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UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,

MARCH 7, 2001

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The meeting was held at 9:30 a.m. in the Versailles Room of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, DR. ROBERT DAUM, Acting Chair, presiding.

PRESENT:

STEVE KOHL, M.D.
KWANG SIK KIM, M.D.
ROBERT S. DAUM, M.D.
DAVID STEPHENS, M.D.
PAMELA DIAZ, M.D.
BARBARA LOE FISHER
JUDITH D. GOLDBERG, D., S.c.D
WALTER L. FAGGETT, M.D.
DIANE GRIFFIN, M.D.
NANCY CHERRY
Executive Secretary

TEMPORARY VOTING MEMBERS:

WILLIAM BRITT, M.D.
CLAIRE S. BROOME, M.D.
THOMAS FLEMING, PhD.
MELINDA WHARTON, M.D., PhD.

INVITED PARTICIPANTS:

MICHAEL GERBER, M.D.
DOLORES LIBERA
PAMELA MCINNES, D.D.S., Msc

FDA REPRESENTATIVES PRESENT:

DR. ROLF TAFFS
DR. KAREN MIDTHUN
DR. LESLIE BALL

MANUFACTURER REPRESENTATIVES:

DR. CLARE KAHN
FLORENCE JAUMIN
DR. MONCEF SLAOUI
DR. JOHAN VANHOOF
DR. BARBARA HOWE
DR. ACHIM KAUFHOLD
DR. BRIGITTE CHEUVART
DR. MICHEL DUCHENE
DR. DAVID WHEATON

PUBLIC PRESENT:

DR. MARGARET REYNOLDS

I-N-D-E-X

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

(9:36 a.m.)

CHAIRMAN DAUM: Good morning and welcome to the VRBPAC meeting. We will begin with asking the Committee members, and those seated at the table, to introduce themselves. Please, Dr. Ball, we will start with you, and we will go right around the table.

MS. LIBERA: Leslie Ball, FDA, CBER.

DR. TAFFS: Rolf Taffs, FDA CBER.

DR. KOHL: Steve Kohl, Oregon Health Science University.

DR. STEPHENS: I'm David Stephens, Emory University.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. DIAZ: Pamela Diaz, Chicago Department of Health.

DR. GOLDBERG: Judith Goldberg, New York University.

MS. LOE FISHER: Barbara Loe Fisher, National Vaccine Information Center.

CHAIRMAN DAUM: Dr. Fleming?

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. WHARTON: Melinda Wharton, Centers for

Disease Control.

DR. BROOME: Claire Broome, Centers for Disease Control.

DR. GERBER: Michael Gerber, Children's Medical Center, Cincinnati.

MS. LIBERA: Dolores Libera, Allergy and Asthma Network, Mothers of Asthmatics.

DR. MCINNES: Pamela McInnes, National Institute of Allergy and Infectious Diseases, NIH.

CHAIRMAN DAUM: And I'm Robert Daum from the University of Chicago. Thank you, we will now turn the floor over to Ms. Cherry for the conflict of interest statement.

MS. CHERRY: Before I say that, could I ask any of you who are carrying cell phones, and I know that that probably applies to everybody in the room, to please turn them off during the meeting.

We have, the room seems pretty crowded today, and that would be very disruptive.

Now I will read the statement. The following statement addresses conflict of interest issues associated with the open session of the Vaccines and Related Biological Products Advisory Committee meeting on March 7th, 2001.

The topic before the Committee today is a

discussion of the safety and immunogenicity data pertaining to a combination DTPa-HepB-IPV vaccine. Committee members Dr. Snyder and Manley will be unable to attend this meeting. Dr. Katz is expected to join us tomorrow.

The Director of the Center for Biologics Evaluation and Research has appointed Dr. Britt, who will be here later this morning, and Drs. Broome, Fleming, and Wharton, as temporary voting members for this discussion.

To determine if any conflict of interest existed the Agency reviewed the submitted data, and all financial interests reported by the meeting participants. As a result of this review the following disclosures are made regarding today's discussions.

Drs. Goldberg and Fleming have been granted waivers in accordance with 18 USC 208b3, so that they can participate fully in the discussions.

In addition, in accordance with the Food and Drug Administration Modernization Act of 1997, Section 505, Drs. Goldberg, Kohl, Stephens and Fleming, have been granted waivers which permit them to participate fully in the Committee discussions.

Drs. Broome, Daum, Goldberg, Griffin,

Kohl, Snyder, Stephens, and Ms. Libera, have associations with firms that could be, or appear to be, affected by the Committee discussions.

However, in accordance with 18 USC 208 in section 2365.502 of the Standards of Conduct, it has been determined that none of these associations is sufficient to warrant the need for a waiver, a written appearance determination, or an exclusion.

In the event that the discussions involve specific products or firms not on the agenda, and for which FDA's participants have a financial interest, participants are reminded of the need to exclude themselves from the discussions. Their recusals will be noted for the public record.

In the interest of fairness we ask that any other individuals who may wish to participate in this meeting state their name and affiliations, and any current or previous financial involvements with any firm whose products they wish to comment on.

Copies of all waivers addressed in this announcement are available by written request through the Freedom of Information Act.

CHAIRMAN DAUM: Thank you very much, Nancy. Ladies and gentlemen, we are reminded of our frailty in our short existence on this planet, by

events, sad events that have occurred since we met last.

One of our Committee members, Ms. Barbara Loe Fisher has had the untimely and unfortunate passing of her spouse. Ms. Fisher, I wish to tell you, on behalf of myself, and on behalf of the Committee, that your loss is in our thoughts. To the extent that we can, we share your pain, and we hope that you heal in peace and in reflection.

MS. LOE FISHER: Thank you, Dr. Daum. I want to thank the Committee and you, and Dr. Greenberg, and the FDA staff for extending your condolences to me personally and as a Committee in the past few weeks. It meant a lot to me.

And I would also like to thank anyone in this room who gives blood, especially platelet. My husband died of a sever autoimmune blood disorder, and the giving of blood meant that it extended the period of time that he had to spend with us, and in many cases it saves people's lives.

CHAIRMAN DAUM: It would be remiss if I didn't point out that there is also joy in this human existence of ours. Dr. Snyder is not with us during this meeting because he is off to attend to the birth of a grandchild. So that, as always, we mix the

sorrow with the joy.

And now to the business of the Committee this morning. We are going to begin an open session to consider some issues related to Infanrix HepB-IPV from SmithKline Beecham Biologics.

We are going to begin, please, by calling on Dr. Rolf Taffs from the FDA, to introduce the topic to us.

While you are setting up, Dr. Taffs, I'm just going to take a second here. I'm remiss, I did not announce the open public Hearing that we are going to have.

There will be another opportunity later, and there are several individuals who have declared a possible interest to speak later. But does anyone want to speak now?

(No response.)

CHAIRMAN DAUM: Good. In that case, Dr. Taffs, I apologize to you, and turn the floor over to you.

DR. TAFFS: Thank you. It is my responsibility and my pleasure this morning to welcome the members of this Advisory Committee and all others present to the important topic of consideration of this combination vaccine, Infanrix DTPa-HepB-IPV. I

promise to keep my introductory comments brief.

If I could have the next slide, please? The DTPa-HepB-IPV combination vaccine that is the subject of today's meeting, is comprised of the following components.

DTPa as in Infanrix-DTPa, a licensed vaccine, incorporating diphtheria and tetanus antigens produced under license by Chiron Behring. The hepatitis B surface antigen, as in Engerix-B, also a licensed vaccine, and IPV, that has not been previously licensed in the United States.

Next slide, please. I would like to update those present on certain matters, that during the last 11 months, a number of significant updates have taken place regarding recommendations for the sourcing of materials of bovine origin that are used in the manufacture of vaccines.

These include a letter to manufacturers of biological products on recommendations regarding bovine spongiform encephalopathy from April 19, 2000, as well as a joint meeting of the Transmissible Spongiform Encephatolopathies Advisory Committee, and the Vaccines and Related Biological Products Advisory Committee that met on July 27th of 2000.

The letter to manufacturers reiterated

recommendations that were made in letters issued in 1993 and 1996 from CBER, and appraised manufacturers of the need to be informed of the listing of countries potentially affected by BSE in cattle that is maintained by the USDA.

Next slide, please. These documents were followed by a publication from the Public Health Service on recommendations for the use of vaccines manufactured with bovine-derived materials in morbidity and mortality weekly reports in December 22nd of the year 2000.

And the posting of a webpage by CBER titled Current List of Vaccines Using Bovine-Derived Materials From Countries on the USDA's BSE List, or from unknown countries. And the web address is given in this slide.

Included on the web site, in the section of vaccines that use bovine-derived materials from countries on the USDA's list, is a SmithKline Beecham Biologicals DTP vaccine, Infanrix.

The manufacturer has committed to implementing changes that when completed may lead to the removal of this vaccine from the listing.

Now, based on the proposed initial marketing of the Infanrix DTPa-HepB-IPV because it

contains the same components as Infanrix DTPa, it will also be placed on the list, until the changes indicated by the manufacturer have been completed.

Next slide, please. So proceeding with the purpose of this meeting this morning, CBER is requesting that the Committee assembled here today consider a series of questions and discussions points, and make their recommendations regarding this vaccine.

The following questions pertain to efficacy. The FDA is asking for the Committee's vote on this question. Are the available data adequate to support the efficacy of DTPa-HepB-IPV vaccine, when given to infants in a primary series at 2, 4, and 6 months of age?

If the data are not adequate to address efficacy, what additional information should be requested?

Next slide, please. Discussion point number 2. Please discuss whether available clinical data are adequate to demonstrate the safety of the DTPa-HepB-IPV combination vaccine, when given to infants in a primary series at 2, 4, 6 months of age. Please comment on the increased rates of fever.

If the data are not adequate to demonstrate safety what additional information should

be requested?

Next slide, please. Discussion point 3. Please discuss the data submitted in support of the concurrent administration of other routinely recommended childhood immunizations with the DTPa-HepB-IPV vaccine in infants, that is, haemophilus influenza type b vaccine, and 7-valent pneumococcal conjugate vaccine, Prevnar.

Next please. The final discussion point, number 4, please identify any issues that should be addressed in post-licensure studies, specifically, please include a discussion of the safety and immunogenicity of concurrent administration of other routinely recommended vaccines, for example, Prevnar, the safety and immunogenicity of fourth and fifth dose of Infanrix DTPa, following a primary series of DTPa-HepB-IPV.

The safety and immunogenicity of DTPa-HepB-IPV following a complete or partial primary series of Infanrix or other DTPa vaccine. And, finally, the safety of a primary series of DTPa-HepB-IPV following a birth dose of Hepatitis B vaccine.

