concomitant use data support that RotaTeq can be administered concomitantly with other childhood vaccines in the well baby immunization schedule.

So given the indiscriminate nature of this vaccine, the unpredictability of the vaccine to cause severe disease, and the fact that every child gets infected, this vaccine is an important public health

priority.

Thank you.

CHAIRMAN OVERTURF: Thank you, Dr. Heaton.

We have a few minutes. Are there questions of clarification or comments from committee members? Dr. Markovitz.

DR. MARKOVITZ: Yes. Just curious. How do you actually type these things? You alluded to electrophorotyping. How do you do that? It's kind of interesting in view of the fact you had those placebo cases, you know, the people received placebos who actually seemed to shed virus. That was presumably the vaccine type.

So how do you actually phenotype those or genotype those?

DR. HEATON: Yeah, there's two different systems that we use for our case definition for typing the study. So for the efficacy portion of the study we use PCRN sequencing for typing. For the vaccine shedding portion of the study we used plaque assays. So basically just make up a stool suspension, put in the cell culture, and then we would purify the plaques

and do electrophoresis to identify the serotype.

Does that answer your question?

DR. MARKOVITZ: So, I mean, you just see an electrophoretic gel, that the proteins run in a different size based on the phenotype; is that right?

DR. HEATON: Exactly, and that's what our case definition was based on.

Now, although our case definition wasn't based on it, we also did PCR confirmation of those serotypes as well.

Yes?

DR. FARLEY: This is a follow-up to that. So can you tell that it is definitely a vaccine serotype by those methods?

And I wonder whether you talked about exposure of the subjects to each other in terms of their epidemiologic associations, but what about that health care providers, those who were delivering the vaccine? Is there a risk that it's on their hands, that they may be spreading it from one individual to another?

DR. HEATON: Those are good questions. So

the first question was? I'm sorry. Can you repeat that?

DR. FARLEY: Can you be certain that it's a vaccine serotype based on your typing system?

DR. HEATON: Yes. Based on our typing system, we can have very high likelihood, you know, in the 98 to 100 percent range that those strains are homologous with vaccine strains. So there's very high certainty when we see something that looks like a vaccine strain that it actually is a vaccine strain.

Then with respect to the possibilities of how these children ended up with vaccine strains in their stool, we really could not find the answer for that. We even went so far as to look and see like on the day that that child was in the clinic, were other children getting vaccine, you know, right before or after them? And that was not the case. So it has been a puzzle, and we don't have an answer as to why these children had vaccine strains in their stool.

CHAIRMAN OVERTURF: Yes, Dr. McInnes.

DR. McINNES: I have five questions. I'm sorry if that's a lot.

Could you please remind me? What was the placebo?

DR. HEATON: The placebo was the buffer stabilizer formulation just without the vaccine strains.

DR. McINNES: Okay. The second question is I'm trying to really understand specifically the contact follow-up during the active surveillance and this term "up to one year." Do you mean for exactly one year until age one year? Up to equals until? What is "up to one year"?

DR. HEATON: Certainly. So the question is about what does follow-up mean up to one year, and what it is, it's one year after they receive their first dose. So that was the follow-up.

So children at a minimum had to be followed for 42 days to have considered to complete the study after their last dose, and we continued to follow children for up to one year after their first dose.

DR. McINNES: Okay. The third question is the data that you presented on page 51, and I think

it's your slide 51, which is the intussecption cases in the REST study. I wonder if you could put that slide back up, please.

I'm trying to understand how to read this. You have a total of 11 confirmed cases of intussecption in the REST study within 42 days, and you've got six vaccine and five placebo. But I'm seeing 28 data points there, and I don't know how to read this slide.

DR. HEATON: Sure. The 11 cases occurred within the 42 day period after a dose. So we tried to draw a dotted line that represents the 42 day mark. So everything to the left of this line are the cases that occurred within the 42 day period. So we had the one case after, you know, dose one and so on and so forth.

So the cases that occurred to the right of the line occurred after the 24 day period and between the 365 day.

DR. McINNES: Out of your definition.

DR. HEATON: Yes.

DR. McINNES: Okay, all right. And I have

a question about what efficacy estimates you got out, a single dose or two doses. You didn't mention any of that.

DR. HEATON: That's right, and so the question is about the efficacy after one and two doses of the vaccine. The study was not designed to look at the efficacy of one or two doses. However, we were enrolling year round. So, therefore, that gave us the opportunity to look at like children who either dropped from the study or cases that occurred in between doses.

So if I could have Slide 149, please.

So this is the efficacy. These are the case splits, if you will, in that efficacy cohort looking at G1 to 4, rotavirus gastroenteritis cases that occurred greater than or equal to 14 days after either one dose or greater than or equal to 14 days after two doses.

So looking after one dose in REST, there were 15 cases in the vaccine group and 24 in the placebo group. In Protocol 7, it was of course a much smaller study. There were two cases in the vaccine

group and one in the placebo group.

For two doses, the case split was 23 in the vaccine group, 37 in the placebo group in REST, and then four and four in Protocol 7.

So these data suggest that there likely is some efficacy with one or two doses, and we also looked at this in our health care utilization data for the health care encounters as well to see what the benefit, hospitalizations, emergency department visits would be after one or two doses.

And I believe we have a slide that has those data on it. So if I could have Slide 150, please.

This shows the efficacy of RotaTeq against hospitalizations and emergency department visits with one dose only, and if you look at just with one dose, efficacy against the combined endpoint was 28 percent. Efficacy against hospitalizations was 18 percent and against emergency department visits was 36 percent.

Then after two doses, which is on the next slide, the efficacy went up pretty substantially. For the combined endpoint it was 80 percent against just

hospitalization, 84 percent, and emergency department visits 73 percent.

So I say this with the caveat, you know, these numbers are small, but it does look like again there's some benefit from one or two doses, but clearly that third dose provides a substantial increase in the magnitude of protection.

CHAIRMAN OVERTURF: Was there any stratification of those as to interval between doses? I assume that you picked 42 days for your first look at intussecption because that was the minimal period of time between three doses and the primary series, but I wondered if there was any effect if the doses were delayed or if there was -- whether you had any opportunity to look at that.

DR. HEATON: So the question is was there any effect of the dosing interval on efficacy?

CHAIRMAN OVERTURF: Yes.

DR. HEATON: Okay. No, we actually looked at that. We did part of the efficacy study in Finland where they're generally on a two, three, four month schedule, and then in the U.S. where they're on a two,

four, six month schedule, and the efficacy estimates were very similar.

For example, I believe the efficacy in Finland was against any severity of disease was about 74 percent, and then in the United States concomitant use cohort, it was about 89 percent with very overlapping confidence intervals. So it was very similar on the two schedules.

CHAIRMAN OVERTURF: Dr. Word.

DR. WORD: I was just going back to your clinical scoring for the acute gastroenteritis. I'm sorry we can't see each other. And you defined I think it was severe the score had to be greater than, I think, 16, and when I add it up, could you just explain how you came about the scoring because, say, for example, when I just compute, I got a score of 12, which would have fallen into the moderate disease, and the person had a seizure for one day, temperature for one day, diarrhea and so on, and it wouldn't have gone into your category of severe, but I would have considered that something significant.

And so it changes your -- when you said

efficacy is 98 percent, I think, for severe disease versus 75 percent for the others. So how did you just come about creating this or choosing?

DR. HEATON: Certainly. So the question is about the scoring system and how it works. So the scoring system is based on not only the intensity symptoms, but also on the duration of symptoms, and so I've given different numerical values depending on both of those things.

So if I can have the slide with the scoring system, it's a bit complicated, but maybe this will help you understand it. So Slide 1555.

So here's what basically we do. We look at diarrhea. So we look at the number of stools per day, and if they have two to four they get a score of one; five to seven, they get a score of two; and greater than eight they get a score of three.

And we also look at the duration of diarrhea in days. We do the same thing for vomiting, the number of episodes per day, the duration in days. With temperature we look at the degrees of temperature, you know, how high it is and the

duration, and then behavioral symptoms as well.

And the way we get this information is the parents literally record daily on a diary, what symptoms the children have, and then that's transferred to a work sheet, and then we use a computer algorithm to look at the scoring system or to look at the score.

And I can tell you that we validated the system in one of our Phase 2 studies, and what we did is we looked at the parental reports of symptoms, and we looked at how that compared to an independent physician assessment of the severity, and they correlated very well.

In fact, for the three categories, the confidence intervals didn't even overlap. They correlated very well with the physician assessment of severity.