I think very much, and I now turn the floor back to the Chair.

CHAIRMAN DAUM: Thank you, Dr. Taffs. It

is now time to hear from the sponsor of this proposed product. And I've been given to believe that there are three speakers, Drs. Kahn, Howe, and Kaufhold, and that to remind you, before you start, that there are 50 minutes allotted for this part of the presentation.

I see Dr. Kahn up there, so I think we have the right information.

DR. KAHN: Good morning. If everyone can hear me?

Good morning, members of the Committee, FDA, ladies and gentleman. GlaxoSmith Kline is pleased to be here today to present the candidate infant vaccine, Infanrix DTPa-HepB-IPV.

The agenda, my name is Clare Kahn, I should say at the outset, and I'm vice president for U.S. regulatory affairs, responsible for vaccines. So following my introduction Dr. Barbara Howe, who is vice president and director of clinical R&D, North America, responsible for vaccines, will provide an overview of the clinical data with an emphasis on immunogenicity, and following that, Dr. Achim Kaufhold, head of pediatrics vaccine development unit at SB Biologicals in Rixensart, Belgium, will provide a corresponding overview of this clinical safety, and then I will make final conclusions.

The product is a liquid combination of diphtheria and tetanus toxoids, three acellular pertussis antigens, that is PT, SHA, and potactin, Hepatitis B recombinant, and inactivated poliovirus vaccine types 1, 2, and 3.

All component antigens are produced by SmithKline Beecham Biologicals in Rixensart, Belgium, with the exception of DT adsorbed, this is manufactured by Chiron Vaccines in Germany, and shipped for further manufacturer to SB Biologicals, and included in the combination.

The generic name, spelled it all out, is diphtheria and tetanus toxoids acellular pertussis hepatitis B recombinant inactivated polio virus vaccine. And the trade names provides good clarity for the physician in that it not only spells out the component antigens in the vaccine, but its relationship to our DTPa vaccine, which is currently marketed, which is Infanrix.

The vaccine is indicated for immunization against diphtheria, tetanus, pertussis, all known sub-types of hepatitis B virus, and poliomyelitis caused by polio virus types 1, 2, and 3.

As a three dose vaccination series in infants and children, from 6 weeks to 7 years of age,

prior to the 7th birthday. And just to clarify this, we are talking about immunization prior to the 7th birthday, intended to allow for catch-up for the primary series.

An indication for a fourth dose, following the primary series not being sought at this time, and so booster doses are still required according to the recommended immunization schedule.

The basis for licensure, the components of the vaccine, as I shall review shortly, are included individually, or in combination, in products licensed in the U.S. and/or in many world-wide markets.

And the development of the candidate was based on CBER's guidance for industry for evaluation of combination vaccines for preventable diseases, which was published in April of '97, in which one would show the combination vaccine is not inferior to separately administered U.S.-licensed vaccines, with respect to immunogenicity, as a surrogate for efficacy, and in regards to safety.

And a word about the components, now. The DTPa components are identical in terms of manufacturing composition to those in our currently licensed DTPa vaccine, which is Infanrix.

And just to remind you that Infanrix is

licensed in the USA in January of '97, licensed in 69 countries, with over 31 million doses distributed world-wide. In fact that is more than 50 million doses if one counts DTPa in combination.

The hepatitis B component is similar to our licensed engerix-B, that was licensed nearly 12 years ago in 1989, apparently licensed in 145 countries, with more than 500 million doses of that vaccine distributed as a monovalent vaccine.

So now the IPV component, and GSK does not have a U.S. licensed IPV vaccine, but this component is an enhanced potency IPV inactivated trivalent polio vaccine similar to the Aventis Pasteur vaccine, IPOL, similar in that the manufacturing process is similar, it is CFR and WHO compliant. And the same cell line were used for the manufacturing process in that very cells.

It also contains the same three strains, types 1, 2, 3, and the same antigen content as IPOL, so that would be Mahoney strain, 40 antigen units. And if you want, it is ADU and the Saukett strain, 32 DU.

Now, our IPV vaccine has been in clinical development since 1989, with 78 trials conducted in more than 26,000 infants and children, either as IPV

alone, or in combinations.

It was first licensed in France in '96, and licensed outside the U.S. in quite a variety of combinations shown here, DTPa-IPV in six countries, DTP-IPV, and mixed with Hib before administration in 36 countries.

And shown in yellow here is our candidate combination licensed as such in 17 countries, and licensed with mixing with Hib before administration in 19 countries.

And for this combination, for the IPV, over 8 million doses of IPV equivalents have been distributed to date.

So this is the vaccine composition. As I mentioned, the DTPa, the hepatitis B and the polio components are the same, and in the same content as in the separately licensed vaccines of the U.S.

We point out that there is an aluminum adjuvant, .7 migs of aluminum, as an aluminum source, this is lower than one would have if one would have the separate vaccines. And there is phenoxyethanol as a preservative in common with Infanrix. And there is no detectable thimerosal in the final product.

So manufacturing changes have been made during the process of clinical development. There are

in fact three lots, first, second, and third lot series. Third lot series actually being the launch material that we propose.

For the pertussis component there have been 2 successive purification scale-ups, all of which have been approved and in use for the currently licensed Infanrix.

In going from the first to the second lot during development we added one additional purification step for hepatitis B, which triggered the clinical bridging trial in addition to the usual technical bridging.

So for the launch material we have this final PA scale-up a minor volume increase in the hepatitis B purification, and the introduction of new working seeds for the IPV. The technical bridge was sufficient to bridge to the launch material.

So with that let me just say that regarding the status of the BLA review, all the BLA questions, including the complete response letter, have been responded to, and we are now in active discussion on those responses with the Agency.

And a pre-approval inspection has also been satisfactorily completed. So it is now time to move onto the clinical presentation, and may I

introduce Dr. Barbara Howe, to talk about the clinical immunogenicity. Thank you.

DR. HOWE: Good morning everyone. Can I be heard okay?

So in the next few minutes what I would like to do is to, first of all, overview the contents of the file in support of the Infanrix HepB-IPV and then this will be followed by a review of the pivotal and major supportive studies which had immunogenicity as their primary objective.

A total of 12 clinical trials, in which infants received one or more doses of Infanrix HepB-IPV were conducted in ten countries. Three in North America, 2 in the U.S.

And these evaluated five different primary immunization schedules, and involved 11 different production lots of vaccine. In total more than 7,000 infants received more than 20,000 of Infanrix HepB-IPV in these 12 trials.

Now, the three studies that are highlighted in yellow on this slide, studies 011, 15, and 44, are the pivotal trials, which will be the focus of the presentations which follow.

There are two additional U.S. studies which employed related combination vaccines, and these

provided supportive data for the file.

In study DTPa-HepB-030, a combination DTPa vaccine, which is similar to Infanrix HepB-IPV, with the exception of the IPV component, provided support for a schedule change in the hepatitis B component from the license 016 to 246 as part of the combination.

Then we have study 003, another U.S. study. And in this study Infanrix HepB-IPV was used to reconstitute GlaxoSmith Kline's Hib vaccine, and which was administered a three dose primary series, following a birth dose of HepB, and this provided supportive safety data for use of Infanrix HepB-IPV in this manner.

If we focus now on the six trials from which the most important data for the U.S. file are derived, in accordance with the FDA guidance for industry, for the evaluation of combination vaccines, and in support of the proposed indication, the following critical objectives were included.

First of all from an immunogenicity point of view, comparison to U.S. licensed separate administration vaccines was provided in study 015, a U.S. study. And this study also had as an objective an evaluation of the immunogenicity and safety of

Infanrix HepB-IPV, co-administered with U.S.-licensed Hib vaccine.

For lot consistency study 044 provided data on three production lots of vaccine, and from the point of view of the schedule change for HepB, DTPa-HepB-030, again, provided immunogenicity data from 246, the hepatitis B component in the combination given at 246, the licensed 0, 1, 6 months of age.

From the point of view of safety an evaluation of common, that is solicited adverse events, following Infanrix HepB-IPV as compared to U.S.-licensed separate administration products was provided in two studies, study 015 in the U.S., and study 011 in Germany.

And the latter study, which involved more than 5,000 infants, and had safety as its primary objective, also provided an evaluation of less common events, that is, those that occurred at about a rate of 1 in 100.

And then, finally, study 003 provided safety data following a birth dose of HepB. It is important to state up front that all of the pivotal studies in the file were analyzed as equivalents, or non-inferiority trials.

And the objective of equivalence trials

are to show that two treatments are similar, not necessarily identical, to rule out superiority of the separate components by a pre-specified amount, which is felt to be clinically important.

As such the difference must be felt to be important clinically in order to justify use of the combination vaccine.

Practically speaking, then, what one does is to first of all pre-specify a clinically relevant difference, here shown as delta, and this sets the limit for non-inferiority.

The difference between treatment groups is then calculated and in this example, we have the separate minus the combined vaccine, and 90 percent confidence intervals are built around the absolute difference.

If the upper limit of the confidence interval exceeds the pre-specified limit then we consider that non-inferiority is not shown. However if the upper limit of the 90 percent confidence level is within this limit, then non-inferiority is demonstrated.

Now, in the case of equivalence trials, both upper and lower limits are pre-specified, and if the upper or the lower limit of the 90 percent

confidence interval on the treatment exceeds the pre-specified limits and equivalence is not shown, if both upper and lower limits are within the pre-specified limits equivalence is considered to be demonstrated.

A few words about the end points in the immunogenicity trials, so serum samples were -- measurement of the humoral antibody were generally obtained prior to vaccination, and one month after the third dose of vaccine.

For those products, for the antigens and combinations that are already part of U.S.-licensed products, such as DTPa and hepatitis B, the assays that were employed were similar to those used and approved by FDA under the existing license application.

This slide first summarizes the parameters for which a correlate of protection has been established, all of these were considered to be co-primary endpoints in the trial.

So seroprotection rates for anti-diphtheria and anti-tetanus were assessed via an ELISA with seroprotection defined as a titer greater to .1 international units per ML, anti-HBS was assessed via commercial RIA, with seroprotect cutoff of ten million international units per ML, and polio was assayed

using a cell culture neutralization assay WHO protocol, and seroprotection was defined as any detectable neutralizing antibody.

The clinical limit defining non-inferiority for all of these parameters -- if you would go back, please -- was ten percent. Next slide.

Now, for the response for pertussis, for which a serologic correlate has not been established, the co-primary endpoints took into account both because response rates to the pertussis, as well as the geometric mean antibody titers.

And here vaccine response was defined as appearance of antibody in initially seronegative subjects and at least maintenance of antibody in initially seropositive subjects.