Does that answer your question?

CHAIRMAN OVERTURF: Dr. Royal.

DR. ROYAL: How far out have you been able to carry your subsequent season surveillance? And do you think that you'll continue to see a decrease in

prevention or protection to the point where it may be necessary to revaccinate?

DR. HEATON: Yes. So the question is about the persistence of efficacy through the second or season and beyond.

For the Phase 3 studies, we've looked at efficacy through the second season. As I shared with you in the primary presentation, the efficacy during the second season against severe disease did persist. It was 88 percent against severe disease.

Efficacy against any severity of disease was about 62 percent, but certainly the confidence intervals overlapped with that of the first season efficacy.

In addition, we looked at the second season efficacy or efficacy during the second year of life for the hospitalizations and emergency department visits, and what we found is that efficacy persisted. For hospitalizations and emergency department visits in the second year of life, the reduction was still in the, you know, mid-'90s just like it was for the first year of life.

We have not looked at efficacy beyond that second year of life or that second rotavirus season at this point. Clearly the bulk of hospitalizations with rotavirus gastroenteritis occur in the first two years of life, and that's when children are most vulnerable to the dehydration and from rotavirus gastroenteritis. So we're really wanting to make sure we have good protection during those first two years of life.

I actually have the data that you want to see about the second season for the health care utilization endpoints. So if I can have Slide 530, please.

So this is looking at the efficacy against the hospitalizations and emergency department visits by age. So if you look at kids less than a year old, there was a 92 percent reduction in the rate of hospitalizations, and if you look at children who were between one and two years of age, it was almost a 95 percent reduction.

DR. ROYAL: Were there differences in international sites versus U.S. sites in that second season?

DR. HEATON: So the question is were there differences in international and U.S. sites for the second season. We did not split it out by the second season, but I can tell you that the overall for the full two years, the rate reduction was the same regardless of what country you're talking about. Clearly patterns of health care seeking are different, but when you looked at the rate reduction in the vaccine and placebo groups, it was the same for all the different analyses that we did.

CHAIRMAN OVERTURF: We have time for one more question. Dr. Self.

DR. SELF: Maybe two quick questions?

CHAIRMAN OVERTURF: Yes.

DR. SELF: Thanks.

So the risk of intussecption associated with the rhesus vaccine has obviously had a big impact on the program is important, but I'm having a hard time placing that in context of your data. Could you go back to Slide 51 and comment and tell me where that relative risk fits here and comment on your ability to distinguish the relative risk associated with your

vaccine and that one?

DR. HEATON: So the question is to comment on the results of our trial compared with the relative risk seen with RotaShield, and also distinguish the risk between the two vaccines.

So clearly, you know, REST was not a head-to-head study with RotaShield. It was clearly designed to compare the risk of intussecption among vaccine recipients as compared to placebo recipients.

And as I showed with you earlier in the primary presentation, we did have high power, approximately 90 percent power, to detect a risk of intussecption similar to that reported for RotaShield, and that really came from the seven day stopping boundary because that was the time period of greatest risk of intussecption with RotaShield. We had a stopping boundary. If we would have seen an increased risk of intussecption during that time, we would have stopped the study early.

So we had that kind of power to detect the risk of intussecption with RotaShield.

The other thing that can be pointed out

here is the difference in the pattern of cases. You recall that with RotaShield the highest risk was during the first two weeks after dose one. We saw no cases during the first two weeks after dose one, and we didn't see a clustering of cases at any time after a dose.

The other thing we've looked at, we said, "Well, what if we did have a risk of intussecption with RotaShield? How many cases would we have expected to see within that first two week period after the first dose?"

And depending on the study that you look at and the estimated relative risk, we would have expected to see between six to 12 cases within the first two week period after the dose had we had a risk of intussecption similar to that reported for RotaShield, and in fact, we saw zero.

So does that answer your question?

DR. SELF: Not exactly. What's the best estimate of the relative risk associated with RotaShield?

DR. HEATON: Well, it varies from study to

study.

DR. SELF: Within the 42 day window, best estimate integrating the data that exists.

DR. HEATON: The estimate of relative risk of RotaShield within the 42 day window after a dose. I think I'm going to have Dr. Heyse, our statistician, can comment on that for you. He's looked at that.

DR. HEYSE: As was indicated, there is not a single relative risk that has been associated with RotaShield because there is the pattern over that 42 day period. If you would go back to -- in fact, during the days one to seven after the first dose, the relative risk associated with RotaShield was actually above 20. If you would go out to the 42 days, it does dampen down somewhat, but it is still above ten.

Probably the best way to put this into context is to remind you of the numbers that Dr. Heaton just expressed. For our particular study design and assuming a background incidence of intussecption of one per 2,000 person-years, which was very close to what we observed, we would have expected six to 12 cases during that period, and we observed

none.

The reason it's difficult is because the way that the Murphy paper reported intussecption. It was really specifically over the time intervals. The Monte Carlo simulation that was used to assess the power of the study actually was able to introduce and integrate in a risk profile so that it was not just a single number that was used to characterize RotaShield.

DR. SELF: My second question. So let me back up. Could you give a little more detail about the plans for the post marketing observational study in terms of the design parameters for assessing safety and also your plans for long-term follow-up to assess durability protection in years three, four, and five?

DR. HEATON: Certainly. So as I had outlined earlier, we do have kind of a multi-component plan to look at the safety of the vaccine in the post licensure setting, building what we have already done in REST with over 36,000 vaccinees.

We will be doing another study, an active surveillance in an HMO setting, looking at cases of

intussecption, you know, as they accrue essentially in real time.

So what specific details of the plan can I share wit you or would you like to hear?

DR. SELF: Well, how accurately will you be able to assess rates of intussecption? How large do you anticipate this study being? And then I would also like to hear about the second point, about durability. You presented morbidity and mortality for the first five years, and you demonstrated protection, I think, for the first two of those five. You know --

DR. HEATON: Certainly.

DR. SELF: -- what are you going to be able to say about years two through five?

DR. HEATON: Right. So Dr. Chris Mast is the epidemiologist who will be heading up the post licensure surveillance study. So I'm going to have him comment on that first, and then I'll come back and finish up about the efficacy surveillance.

DR. MAST: I'm Dr. Chris Mast from the Department of Epidemiology at Merck.

And if I could have Slide 1204, please.

Sorry. Twelve, zero, three.

As Dr. Heaton mentioned, we had proposed a pharmacovigilance plan which has several components. There's the enhanced reporting of past events that come into Merck. That will be taken together with all of the preexisting and actually future studies that we had planned to look at the safety with respect to this vaccine.

And then in addition to that we will also be doing a post licensure study, and the purpose of the study is twofold. First, the study is designed to demonstrate the continued favorable safety profile of RotaTeq with respect to intussecption by conducting surveillance to monitor the occurrence of intussecption among vaccinees and also to assess any temporal trend between vaccination and intussecption.

Secondly, the study will also assess general safety with respect to adverse experiences other than AEs, other than intussecption.

Next I'd like to describe the specific objectives of the study.

Twelve, zero, four, please.

This slide shows the two main objectives of the post licensure study to monitor the safety of RotaTeq with respect to intussecption and general safety. First, for intussecption, the study will utilize a signal boundary detection system to monitor in an ongoing fashion the increased rate of intussecption should one exist among vaccinees compared to the expected background rate.

Our proposed study design allows for a rapid detection of a potential safety signal during the study.

And secondly, for general safety, there were actually two sub-objectives. The first is to describe the occurrence of adverse experiences among RotaTeq vaccinees in specified exposure periods, and the second sub-objective is actually an analytic objective which would compare the rate of adverse experiences among RotaTeq recipients to two comparison time periods.

The next slide will highlight the design and setting of the study. This slide shows the proposed design of the study in a post licensure

setting to monitor both the safety or RotaTeq with respect to intussecption and general safety.

First, we will conduct this study in approximately 28,000 infants. The design is a prospective surveillance study where with the age at the first dose of administration will be like that will be indicated and it was conducted in REST.

The dosing schedule will be two, four, six, and six months, and the follow-up period for safety will be the 30-day interval after each dose.

We propose to conduct this study in a large managed care organization, and the outcome of the study is the detection of a potential safety signal utilizing prespecified criteria for both intussecption and general safety.

Now, I would like to just take a minute to describe some of the strengths of this study and why we want to conduct it in this way. Because we're conducting it in a managed care organization, we'll be able to do a couple of things. First, we will be able to link vaccination status with clinical outcomes, such as intussecption.