Again, the clinical limits defining non-inferiority for vaccine response were set at ten percent, and for the geometric mean titers a maximum of 1.5.

Okay. So if we move now to review of the primary immunogenicity studies, and we start with study 015, this study was conducted in order to rule out important differences between the immune response to each antigen in the combined vaccine, as compared to separately administered U.S.-licensed products, and

also had co-administration with U.S.-licensed Hib vaccine.

This was an open study in which 400 subjects were enrolled, and randomized equally into one of four groups. Group one received three doses of Infanrix HepB-IPV, co-administered with U.S.-licensed Hib, this is Adventis' Hib, given at 2, 4, and 6 months of age.

Group two received two doses of Infanrix HepB-IPV co-administered with Hib, at 2 and 4 months of age. And then at six months of age they received a combination DTPa-HepB co-administered with Hib, and oral polio. So this was our sequential IPV OPV arm.

Group 3 received three separate injections. That is the combination DTPa-HepB, co-administered with Hib, and this is U.S.-licensed IPV manufactured by Adventis, and this was at 2, 4, and 6 months of age. So this is our separate injection U.S.-licensed IPV arm.

And group 4 received standard of care, separate administrations, this is GlaxoSmith Kline's DTPa Infanrix, our hepatitis B, Engerix-B, Hib, and Lederle's oral polio.

I just want to emphasize that at the time that the trial was performed, actually, this was the

standard of care, that is oral polio was the standard of care.

For the purposes of the remainder of the presentation I'm going to primarily focus on the comparison of group 1, three doses of the Infanrix HepB-IPV, to separate administrations in group 4.

This slide then summarizes the immune response to diphtheria, tetanus and Hep-B, with seroprotection rates shown as the height of the bars, and geometric mean titers listed at the top.

You can see that for all three antigens, diphtheria, tetanus and Hep-B, high seroprotection rates, 99 to 100 percent were achieved in both groups, with geometric mean titers that were higher following the combination, than following separate administration.

Here, then, the response rates for the three pertussis antigens. Again we see high vaccine response rates that is greater or equal to 91 percent correlates of the group. This is a combined vaccine versus separate administration, with GMTs to PT and Pertactin, which were higher following the combination, than following separate administration, and GMT to FHA was somewhat higher following the separate administration, than following the

combination.

Here are the results for polio. You see high seroprotection rates to all three polio serotypes. Of course there was a further relevant control group for polio in this study, namely the U.S.-licensed IPV.

And so this slide compares three doses of, or one month after the third dose of the combination, as compared to U.S.-licensed IPV.

If we look, then, at the comparison of the geometric mean titers, first looking at that, comparing the combination versus oral polio, what you see is that the GMTs to polio 1 and 2 are higher following oral polio, as compared to the combination.

But the GMT to polio 3 is higher following the combination than following oral polio. However if we look at a comparison of geometric mean titers comparing the combination to U.S.-licensed separate injection IPV, you see that for all three polio serotypes the GMTs were higher following the combination, than following separate injections.

That was the descriptive analysis. But what is important, of course, is the non-inferiority testing. So this slide shows non-inferiority testing for seroprotection and vaccine response rates to each

of the contained antigens.

And the absolute difference is taking the rates for the separate injection, or separate administration, minus that for the combined vaccine are shown above the horizontal bars.

And then we have the 90 percent intervals plotted horizontally. What you can see is that for all parameters, other than FHA, the upper limit of the 90 percent confidence interval is within the pre-specified limit at 10 percent. For FHA the upper limit of the confidence interval marginally exceeded this limit.

You will recall that I said that for -- since there is no correlate protection for pertussis, that geometric mean titers for the three pertussis antigens were also taken into account as co-primary endpoints, and this slide shows the non-inferiority testing for the ratio of GMTs.

Here we take the ratio of GMTs, they have calculated in the 90 percent confidence intervals built around the ratio. You can see that for all three pertussis antigens the upper limit of the 90 percent confidence interval was within the pre-specified limit of 1.5.

What I would like to do is sort of quickly

walk you through the reverse cumulative distribution curves, because they are important to look at as well. And what you are going to see is a series of slides that shows the combined vaccine, the results following the combined vaccine in black, and that following separate administration in red.

And what you are going to see is a similar pattern, that is, a similar shape for the curves themselves. But generally with that, the curve for the combined vaccine to the right of that is separate administration indicative of the higher titers.

So these are the curves for anti-diphtheria, anti-tetanus, anti-PT, FHA, pertactin, and anti-HBS.

Now, on the polio slides we have the curve for the combination vaccine in black. Still that oral polio in red, and also we have the curve for IPV. And what you can see for polio 1 is that the curve following the combined vaccine falls largely between that of oral polio, and an activated IPV separate injection.

The same pattern is seen for polio 2. And for polio 3 the curve following three doses of the combined vaccine is to the right for both OPV and IPV.

Now, study 015, as I had mentioned, also

afforded the opportunity to evaluate the response to co-administered U.S.-licensed Hib. And here are the results for anti-PRP, one month after the third dose.

You can see that the proportion who achieved a titer greater than .15, as well as greater than equal to 1, as well as the GMC, were comparable between the two groups. This is the combined vaccine co-administered with Hib, and this is Hib given as a separate injection with other routine administered separate vaccines.

So from study 015 we can conclude that Infanrix HepB-IPV is at least as immunogenic as U.S.-licensed separately administered vaccines, including oral polio, with respect to the response rates to all of the antigens.

It is also at least as immunogenic as U.S.-licensed IPV with respect to the response rates to polio 1, 2, and 3. And there does not appear to be any negative impact on the immunogenicity to the co-administered Hib vaccine.

We move to the next study, study 044, which studied clinical consistency with regard to immunogenicity of the three production lots of Infanrix HepB-IPV.

And this was a U.S. study in which a total

of 484 subjects were enrolled in randomized equally into one of four groups. Groups 1 through 3 received one of three production lots of Infanrix HepB-IPV, lots A, B, and C, co-administered, again, with U.S.-licensed Hib vaccine.

Group 4 received Infanrix HepB-IPV from another lot series co-administered with Hib vaccine, and this was done in order to asses a manufacturing change.

For the purpose of this presentation I'm going to focus now on the lot consistency data. This slide shows the immunogenicity results for diphtheria, tetanus and hep-B. You can see that high rates of seroprotection were achieved in all three lot groups, for all three antigens.

Here are the results for the pertussis. Vaccine response rates were high, greater than equal to 91 percent for each pertussis antigen, regardless of the lot used.

This was with the exception to the response to Pertactin, for which one lot achieved a somewhat lower response, that is 84 percent.

Here are the results for the three polio serotypes, essentially one hundred percent of all subjects in all three lots achieved detectable

neutralizing antibody to polio.

Again, that was the descriptive results, here are now the equivalence testing results. The lots were shown to be statistically equivalent with respect to diphtheria, tetanus, and Hepatitis B. You can see that the upper and lower limits of the 90 percent confidence intervals were within the pre-specified limits.

Similarly the three lots were shown to be statistically equivalent for all three polio serotypes. However, although the absolute difference between the lots did not exceed the limit, the 90 percent confidence interval on the difference between lots exceeded the limit for FHA and for Pertactin, for two of the three lot comparisons.

This slide then shows the equivalence testing for geometric mean titers in this study. And what you can see is that the 90 percent confidence interval in the GMT ratios was within the pre-specified limits for all three pertussis antigens, with the exception of a marginal exceeding of the lower limit for one of the three lot comparisons for Pertactin.

I'm just going to show you the reverse cumulative curves for the pertussis antigens from this

study, then. And what you will see is that the distribution of titers in all three lots is remarkably similar for anti-PT, anti-FHA, and here is anti-PRN.

Now, importantly, the same three lots were evaluated for lot consistency when extemporaneously mixed with GlaxoSmith Kline's Hib vaccine, and these were studied in two additional studies, study 027, which is a U.S. study.

The vaccine was administered on a 2, 4, 6 month schedule, and study 048, which was done in Germany, on a 3, 4, 5 month schedule. And data from both of these studies were provided to you in your pre-read materials.

I'm just going to show the results from study 027. This is the design of study 027. Again, these are the identical three lots, lots A, C, and B, from the study 044 of Infanrix HepB-IPV, extemporaneously mixed with Hib vaccine, and given to approximately 360 infants per group, 2, 4, and 6 months of age.

The identical criteria for equivalents were applied in this study. And what you see is that for all three pertussis antigens, the 90 percent confidence interval on the lot comparisons for vaccine response rate for all three pertussis antigens were

met, they fell within the pre-specified criteria.

And consistency was also demonstrated with respect to the geometric mean antibody titers in this study.

So from study 044 the pre-specified limits for equivalence were exceeded for two out of the nine valencies. And both of these were pertussis antigens.

One possible explanation for the lack of consistency in this study was the observation that there was an imbalance in the twin groups in the pre-existing, that is maternal antibody, across the lot groups.

It has previously been recognized that infants with high pre-existing titers are more likely to have a lower response to pertussis antigens, particularly FHA, and Pertactin.

Importantly, though, the same three lots were evaluated into additional studies mixed with Hib, and in these two additional studies they were shown to be statistically equivalent for all nine antigens, including FHA and Pertactin.

So from these studies we conclude that equivalence has been demonstrated for all parameters.

The last study I would like to review is study DTPa-HepB-030, this was conducted in support of

the schedule change for the hepatitis B component. As I mentioned previously, the combination of the vaccine is similar to Infanrix HepB-IPV with the exception of the IPV.

So this was an open randomized study conducted in the U.S. Group 1 received the combination DTPa-HepB co-administered with Hib, and oral polio, at 2, 4, and 6 months of age.

And group 2 received co-administered Infanrix, Hib, oral polio, at 2, 4, 6. And then our Hep-B and Engenrix-B was given at birth, 1, and 6 months of age.

Here are the results. It shows the seroprotection rates, 99 and 100 percent. This is for the combined vaccine given at 2, 4, 6. This is for Engerix monovalent 016, with a GMT of 1,000 in those who received the combination on a 2, 4, 6 month schedule, as compared to 3,700 in those who received the monovalent vaccine.

If we look at the non-inferiority testing on the seroprotection rates, you can see that the upper limit of the 90 percent confidence interval was below the specified limit of ten percent, and the primary objective of the trial was, therefore, met.

Now, in order to put the GMT result into

perspective, we reviewed data in the published literature in the two U.S.-licensed monovalent Hep-B vaccines, Engerix and Recombivax.

And you can see results plotted from the literature. This is Engerix-B in red, Recombivax two and a half and five in yellow. And these data have been plotted, then, against the results from the study I just showed you, DTPa-HepB-030 in green, and multiple studies involving Infanrix HepB-IPV given according to a 2, 4, 6 month schedule.

And what you can see is that the results achieved with these combinations on a 2, 4, 6 month schedule, are in line with that published in the literature for the monovalent Hep-B vaccines.

So from this study we conclude that the combination given at 2, 4, and 6 months of age is at least as immunogenic as monovalent Hep-B given at 0, 1, and 6 months of age, with respect to the seroprotection rate to Hep-B.

The GMT on a 2, 4, 6 month schedule was lower as compared to 0, 1, 6, as one would expect, given the fact that the interval between the second and the third dose was shorter. This is a schedule effect.

The lower GMT is not thought to be

clinically relevant. However, given the fact that the GMT is in line with that previously reported following the administration of the two U.S.-licensed monovalent vaccines, which have been shown to provide long-term protection against disease.

Additionally the GMT was more than 100 times greater than the seroprotective cutoff. And individuals with titers greater than equal to ten should continue to be protected from both symptomatic and chronic infection on the basis of immunologic memory, given the absence of detectable antibody.

So the overall conclusions on immunogenicity are that Infanrix HepB-IPV is at least as immunogenic as separately administered vaccines in head to head trials involving Infanrix, Engerix-B, oral polio, and IPV.

And although I didn't show data, I think it is important to mention that we also looked at a comparison of antibody titers following Infanrix HepB-IPV to historical data following the immunogenicity achieved in two efficacy trials for Infanrix that were provided the basis for licensure for Infanrix, and the titers were comparable.

Additionally, Infanrix HepB-IPV has demonstrated lot to lot consistency. There is no

negative impact on the co-administered Hib, and hepatitis B, as part of the combination given on a 2, 4, 6 month schedule is at least as immunogenic as monovalent 0, 1, 6, in terms of seroprotection for hepatitis B.

I would like to turn the podium over now to my colleague Dr. Achim Kaufhold, who is in charge of the pediatric vaccine development unit in our central headquarters in Belgium, and he is going to provide you with an overview of the clinical safety for this product.

DR. KAUFHOLD: Good morning, everybody. Before I come to the summary of key data obtained in the clinical trial program, I would like to emphasize that we can build on a large experience with individual components of the DTPa-HepB-IPV vaccine.

First, individual components have been studied extensively. Second, individual components administered simultaneously in separate injections are in wide use. And third, individual components contained in similar combinations are currently in wide use.

Indeed, GlaxoSmith Kline has licensed, and is currently marketing a variety of DTPa combination vaccines in many countries around the world. A DTPa

vaccine, Infanrix, a DTPa-HepB combination, a DTPa-IPV-Hib combination, DTPa-IPV vaccine.

The DTPa-HepB-IPV combination we are discussing today, as well as hexavalent DTPa-HepB-Hib vaccine were simultaneously licensed in October 2000 in all 15 European member states, and in a few other countries.

In most European countries the larger hexavalent combination is preferred over the DTPa-HepB-IPV combination vaccine, and has been launched thus far in two countries, in Germany and in Switzerland.

Today almost 50 million doses of these DTPa based combination vaccines have been commercially distributed, and all of these combinations are well tolerated in clinical practice.

The extensive clinical trial experience, and the post-marketing surveillance have not raised any signal of concern with regards to safety.

In the next 20 minutes I would like to give an overview of the safety and reactogenicity of DTPa-HepB-IPV when co-administered with commercially available Hib vaccines.

My presentation will focus on the comparison to separately U.S.-licensed vaccines. I

will share with you data of common AEs that were obtained in the pivotal studies 011 and 012.

The occurrence of less common AEs was specifically addressed in the last safety study, 011. Safety following a birth dose of hepatitis B was evaluated in study 003. And finally, I will briefly comment on the serious adverse events and death that contained in the clinical trials contained in the BLA.

A few words regarding the methodology applied that in general were standardized across all trials for solicited local and general AEs all infants were followed for four days after each dose. That means on the day of vaccination and the subsequent three days.

The parents were asked to complete diary cards. In the two U.S. study, 011 and 044, additional telephone calls were made between day 1 and day 3 post-vaccination, in order to encourage parents to complete the diary cards, and to check on the status of the child.

This active surveillance allowed an unbiased assessment of the frequency, severity, and duration of local symptoms, pain, redness and swelling, and general signs and symptoms.

Next. In addition all other AEs, whether

or not considered related to the candidate, or the comparator vaccine, were recorded as unsolicited AEs. The follow-up period for 30 days following each dose.

Prior to analysis all unsolicited symptoms were classified according to the WHO body system and preferred term. Special attention was paid to promptly gather all information of serious AEs.

The follow up period for throughout the vaccination course, up to 30 days after the last dose was administered. Overall, in the 12 clinical trials contained in the BLA, a total of 7,028 subjects received at least one dose of vaccine, so that all together almost 21,000 doses of DTPa-HepB-IPV were administered.

As you can see here, compliance for reactogenicity reporting was very high in all studies. Symptom sheets were completed for more than 99 percent of subjects enrolled in the trials.

All data that I will present are based on the analysis of the according to protocol cohort. But I would like to point out that the results obtained from the ATP analysis are virtually identical with the conclusions drawn from the ITT analysis.

You are already familiar with the design of the U.S. 015. This was an open randomized trial

with four groups of 100 subjects each.

I will limit this presentation to the comparison of group one, the combined group, three doses of DTPa-HepB-IPV co-administered with Hib, to group four, that received -- in which infants received separate injections of U.S.-licensed vaccines, DTPa, Infanrix, HepB, Generix-B, Hib from Aventis Pasteur, and Lederle's oral polio vaccine.

And this was the standard of care at the time the trial was conducted in the U.S.

Infants of group one received two injections that were given intramuscularly into opposite limbs. While infants of group four received three injections, along with oral polio vaccine.

In the following I will compare the local symptoms only for the DTPa-HepB-IPV group one, and the DTPa injection sites. At the DTPa based injection was generally thought to be more reactogenicity than the reactogenicity elicited by the other vaccines.

But please keep in mind that the additional HepB and Hib injections would also contribute to the overall reactogenicity profile.

Having said this, you will appreciate that the incidence of pain was very similar for dose 1, dose 2 and dose 3, for both the DTPa-HepB-IPV and the

DTPa injection site.

This is true for any pain, as well as for pain that was judged to be graded 3 in intensity. So clinically more relevant pain.

For redness at the injection site the incidence appears a little bit higher for the DTPa-HepB-IPV as compared to the DTPa injection site. There was no increase by dose, and the incidence of redness above 20 millimeters was very low in both groups.

For swelling we see a very similar picture. A slightly higher incidence for the DTPa-HepB-IPV, as compared to the DTPa injection site, a slight increase from dose 1 to dose 2, but no further increase after dose 3.

If you compare the incidence of solicited general symptoms between the combined group, and the separate injection control group, over the four day follow-up period, over the full three dose vaccination course, you can see that the figures are virtually identical for all symptoms other than fever, greater or equal than 100.4 degree fahrenheit.

Fever was 41 percent in the combined group, versus 29.6 percent in the separate administration control group, although as you can see

here, the 95 percent confidence intervals overlapped.

Importantly there was no difference in the incidence of clinically more relevant symptoms rated 3, and this includes a low rate of fever above 103.2 degree fahrenheit.

Now I come to the large German safety study 011 that was initially designed as an uncontrolled safety study, in which infants were randomized to receive the candidate vaccine, along with one of four different Hib vaccines at 3, 4, and 5 months of age.

After enrollment of almost 1,600 children, the study protocol was amended. The amended design allowed for the introduction of a control group, group 5, of U.S.-licensed vaccines, namely DTPa Infanrix, Hib from Aventis Pasteur, and Wyeth-Lederle's OPV.

This design was implemented upon consultation with the FDA, and was in line with the guidelines for the evaluation of the combination vaccines that were published in April '97.

There was an imbalance between group in the sense that the control group did not receive the hepatitis B vaccine. This was necessary, as German physicians and parents do not accept more than two injections at the same visit. And this illustrates,

very practically, the need for pediatric combination vaccines.

Regarding the comparison between groups for systemic reactogenicity, however, the design implied the bias in favor of the separate administration control group.

The study was analyzed as a non-inferiority trial. The primary endpoint was the proportion of subjects reporting at least solicited symptom graded 3, a clinically relevant symptom.

And non-inferiority was demonstrated if the upper limit of the 90 percent confidence interval for the difference between the pool that had the IPV group, and the control group was below the up priority clinical limit of 7.5 percent.

The percentage of subjects with any grade 3 solicited symptom was 16.2 percent for the pooled candidate vaccine group, and numerically higher, 20.3 percent, for the control group.

The absolute difference was 4.1 percent, and the upper limit of the 90 percent confidence interval for the difference between groups, was below the pre-specified clinical limit, 7.5 percent, for non-inferiority.

Thus the primary objective of this trial

was met.

Let's now look again at the incidence of local symptoms by dose. Again, as seen for study 015, also in this large comparative trial the incidence of pain was similar between both DTPa-HepB-IPV and DTPa injection sites.

Any redness appears to occur slightly more frequent at the DTPa-HepB-IPV injection site, as compared to the DTPa injection site. There was a slight increase from dose 1 to dose 2, but no further increase after dose 3. And redness greater than 20 millimeters was, again, equally low in both groups.

For swelling the picture looks very similar. And, importantly, the incidence of more pronounced local reaction, injection site reactions, were equally low for both vaccines.

When looking at general symptoms please keep in mind that the separate injection control group received one systemic antigen less, the hepatitis B antigen. Thus, as already mentioned, the comparison is biased in favor of the control group.

For the percentage of subjects for the solicited general symptoms there were two differences between groups, unusual crying was observed more frequently in infants receiving separate

administration of vaccines, while the infants in the candidate vaccine group had a higher rate of low grade fever, 40.6 percent versus 27 percent.

Again, as already observed in study 015, the incidence of clinically more relevant grade 3 symptoms was low in both groups for all symptoms, including high fever. Restlessness and unusual crying occurred more frequently in the separate administration control group, and these differences were statistically significant.

Regarding unsolicited symptoms, an important secondary objective of this large safety trial, the rates were similar between DTPa-HepB-IPV plus Hib, versus DTPa plus Hib plus OPV recipients, for all unsolicited AEs, for unsolicited AEs considered related, or possibly related, and for less common AEs. There were no unexpected AEs.

And you can find a comparison of the rates of unsolicited symptoms occurring at a frequency above one percent in your briefing document.

Let me summarize, now, the key findings of study 011. The candidate vaccine was at least as safe as separately administered U.S.-licensed vaccines, with respect to the percentage of subjects with any grade 3 solicited symptoms.