Now, we can do this rapidly by doing electronic scanning of medical records for potential safety signals, such as intussecption. These features allow rapid detection of intussecption and any potential safety signal should one exist.

And this can be done as the study is ongoing. So as opposed to traditional post licensure studies where there's reporting on sort of an annual or semi-annual basis, this study will be able to assess safety basically in real time.

In addition, this study will use many of the features that we utilize in our REST study. First, all cases of intussecption will be adjudicated by an independent panel, and secondly, the safety data will be reviewed in an ongoing way.

So not only will we look for statistical criteria, but we will also be able to evaluate patterns in the data that would suggest any clinical significant events.

So in this context, I think we have high confidence in the ability of this study in 28,000 subjects to detect potential safety signals among

vaccinated subjects early if they should occur.

DR. SELF: The expected rates went in 2000. How large an increase over that would this study detect reliably?

DR. MAST: I'm sorry. I didn't quite hear your question.

DR. SELF: If the background rate is one in 2,000, how large an increase over that background rate would this study design be able to reliably detect?

DR. MAST: I would like to describe how we propose to monitor intussecption in the post licensure study. If I could have Slide 1209, please.

This graph shows an example of the signal boundary that we would use to monitor the occurrence of intussecption as it accrues, and this is based on a background rate of one per 2,000 subjects.

On the Y axis is the number of intussecption cases. On the X axis is the number of vaccinees that would accrue during the study period. This white dotted line, as you referred to, represents the background rate of one per 2,000, intussecption

per 2,000 person-years.

The blue line represents the signal boundary, and each dot represents an intussecption case that would occur during the study period. Anything below this blue line for X number of vaccinees would represent a situation in which the background rate or, rather, the rate of intussecption among vaccinees was not statistically significant in the background. Anything above that for X number of vaccinees would suggest a potential safety signal.

So, for example, if there were five cases of intussecption among 20,000 vaccinees, that would not represent a safety signal. That would not be statistically significantly different in the background.

However, if we were to see ten cases among 20,000 vaccinees, that would be significantly different than background, and that would suggest to us that there was a signal that we should follow up on.

DR. SELF: So if the rate is one in 1,000, would this study design be able to reliably

detect that by the end of follow-up?

DR. MAST: So the question is what kind of signals would this study be able to detect. And what I'd like to do now is go to the slide where we can show you some of the relative risks that we will be able to detect. Slide 1212, please.

This slide shows the examples of probability of early detection in a study with 28,000 subjects. For example, looking at the top line, if the relative risk were ten, we would be able to detect this fairly early in the study after seeing only four cases among 6,751 vaccinees. We'd have a 97 percent probability of detecting that signal.

Moving down, even for a relative risk of four, we would have an 86 percent probability of detection among seven cases in approximately 20,000 vaccinees.

So the point of this slide is to show that during an ongoing study, we could detect signals fairly early, even before the end of the study, and during continuous monitoring.

CHAIRMAN OVERTURF: Dr. Karron.

DR. KARRON: Just one last question, and I wanted to go back to that Slide 51. My question really has to do with the issue of intussecption around dose two and the age. And actually just, first of all, a point of clarification. My understanding of RotaShield is that although post licensure the signal was detected around dose one, in fact, pre licensure the concern was raised around dose two. Is that a correct understanding as far as you know?

Yes. Oh, someone is nodding.

But I guess my real question has to do with the issue of age of the vaccinees and the placebo recipients around dose two because I think if I read the protocol correctly, the possible age range at dose two could be anywhere from ten to 22 weeks depending on when they get their first dose and then when they get their second dose.

So I was wondering if there were any differences that you noted either in age of vaccinees with intussecption compared to other vaccinees or vaccinees getting dose two compared to placebo recipients getting dose two or any of those.

DR. HEATON: Certainly. Yeah, so the question is did we notice any age differences particularly for cases of intussecption among vaccine and placebo recipients. And could there be a shift of vaccine intussecption cases to a younger age?

We did look at this very carefully because obviously this was of concern with RotaShield, and we plotted the ages out and compared that to background, and we actually have a slide of that, Slide 131.

What we have here is, again, we have the New York State data showing the peak age of intussecption. These are hospitalizations for intussecption by month and age, and then although the denominators are very different, we plotted our cases that we saw in REST, again, with the yellow bars representing vaccine recipients and the white bars representing placebo recipients, and as you can see here, there really was no shift in age. The age was what we anticipated based on what we know about background intussecption.