There were similar rates of solicited symptoms with the exception of unusual crying, restlessness, that occurred more frequently in the separate versus the combined group, and low grade fever that occurred more frequently in the combined group versus the separate administration control group. And there were similar rates of unsolicited symptoms.

Now, one of the questions, question number 2A, that is to be addressed by the panel is the following. There were higher rates of fever above 100.4 degree fahrenheit in DTPa-HepB-IPV plus Hib recipients in studies 011 and 015, as compared to the control vaccine recipients. What is the clinical relevance of this finding?

We have looked into this very carefully and did a variety of comparative analysis between groups. Indeed, there was no difference between groups in the duration of fever. In the vast majority of infants fever lasted for one or two days.

In more than 98.5 percent of children the fever episode resolved during the four day follow-up periods. There was no difference in the use of anti-pyretics across groups in both studies.

There was no difference between groups in

the number of sepsis work-ups within seven days post-vaccination. There was no difference between groups in the incidence of febrile seizures occurring within seven days post-vaccination.

Indeed there was only one case, in study 011, that occurred after dose 1, in the DTPa-HepB-IPV plus Hib vaccine recipient. A diagnosis of an underlying convulsive disorder was made, and the investigator stated that the event was not related to vaccination.

If you look at hospitalizations with any fever within seven days post-vaccination, there were 11 cases among 4,695 equals .23 percent DTPa-HepB-IPV recipients, and 3 cases among 776 equals .39 percent control vaccine recipients.

Thus there is strong evidence that the higher incidence of low grade fever did not result in clinically relevant consequences.

The safety of the candidate vaccine following the administration of a birth dose of hepatitis B is of practical relevance. This question -- next slide, please -- was addressed in a randomized trial conducted in the U.S.

In study 003 one group of infants received a dose of hepatitis B at or shortly after birth, while

the comparator group did not receive a hepatitis B dose at birth. And then three doses of the combination vaccine were given at 2, 4, and 6 months of age.

The combination vaccine was the identical liquid DTPa-HepB-IPV combination under consideration today, but it was used to reconstitute revitalized POP tetanus conjugate prior to injection.

The primary end point was the percentage of subjects reporting any grade 3 solicited symptom during the eight day follow-up period after any of the three doses of the combination vaccine.

This occurred in 23.2 percent of subjects that had not received a hepatitis B dose at birth, and in 20.2 percent, 20.6 percent of subjects that had received hepatitis B at birth.

Non-inferiority was shown as the upper limit of the 90 percent confidence interval for the difference between groups was below the priority find clinical image for non-inferiority.

The percentage -- next slide, please -- the percentage of subjects with solicited symptoms observed over the 8 day follow-up period actually tended to be higher for the group that had not received hepatitis B at birth.

There was no difference between groups when we look, again, at the percentage of infants with clinically more relevant symptoms graded 3 in intensity.

Let me now summarize the findings regarding serious AEs and death. In 12 clinical trials 182 subjects reported 199 SAEs, and this translates into 2.1 percent among DTPa-HepB-IPV vaccinees, versus 1.8 percent among comparator vaccine recipients. Eight SAEs were considered possibly, or definitely related to study vaccines.

In brief there were three SAEs considered by the investigator to be related to vaccination, all occurred in study 011. Two of the three cases involved symptoms that were related to the Hib injection sites, while the third case was associated with high fever.

There were five SAEs considered possibly related to vaccination. Four of these cases involved fever, and in three of these cases an alternative cause of fever was diagnosed, possible influenza, possible viral infection, and possible gastroenteritis, or bronchitis.

In the 12 clinical trials contained in the BLA, six unrelated deaths were reported. Five deaths

in 7,028 DTPa-HepB-IPV vaccinees, and one death in 1,764 comparator vaccine recipients.

Here the causes of and relationships to vaccination are listed for the six deaths. All cases were considered unrelated, or probably not related to vaccination.

In study 011 there was one case of sudden infant death syndrome in the candidate vaccine group, and one case of SIDS occurred in the control group. The overall incidence of SIDS was .2 per 1000 infants in the German safety study 011, and this must be seen against an expected backdrop rate in Germany of more than 1 case per 1,000 live births. A rate that is very similar in the U.S.

It is worth mentioning that in the 12 clinical trials with 7,000 DTPa-HepB-IPV vaccinees, no cases were reported of hypotonic hyporesponsiveness encephalopathy, or anaphylaxis.

Ladies and gentlemen, with respect to safety and reactogenicity let me conclude. In 12 clinical trials, 7,028 subjects received almost 21,000 doses of DTPa-HepB-IPV that was an active follow-up with standardized methods across all trials.

Rates of common solicited AEs, as well as less common AEs were similar to separately

administered U.S.-licensed vaccines. Rates of low grade fever were higher, but did not result in clinically relevant consequences.

No unusual pattern or symptom complex were identified for any of the SAEs reported in any of the clinical trials. Three doses of DTPa-HepB-IPV when mixed with Hib, following a dose of HepB were well tolerated.

So the combination of antigens does not place infants at an increased risk of clinically relevant AEs.

Thank you very much, and at this point I would like to hand over to Dr. Clare Kahn.

DR. KAHN: I have some overall conclusions to make pertinent to the consideration of the questions.

Concerning the adequacy of efficacy data for all antigens we show that the combination was at least as immunogenicity as separately administered U.S.-licensed vaccines, and with special regard to hepatitis B, the 2, 4 and 6 schedule in the combination was at least as immunogenic as 016 schedule, in terms of seroprotection for hepatitis B.

Regarding the adequacy of the safety data, GSK has extensive clinical and post-marketing

experience with individual antigens, alone or in combination, the safety of the product has been demonstrated in more than 7,000 infants, even as a three dose primary series, and this safety profile was generally similar to separately administered U.S.-licensed vaccines.

Especial attention has been given to fever, and the rates of low grade fever are higher with this combination than the separate vaccines. This is not so for grade 3 fever.

And, importantly, this difference did not result in clinically relevant sequealling. Regarding the co-administration with U.S.-licensed vaccines, the data show that there is no interaction upon co-administration of Infanrix HepB-IPV with U.S.-licensed Hib vaccine.

And we are planning a co-administration study of Prevnar as a post-approval commitment.

We saw safety data for three doses of the combination product, in fact mixed with Hib, following a birth dose of hepatitis B. And under these circumstances the vaccine was well tolerated, and when comparing those who received a birth dose of HepB to those who did not, there was no increase in any grade 3 solicited symptoms, this was the primary endpoint of

this study, or for the solicited symptoms specific rates of adverse events.

Regarding boosters after the combination, we've experienced in hand with the administration of fourth dose boosters following administration of Infanrix HepB-IPV in the primary series.

But before I describe the scope of this data, let me make the following clarifications. As noted in my introduction, the focus of the current BLA, and this current presentation, is the indication for the use of the combination administered at 2, 4, and 6 months of age, with the recommended schedule thereafter.

But in addition to that we do have some data, and these were submitted to the FDA at their request, they are in the form of synopsis. And these are three studies in which the fourth dose of the series was administered as Infanrix, shown here in the green box, following three doses of the combination.

And here we have safety data in 327 subjects, and immunogenicity in 152. And such data would be from the future supplement to put this data and describe them in the label.

And, furthermore, we have six studies in which all four doses, 2, 4, 6, and 12 to 18 months of

age, the administration of the full combination. And here we have safety in 816 and immuno in 303.

So these data are somewhat supportive, perhaps, of the fourth dose of Infanrix.

Now, the data here for the three doses of combo with the fourth dose of Infanrix were highlighted in FDA's briefing document. And we are happy to address questions on that, should you wish to see that.

But, again, these were only submitted as synopsis officially in the BLA.

Now, the safety and efficacy of Infanrix HepB-IPV in infancy received one or more doses of the DTPa vaccine in the primary series has not been studied.

But in keeping with ACIP recommendations that interchangeability of acellular DTB vaccines in the primary series is not recommended, we suggest that since DTPa in the combination is identical to Infanrix, we suggest that Infanrix DTPa-HepB-IPV may be used to complete the primary series in infants who received one or two doses of Infanrix.

In final conclusion, then, here is the current immunization schedule published in MMWR for 2001. And we've highlighted the three component

vaccines that form the combination.

This is hepatitis B vaccine here in the first year of life in the yellow, and into the second year. Three doses of the primary series of DTPa, and the first doses of IPV.

And as you will see it is possible to have as many as five injections in a single visit, or perhaps elect to defer doses.

So here would be the proposed schedule, looking at the inclusion of DTPa-HepB-IPV combination at 2, 4, and 6 months of age, which is a lot less busy looking.

And the advantages of such combinations are clear. Here you are targeting five diseases with one single injection, and in the primary course for those antigens, for those five diseases, you are reducing -- not yet for that one -- you are reducing those injections from -- not from 9 to 3, so just 3.

And in the first year, for the overall primary course, you are reducing injections from 15 to 9.

And, furthermore, for such a combination vaccine there is the potential for pharmacoepidemiologic or pharmacoeconomic benefit. And in fact outcomes modeling studies have been

conducted by Alan Meyerhoff and presented at meetings last year.

And I know he is in the audience if there is any interest in that aspect of these combinations.

So this formally concludes GSK's presentation for the day, and thank you for your attention.

CHAIRMAN DAUM: Thank you very much, SmithKline presenters, Dr. Kahn, et al. We now will entertain comments from the Committee regarding the sponsor's presentation. Questions? Ms. Fisher.

MS. LOE FISHER: How long did you monitor children for persistence of antibodies to all antigens in the combination vaccine versus the separate injection controls to confirm long-term immunity?

And how long did you monitor children which had acute reactions, particularly the more serious reactions, for development of autoimmune neurological or behavioral disorders following the 30 day acute observation period?

DR. KAHN: Dr. Barbara Howe.

DR. HOWE: So with respect to persistence of immunity we followed infants, after the three dose primary series up until the time of the booster in a number of the trials.

We have data with us in the context of persistence and boosting data. In the U.S. studies that included up to a mean age of 14 months, that is in study 015, we followed the children out until mean age of 14 months and administered a booster dose of, actually, separate injection DTPa and Hib. So Infanrix and U.S.-licensed Hib vaccine.

And in study 044, which was the consistency study, we followed children out to a mean age of 16 months, and administered booster doses there. And I do have data to show that persistence was comparable in those who received the combination vaccine at 2, 4, 6, out to the mean age of 14 months as to those who had received separate administration of the U.S.-licensed products out to the mean age of 14 months.

MS. LOE FISHER: For hepatitis B too?

DR. HOWE: Yes.

MS. LOE FISHER: And then the reactions?

DR. HOWE: In terms of the reactogenicity and the safety data children were followed up until 30 days after the last dose of vaccine.

Some of these children would have gone on to be included in booster trials as well, but not all of the children.

MS. LOE FISHER: So you don't know what happened to those children after 30 days?

DR. HOWE: Unless they were subsequently in booster trials.

CHAIRMAN DAUM: Dr. Stephens, please.

DR. STEPHENS: Two questions. One relates to the demographics in terms of race, ethnicity, sex of the infants used in the study, and any differences that you saw based on those parameters.

DR. HOWE: So your question was about demographics. And for the majority of the studies in the file more than 95 percent of the infants were caucasian, with the exception of the two U.S. trials, which provided much more heterogeneity in terms of ethnicity.

I believe that demographics for study 015, 044 and 011 are all in the FDA briefing document. In study 015 a little less than half of the children were caucasian, 34 percent hispanic, and 10 percent afro-american. And there were assorted other, I think middle-eastern, Samoan.

And in study 044 about 85 percent of children were caucasian.

DR. STEPHENS: The question was actually different than that. It was about differences in

rates of reactions among ethnic groups --

DR. HOWE: I'm sorry, we do not have reactogenicity analyzed by ethnicity.

DR. STEPHENS: Or immunogenicity?

DR. HOWE: Or immunogenicity, right.

CHAIRMAN DAUM: Dr. Gerber do you want to clarify this? I will put you in line here, one second. Dr. Goldberg, Dr. Kohl, then Dr. Gerber.

DR. GOLDBERG: Okay, I have two questions. One relates to, it is in your briefing document, on the lot to lot consistency trial, when you looked at FHA and PRN, where you weren't able to show equivalence crudely, you did an adjustment where you removed the subjects with high baseline titers.

DR. HOWE: Yes.

DR. GOLDBERG: Did you do analysis within strata by baseline titer, and do you have the distribution of baseline titers, and what might the overall impact of that removal be?

You brought the difference down, but not completely. And I'm a little concerned about that. Do you have any more information to bear on that?

DR. HOWE: Yes. I think if I could have the maternal antibody folder? So to take this in a couple of parts, first I will just answer what was the

distribution of the pre-existing antibody titer across the various lot groups.

So this shows the distribution of pertussis titers by antigen, first of all, anti-PT, and what you see plotted here is the distribution of titers. This is, I don't know if you can see it, but 10, 20, 40, and 80 for each of the three lots, with a color coding similar to what you had seen when I showed you the immunogenicity.

You can see the pre-existing antibody titers for anti-PT were actually relatively low. This is typical. And was equally distributed across the three lot groups.

If we see, then, the results for anti-FHA, anti- pre-existing antibody titers to anti-FHA were higher, but again, they were relatively equally distributed at these higher titers. Again, this is greater than equal to 40, this is greater than equal to 80.

If we look at the results for anti-pertactin, again, higher levels of pre-existing antibody for pertactin similar to anti-FHA. If we look at the higher titers, though, this is greater than equal to 40. And then, particularly greater than equal to 80, this is for lot A, B, and C.

Here are the proportion who had the titer greater than equal to 80 at baseline for lots A, B, and C. And lot C was the one that had the lowest response. So you can see the proportion who had a titer greater than equal to 80, with lot C, was 7.1, lot B 0.9, and lot A 2.8.

So this is what I'm talking about, an imbalance in the pre-existing titers.

DR. GOLDBERG: And then did you look at the response within those strata?

CHAIRMAN DAUM: You need to speak right into the microphone, Dr. Goldberg, please.

DR. HOWE: We didn't look within the strata. I can ask our biometrician to explain exactly what the definition of high maternal antibody was, and what was done in the reanalysis.

DR. GOLDBERG: Okay.

CHAIRMAN DAUM: Could you tell us who you are, please?

DR. CHEUVART: Yes, my name is Brigitte Cheuvart, I'm a statistician.

CHAIRMAN DAUM: Right into the microphone, and you are all set. Thank you.

DR. CHEUVART: Thank you. So in terms of vaccine response we had the issue that we were dealing

with vaccine response rate which were quite high, around -- very close to one hundred percent.

Therefore it was difficult to apply a stratified analysis, because the stratified analysis are really based on Asantotic methodology. And we felt that in the context of grades very close to one hundred percent, it would be preferable to do an analysis where we would have excluded subject with high pre-vaccination titer.

Can you show, maybe, the slides with respect to the reanalysis? It is in the folder of all statistics. It is, yes, the next one, please.

So this is illustrating the relationship that we had between the post-vaccination titer, and the pre-vaccination titer, for one of the pertussis antigen. And we had the same pattern for the three pertussis antigen.

So you see that there is really a strong relationship between pre-vaccination titer, and post-vaccination titer. Below you see here the slope with respect to that -- with respect to a regression, for the three pertussin antigen.

And you see that the confidence above 40 slope is excluding minus 1, as well as 1.

MS. LOE FISHER: I'm sorry, does that

exclude -- that excludes the patients, the subjects with the high titers at baseline, or is that all the patients?

DR. CHEUVART: This is fully including all the subjects. With respect to the GMT analysis, what we did, we applied an ANCOVA model to adjust for the possible imbalance with respect to pre-vaccination titer.

For vaccine response, since there were not satisfactory method, exact method dealing with rates very close to one hundred percent, we did supportive analysis, which excluded subject with very high titer.

And how did we select the subject to be excluded? We examined the relationship between the post-vaccination titer over the pre-vaccination titer, with respect to the pre-vaccination titer.

And what you see is subject with pre-vaccination titer above specific value will have little problem. It will be very difficult for those subjects to have a vaccine response. The vaccine response being defined by post-vaccination titer above the pre-vaccination titer.

CHAIRMAN DAUM: Thank you very much. I think we are really going to move on at this point. It is such intense scrutiny on pertussis, it sure

would be nice to know what the protective correlate is and what to interpret here, but I think we will move on.

Dr. Kohl please, then Dr. Gerber, and Dr. Faggett.

DR. KOHL: Before we get to the clinical relevance of the results I would like to ask the manufacturer to verify that, indeed, they set up a priori definitions of non-equivalency.

And although it has been stated several times that all the results were equivalent in terms of serological results, my understanding of both the reading and the presentation this morning was, in looking at the GMT of both hepatitis B, given at a different schedule, and it was done to test whether they were equivalent at those schedules, and also looking at the FHA results in the only data that I think were presented, there was non-equivalency of the GMTs.

DR. HOWE: So with respect to the co-primary endpoints that were mentioned, seroprotection rates to each of the contained antigens, as well as vaccine response rates to the three pertussis antigens, as well as geometric mean titers to the three pertussis antigens, were a priori defined as

primary endpoints, co-primary endpoints.

For all of the other antigens, other than pertussis, the geometric mean titers were secondary antigens. And with the exception of hepatitis B in a couple of the studies, actually, there were not pre-defined criteria for non-inferiority for HepB.

When there was, there was still a secondary endpoint. I just want to be clear that the limits for non-inferiority, and for equivalence, particularly for the pertussis antigens are the same as was used in the context of licensure of Infanrix itself, in order to bridge from efficacy trials, for instance, to a U.S. population.

So, for instance, for immunogenicity bridging for the pertussis antigens there is precedent for those, for those pre-specified criteria.

Does that answer your question?

DR. KOHL: Thank you. Could you just say yes or no? With the FHA levels and the hepatitis B levels by schedule not equivalent?

DR. HOWE: Well, for HepB the endpoint was, in the DTPa-HepB-030 studies, the primary endpoint was seroprotection rates. So the non-inferiority testing was on seroprotection rates to HepB, not to the GMTs.

DR. KOHL: So it wasn't tested there, and it was non-equivalent for FHA.

DR. HOWE: And for FHA you are right. In the 015 study the vaccine response rate marginally exceeded, or the difference in vaccine response rates marginally exceeded the pre-specified limit.

CHAIRMAN DAUM: Dr. Gerber please. Thank you.

DR. GERBER: With respect to the increased incidence of fever in the combination group, I understand that you are talking about temperatures of 100.4 or greater, but less than 103.2.

That is a fairly large range. And what I'm wondering is, what is the distribution of those temperatures, for most of these temperatures of 101, 102, 103, do you have that information?

DR. KAUFHOLD: In the two comparative trials, 015 and 011, we have indeed made this breakdown. In the upper part of the slide you see the results, the breakdown for the study 015.

And in this trial any fever, as well as fever above 38.6 degrees centigrade, and fever above 95 percent degrees centigrade, there was no statistical difference between groups.

However, the trial was not designed to

detect such difference, the sample size was much too small.

Now, if you look at study 011 you see in green highlighted those temperature categories for which there was a statistical difference. So for any fever that is defined as fever greater than 38 degrees centigrade, and fever greater equal than 38.5 degrees centigrade, there was no statistical difference for higher grade fever above 39.5 degrees centigrade.

And in this trial there were only two cases of children who had fever above 40.5 degrees centigrade. One was in the group that received the candidate vaccine, whereas the other case was in the group that received separate administrations of licensed vaccines.

CHAIRMAN DAUM: Dr. Faggett, then Dr. Fleming.

DR. FAGGETT: My question is adequacy of safety data. You mentioned that safety was demonstrated in 7,000 infants at three dose primary series.

One of the earlier speakers mentioned 5,000 infants, 015 and 011 study, and 1,600 children were mentioned in the German safety study. My question is, what is the total number of children in

the safety studies, and is that ongoing, and what is your endpoint in terms of how many you plan to study?

DR. KAUFHOLD: So the total, altogether 7,028 children received at least one dose of vaccine. And as I showed in the main presentation there were only very few subject excluded both from the ITT analysis and from the ATP analysis.

DR. FAGGETT: So how many -- is this ongoing, what is your endpoint, in terms of how many children --

DR. KAUFHOLD: I'm not sure if I understand the question.

CHAIRMAN DAUM: The question is, are there ongoing trials conducting safety data that you are conducting right now, right?

DR. KAUFHOLD: Yes.

DR. FAGGETT: Seven thousand sounds kind of small to me, I mean it is --

CHAIRMAN DAUM: And the answer is?

DR. KAUFHOLD: There are no ongoing trials.

DR. FAGGETT: Okay, thank you.

CHAIRMAN DAUM: Dr. Fleming is next, and wanted to see the last slide that you showed, Dr. Kaufhold. If you could put that back up, please?

DR. FLEMING: Great, I have a number of issues, and I would like to reserve my questions to the end just to avoid overlap. And I did want to, since this slide was put up, it does get at the heart of the issues.

My interpretation of this data are that there is much more strength of evidence here about an increase in fever than your interpretation. I think when you had presented the data on 015 you noted the estimates for the fever greater than 38, that the -- relating to whether the confidence intervals are overlapping. In fact confidence intervals can overlap. That is not the way you assess whether there is a statistically significant evidence of an increase.