And we actually did a statistical test looking at his as well, and the P value, I believe,

was like .8. There was no difference.

Does that answer your question?

DR. KARRON: Actually, not really. I really wanted to know -- I mean, I remember that graph, but my question was really specifically at dose two. If you look at vaccinees and placebo recipients, is there a difference in age or if you look at children with intussecption, I mean, granted there are a very tiny number of children. Were those children on the older end of the age range?

Do you understand my question?

DR. HEATON: I do, and you know, the children who had intussecption after the second dose were of similar ages as to the overall population after the second dose. I got those exact numbers. We've actually looked at those, and I can share them with you after the break. I don't have them right at my fingertips, but I could certainly provide those for you.

DR. KARRON: Thank you.

CHAIRMAN OVERTURF: Dr. Gellin, you get the last question.

DR. GELLIN: These are two quick questions, and this will define the quick question.

What are your plans of manufacturing for monitoring the consistency? It looked like you have a human study of immunogenicity that looked at your consistency loss. Over time what's the plan for that?

And the second question, totally different, is given the discussions about pertussis immunity, is there a plan to look at incidence of pertussis over time in recipients?

DR. HEATON: Sure. The plan for monitoring the consistency of the manufacturing process and any changes, we have procedures in place so any changes that take place in the manufacturing process have to be reviewed. We have SOPs that we have to follow for that, and anything that is significant we would discuss with the regulatory agencies and be monitoring that on an ongoing basis.

With regard to the pertussis immunity, we are going to be looking at the responses to, again, pertussis, to FHA, and Pertactin and other studies. What we're actually doing is looking again at another

subset of children in REST who were not tested already for their responses to pertussis, and then we have another concomitant use study that we're going to be doing in Europe with another Pertactin containing vaccine, and we'll be looking at those responses again.

CHAIRMAN OVERTURF: We need to take a break now. So I will ask that we initiate a break and reconvene at ten minutes after 11.

(Whereupon, the foregoing matter went off the record at 10:55 a.m. and went back on the record at 11:13 a.m.)

CHAIRMAN OVERTURF: I'd like committee members to take their seats, please.

We will begin the second half of this morning's meeting with a very brief follow-up presentation by Merck.

DR. HEATON: I just wanted to follow up on the question that was asked about the age of intussecption cases at dose two. So just to put it into context for you, the median age at dose two for all subject in the Protocol 6 was 16 weeks, and that

was in vaccine and placebo recipients.

The median age among subjects who had intussecption was 11 weeks -- I'm sorry -- was 18 weeks. I'm reading the n instead of the H. Was 18 weeks with a range of 14 to 20, and in placebo recipients, the median age was 15 weeks with a range of 12 to 19.

So does that answer your question?

DR. KARRON: I think so.

DR. HEATON: Thank you.

CHAIRMAN OVERTURF: I'd just make a point since we were a little bit off on timing this morning. We will hear the presentation by the FDA and then, depending on how much time we have left, we will have time to make questions to the FDA presenter prior to the presentations of questions later on this afternoon.

So at this time I'll ask Dr. Tiernan to come forward and -- oh, you're there.

DR. TIERNAN: Okay. My name is Rosemary Tiernan. I'm a medical officer in the Division of Vaccines in the Center for Biologics at FDA.

And I'm going to proceed here with the presentation on Merck's RotaTeq vaccine, and the overview of the talk is that we'll just briefly consider the epidemiology, some aspects of the product, the proposed indication and usage, a little bit about the regulatory history which you're already familiar with, organization of the clinical studies, touch on the efficacy, the safety, and then Dr. Hector Izurieta is going to review the RotaShield experience and talk a little bit about post marketing.

Again, as you've already heard, rotavirus disease affects almost all children within the first few years of life. Rotavirus infection in the United States causes 50,000 hospitalizations per year and 20 deaths annually. Rotavirus infection worldwide has much higher mortality, two million hospitalizations per year and 352,000 to 592,000 deaths per year in children less than five years of age.

The product, RotaTeq, is a live, oral, pentavalent, human bovine reassortant with the serotypes human G1, G2, G,3, G4, P1a and bovine G6 and P7. It's a liquid formulation, and it's stored at two