Your upper limit of the confidence interval for the difference does, in fact, reflect what is on the margin of statistical significance on the 015 trial. You are estimating an 11 percent higher rate.

The lower limit, which you would be using in a non-inferiority sense clearly is not satisfying in non-inferiority criteria, in fact, it is on the edge of being statistically significantly greater.

You have in 011 clear cut evidence of a

statistically significant greater rate of fever. The estimate is 13. -- the difference is 13.7. The lower limit of the confidence interval is close to zero.

And in addition to that you have certain trends that, granted, is under power for the fever greater than 38.6, but you have consistent trends in the two.

These data are improperly interpreted as not providing statistically significant evidence of an increase in fever. Clearly there is, and it is consistently seen in these two studies, as it is seen in the 044 trial.

CHAIRMAN DAUM: Thank you, Dr. Fleming. Dr. Ball next, then Ms. Fisher.

DR. BALL: I wanted to comment that some of the questions that you are addressing now, as well as what Dr. Gerber addressed, which is with regard to what degree of fever are found in my slides, and I will be discussing that later.

And I don't know if you have the information in front of you, but it may be easier for people to see that slide, because I know I can't see that slide.

But if you have my briefing, or my slides, slide number 31 addresses the incidence of fever in

study 011, and it breaks it down to fever greater than 38.6 degrees, and 39.5 degrees.

And as you can see here with the asterisk the difference is for the groups, for fever greater than 38 degrees, and greater than 38.6 degrees, were statistically significantly different.

Study 015 was addressed in slide 35, with the same information, fever greater than 38 degrees, fever greater than 38.6 degrees, and fever greater than 39.5.

And as Dr. Fleming pointed out, fever with greater than 38 degrees in this study was on the margin of being statistically significant. But the trends were the same in both studies.

CHAIRMAN DAUM: Thank you. I know that you are planning to return to this topic in some depth, and the Committee members will have a chance to reflect on this issue further after the FDA presentation, as well.

Ms. Fisher, please.

MS. LOE FISHER: I'm interested in the -- getting more information about the two seizure cases. One was, I think, in the adverse event category of febrile seizure, which was then determined to be caused by an underlying seizure disorder, the other

was a death that had the cause of death listed as an underlying seizure disorder.

Was this the same patient, and what determination was made that the seizure, was this the first time that the seizure had occurred following the vaccination, had there been pre-existing seizures?

And what was the determination, how did you determine that they were not connected to the vaccine? And I have the same question on the deaths. Because you had five deaths in the combination group and only one death in the controls.

That seems pretty significant to me, and what determination was made that those deaths were not, indeed, in some way connected with the combination vaccine?

DR. KAUFHOLD: You are right, there were five deaths in the group that received the combination vaccines. That includes all trials that are contained in the BLA, and one death in the comparative vaccine.

If you now look at the denominator you can, and the denominators between those two groups are, obviously, very different. So if you compare the percentages the figures are virtually identical.

Perhaps we can have another look at the slide that lists all the deaths, perhaps that went too

fast.

Altogether there were three cases of sudden infant death syndrome, the next one please, three cases of sudden infant death syndrome. I highlighted in my presentation, in the comparative study 011 there was one case, in the group that has received the candidate vaccine and one case in the group that received separately administered licensed vaccines.

Then there was one case of neuroblastoma, and one case of congenital immunodeficiency. And if you will read the narratives, we -- one can support only the conclusion of the investigator that stated that these cases are certainly unrelated to vaccination.

With regard to your question regarding convulsive disorder, yes, there were altogether two febrile convulsive disorders in study 011. And one occurred after four days post-vaccination, and the other case occurred more than two weeks post-vaccination.

The case with the febrile seizure is the same, that was diagnosed to have an underlying convulsive disorder, and this child died later on.

MS. LOE FISHER: So it was the same

patient?

DR. KAUFHOLD: It was the same patient.

CHAIRMAN DAUM: Dr. Diaz, then Dr. Broome, and then I think we are going to take a break.

DR. DIAZ: Thank you. I have just a couple of questions. The first in regards to immunogenicity.

Do you have -- how did the anti-PRN data vary lot-to-lot consistency for the original Infanrix? Did you see the same kinds of differences in the immunogenicity lot-to-lot?

DR. HOWE: I have to go back to look at the exact definition of lot consistency at the time that Infanrix was licensed, to be quite honest.

And I don't think that the same criteria were applied. Maybe another way -- I mean, I can certainly share with you how this data compare with anti-PRN results, or other antigens, results for other antigens.

With respect to the efficacy trials that data I have with me. I don't know if that helps to answer your question. But I can say that the criteria for consistency were not -- those same criteria were not applied to Infanrix in the context of that licensure, because that was years ago. These were

subsequently developed.

DR. DIAZ: And in the studies today, that are being presented, were the same -- it may be implied, but I don't recall seeing it in your data. Were the same lots used to prepare the combination vaccines that were used for the control lots in the studies?

DR. HOWE: In terms of the -- no, these were commercial lots of, for instance, it would be a commercial lot of purchased Infanrix, or commercial lot of Engerix-B.

In terms of, for instance, the Lederle OPV could have been multiple lots.

DR. DIAZ: And how were those lots chosen?

DR. HOWE: They were just chosen as to what was available commercially, on the market. In terms of the Infanrix and the Engerix-B there was, in general, a single lot used throughout the course of the trial. That was true for the Hib vaccine, as well.

But these were commercial products that we would purchase.

DR. DIAZ: So from study site to study site the lot may have varied in terms of the control group?

DR. HOWE: No, no. The lot was the same for Infanrix, for Engerix-B, and for Hib in the trials. The lot would have been provided to the site, but it was a commercial lot, I'm sorry.

And then for oral polio, in the trials we did allow the sites to purchase their own. So that is the only one for which we used various lots.

CHAIRMAN DAUM: Thank you, Dr. Howe. Dr. Broome, please.

DR. DIAZ: Just one other question if I could, please.

CHAIRMAN DAUM: If it is very brief.

DR. DIAZ: You've looked at children post-vaccination up to four days, and then at 30 days, correct? And I recognize that in the recommendations from the FDA to the manufacturers they recommend following children up to seven days, initially.

And I was just curious why you chose four days as your cutoff.

DR. HOWE: So for the detailed reactogenicity analysis the period of solicitation was four days.

DR. DIAZ: For safety?

DR. HOWE: For safety, yes. And then for -- but, however, for unsolicited symptoms the period

for follow-up was 30 days after each vaccine dose. And then for serious adverse events they were followed throughout the entire course of the trial, for up to 30 days after the last dose.

DR. DIAZ: I was just curious if there was a reason.

DR. HOWE: Well, four days, I think, is more typical of inactivated products. For instance, in some later trials we may have had an eight day period of solicitation, but these trials were all designed for four days.

DR. DIAZ: I just noticed that the industry guidelines recommended seven days.

CHAIRMAN DAUM: We are going to move on now. Please, Dr. Broome?

DR. BROOME: I'm still interested in this issue with the possible lack of lot consistency with the pertussis antigens.

The reverse cumulative distributions you are showing are all for post-vaccination, they do not include pre-titers. And in the reverse cumulative distribution, in study 44, there seems to be a slight but consistent left shift for lot C.

So I wondered if you could show me the reverse cumulative distribution for study 027, in

terms of whether that was seen in that, you know, other larger study.

(Unmiked answer.)

DR. BROOME: It is a fairly slight left shift, but I thought that was somewhat interesting for the anti-PRN. And it wouldn't, you know, it is independent of the high pre-existing titer. So it looked like an observation worth noting.

CHAIRMAN DAUM: I don't suspect the person trying to bring the slide up has too much anxiety at this moment.

DR. BALL: Dr. Daum, can I just interject? This was one issue that we looked at, and I think they are having a difficult time finding the slide. But the backup slide which unfortunately I didn't bring today, shows that those lots were basically superimposable.

There wasn't that difference in that outlier, the lot, in study 027.

CHAIRMAN DAUM: Can we accept that?

DR. BROOME: Sure.

CHAIRMAN DAUM: Here we have the slide. Take the anxiety off for a moment, distract it.

DR. HOWE: These are the three lots, then, in red, yellow, and black, lots A, B, and C. And

these are for anti-PT. But if you could just go to anti-FHA? And what we really want to see is the anti-PRN.

Those are very superimposable, anti-FHA, and here is anti-PRN.

CHAIRMAN DAUM: Thank you very much. Thank you for the sponsor's presentation. We will revisit some of these issues, I'm sure, when we hear from the FDA, and have Committee discussion.

We will take a 15 minute break and reassemble at 11:35.

(Whereupon, the above-entitled matter went off the record at 11:24 a.m. and went back on the record at 11:44 a.m.)

CHAIRMAN DAUM: I'd like to get started so that those of us like lunch can get there.

Before we move on to the FDA's presentation on this issue, I would like to ask a favor, or make a request of our audience members today. A number of people have complained to me that there is sufficient amount of buzzing and talking there that they have actually been distracted from being able to hear what is going on in the meeting.

And I would like to request that people minimize, or eliminate that kind of conversation, and

maybe step outside for a moment if they need to have a conversation while the meeting is going on. Thank you.

There is one more announcement, we will turn the floor over to Nancy.

MS. CHERRY: Yes. I understand -- I know that there is a binder with briefing materials that is out on the table, or that was out on the table. I understand that all of the sponsor's briefing materials have all been given out.

And now the binder has disappeared. So if you look around and you see your neighbor with that binder, would you kind of -- since we asked you not to talk, but at least jab that person in the elbow and hint that they take it back to the table out there, and give it to Dennise and Rosanna. Thank you. The binder has a copy of the briefing materials.

CHAIRMAN DAUM: I think we will call on Dr. Ball at this point.

DR. BALL: Good morning. I will be presenting the FDA's clinical review of GlaxoSmith Kline's DTPa-HepB-IPV combination vaccine.

My intent is not to present all the material that was presented this morning, nor present everything that was in the briefing document from the

FDA, but to highlight some issues for your consideration.

First I will discuss the proposed indication and provide an overview of this combination, and the FDA's approach to combination vaccines. Next I will discuss the clinical studies submitted in the license application to support efficacy and safety of this combination vaccine.

I will present the available data on concomitant vaccines, and as was noted, this will consist of data with concomitant Hib vaccine. Prevnar was not licensed, nor was it commercially available at the time the studies were conducted, and at the time the BLA was filed.

In addition I will discuss some limited data on the fourth dose of Infanrix following a primary series of the DTPa-HepB-IPV vaccine. Finally I will present the questions and discussion points for the Committee.

The proposed indication, as was mentioned earlier today, for this combination is a three dose primary series, given at 4 to 8 week intervals, with the customary age of administration, 2, 4, and 6 months of age.

This slide presents the current

recommended childhood immunization schedule to illustrate how this combination would fit in the existing schedule.

The combination under discussion today contains the components that are in light yellow, namely DTPa, HepB, and IPV. The proposed schedule, as was mentioned, would fit under this time frame, 2, 4, and 6 months of age.

So what would this vaccine mean in terms of injections administered to infants during the primary series? Under the current recommended childhood immunization schedule an infant would typically receive four to five injections per visit, depending on the formulation used, as illustrated here.

With this new combination vaccine, if it is used in the primary series, and if it would receive up to three injections per visit in the primary series, namely that of the combination Hib and the pneumococcal conjugate vaccine.

Next slide. As we heard, earlier today, the hepatitis B vaccine consists of two vaccines that are currently licensed in the U.S., namely Infanrix, DTPa and hepatitis B, Engerix-B, as well as the IPV component that is not currently licensed in the U.S.

In the FDA approach to the licensure of combination vaccines, there are two regulations that I wanted to mention.

First a new license is required when already licensed products are combined, or when unlicensed components are added to a licensed vaccine. Secondly, products may be combined if each component makes a contribution to the claimed effects, and combining does not decrease the purity, potency, safety, or effectiveness of the individual components.

In addition the FDA's approach to combination vaccines is outlined in the 1997 guidance document for industry, which states: Clinical studies of combination vaccines should be designed to rule out clinically meaningful differences.

The approach taken for licensure of this combination has been through the evaluation of immunogenicity of each component in the combination, rather than clinical end point efficacy studies.

In other words, efficacy is inferred from immunogenicity. The objectives of the clinical studies of the combination have been based in first demonstrating non-inferiority of the combination, compared with separately administered U.S.-licensed vaccines, namely Infanrix, Engerix B, oral polio, and

in study 015, IPV.

Note that polio vaccine was the standard of care at the time of studies to support licensure were conducted.

In addition, for those components having a generally accepted immune correlate of protection, namely D and T, hepatitis B and IPV antigens, the clinical studies have sought to demonstrate that the immune response to the combination exceeds these correlates.

The objectives of the clinical studies in support of licensure have been to demonstrate the immunogenicity and safety of DTPa-HepB-IPV, to evaluate the immunogenicity when vaccine is given concomitantly under the recommended schedule, immunization schedule, and to demonstrate that the vaccine can be manufactured consistently, and to demonstrate that clinical bridging between the two sequential lots following a manufacturing change.

You have heard, earlier today, about the clinical studies submitted in support of licensure. I will be concentrating on the three pivotal studies that are in this slide namely study 011, which was the large-scale safety trial conducted in Germany under a 3, 4, 5 month immunization schedule.

Study 015 evaluated the immunogenicity as safety on the schedule of 2, 4, and 6 months of age. Study 044 examined DTPa-HepB-IPV for lot consistency and manufacturing bridging from the first production lot to the second lot series.

The total number of subjects receiving the combination in the pivotal trials was over 5,000. In addition to the pivotal trials Dr. Howe discussed data from supportive studies not conducted under USIND that were submitted to the license application.

These studies used the same procedure for evaluating safety immunogenicity generally speaking, as the pivotal trials, but utilized different schedules at times and comparators that were not U.S.-licensed vaccines.

The total data base of subjects receiving the combination in the pivotal and supportive trials was approximately 7,000, with 764 of these subjects receiving the combination at the 2, 4, 6 month schedule.

Additional data were provided through studies of related DTPa Infanrix combination that were not licensed in the U.S. These Infanrix-based combinations were DTPa-HepB-IPV Infanrix with Hib, as was mentioned earlier today and the combination DTPa-

HepB vaccines.

These studies provided additional data on lot consistency, the safety of the primary series following a birth dose of hepatitis B vaccine, and data on the change and schedule of the administration for hepatitis B combination for the hepatitis B component in a combination.

This slide presents the demographics of the clinical studies as DTPa-HepB-IPV that was submitted in the license application, with specific data on the pivotal trials, and total data for both the pivotal and supportive studies.

As highlighted in blue the majority of infants studied in the clinical studies were caucasian. The population was diverse in a pivotal study conducted in the U.S.

Now I will move on to examine the studies evaluating the immunogenicity of the combination vaccine. The primary immunogenicity endpoint included the percent of subjects achieving immune response correlated with protection for the D and T, Hib and polio components.

For the pertussis components the immunogenicity endpoints evaluated were the percent of infants showing response to PT, FHA, and Pertactin.

In addition geometric mean titers were evaluated.

In assessing the immune response the statistical approach used for evaluating the combination vaccine compared with a separate administration of U.S.-licensed vaccine, was for testing for non-inferiority.

For non-inferiority testing a one sided equivalence test was used with an alpha of five percent. To evaluate manufacturing consistency a two-sided equivalence test was used.

AS was mentioned earlier today, pre-specified limits for defining non-inferiority were maximum difference of ten percent for seroprotection vaccine response rates to D and T, pertussis, hepatitis B and polio antigens.

For GMTs the pre-specified limits for non-inferiority were maximum ratio of 1.5 on the GMTs for the pertussis components, and 2.0 for the hepatitis B component. And hepatitis B GMTs -- I'm sorry, go back for a second. Hepatitis B GMTs were considered a secondary endpoint.

Now we will discuss the specific clinical studies. The objective of study 015 was to evaluate immunogenicity and safety of a primary series of the combination compared with separately administered

U.S.-licensed vaccines.

The study was conducted in the U.S. on a 2, 4, 6 month schedule. This slide depicts the study groups to which the infants were randomized. In the study I will concentrate on group one which received the combination with Hib vaccine, and group 4, which received the -- I'm sorry, separately administered Infanrix, Engerix-B, Hib, and OPV.

Group 2, as was mentioned earlier, evaluated the combination vaccine given in a sequential schedule, which is no longer the recommended schedule in the U.S.

In addition group 3 examined the combination DTPa, hepatitis B, which is no longer licensed in the U.S., and is no longer under consideration today.

This data presented, in terms of the immune response for the two eligible groups, as I mentioned, group 1 and group 4. And the difference of immune response was seen with a 90 percent confidence interval on the difference.

Note the statistical methodology was non-inferiority, a one-sided equivalent testing, for sero response and vaccine response. The upper bound of the 90 percent confidence interval should not exceed 10

percent.

Dr. Howe earlier presented the immune response data for all the antigens contained in the combination, and noted that all pre-specified immunologic endpoints for demonstrating non-inferiority of a combination, compared to the separately administered vaccines were met, with the exception of the percent responders to FHA.

This slide presents the vaccine response to pertussis antigens, to each of the pertussis antigens, and highlighted in blue is FHA, which exceeded the pre-specified limit of ten percent.

I think it should be noted that variability of immune response to FHA has been noted previously, specifically in studies used to support licensure for Infanrix DTPa.

In the German household contact study multiple lots of Infanrix were used showing various immune responses to FHA, but efficacy did not appear to differ among these lots.

The second pivotal study of immunogenicity was study 044, which evaluated lot consistency in manufacturing bridge. This study was conducted in the U.S. on a 2, 4, 6 month schedule.

This slide depicts the study groups in

study 044, which evaluated lot consistency in groups 1 through 3, which consisted of three lots of the second lot series in the combination and mixed with Hib.

It should be noted that as compared with the previous presentation by the manufacturer, we've labeled lot C, and lot C are different on the lot that was labeled lot C by GSK we have labeled lot B.

The study also compared pooled lots from the first lot series, I'm sorry, from the second lot series to group four, which contained one lot of the first lot series.

I think it is also important to note that in this study there was no separate administration control arm.

This slide depicts the immune response data for lot consistency. We have the vaccine response rates here, and the GMTs here. And in the middle columns here are the groups 1 through 3, and here are the maximum 90 percent confidence interval limits on the pair wise differences between the three groups.

And for the GMT the maximum 90 percent confidence interval limit on the pair-wise ratio. As was noted earlier today by Dr. Howe, all pre-specified

immune endpoints were demonstrating equivalence, that is lot consistency of the second series of DTPa-HepB-IPV were met with the exception of the percent responders to FHA and pertactin, as well as the GMTs to pertactin.

This slide presents the immune response data for the manufacturing bridge from the first to the second lot series. All pre-specified immunologic endpoints were demonstrating non-inferiority were met, with the exception of the percent responders to pertactin.

Here are the upper limit of the 90 percent confidence interval was 12.3 where pre-specified limit was 10 percent.

Now I will present information on the immune response to the hepatitis B component in the combination vaccine. Engerix B, GlaxoSmith Kline's hepatitis B monovalent vaccine is currently licensed under 0, 1, and 6 months schedule.

For the proposed indication the schedule is 2, 4, and 6 months. Several studies in the license application evaluated the immune response of the combination on a 2, 4, 6 month schedule. And these data are presented here.

The observed hepatitis B immune response

in infants receiving the combination was significantly greater than the 10 international units per mil, the level considered protective against hepatitis B disease.

In these studies 99 to 100 percent of infants achieved levels considered seroprotective with the GMTs ranging from about 1,400 to close to 1,700.

Note that none of the infants in these studies received a birth dose of hepatitis B. So it is important to note that no data were submitted as part of the license application that directly compared the hepatitis B immune response of the combination vaccine given at 2, 4, and 6 months of age to the immune response of Engerix-B administered at birth, 1, month, and 6 months of age.

Supportive data for the change in schedule for the hepatitis B were submitted from study DTPa-HepB-030, which evaluated SmithKline Beecham's DTPa-HepB combination that is not licensed in the U.S., and the data were presented on the next slide.

So the DTPa-HepB-030 compared the hepatitis B immune response to the hepatitis B DTPa combination, given at 2, 4, 6 months of age, to hepatitis B given at 0, 1, and 6 months of age.

The immunogenicity of the DTPa hepatitis

B combination on a 2, 4, 6 month schedule, compared with the standard 0, 1, 6 month schedule, met the pre-specified criteria for non-inferiority with respect to seroprotection, with 99 percent of the subjects given the vaccine on a 2, 4, 6 month schedule, having host vaccination levels above the level considered seroprotective.

The hepatitis immune response to GMTs were lower when the hepatitis B antigen was given on a more compressed schedule of 2, 4, and 6 months of age. However, the hepatitis B immune response of the combination was well above the level considered protective.

Now I will move on to the studies evaluating the safety of DTPa-HepB-IPV vaccine.

The objectives of these pivotal studies was to compare the rates of adverse events following administration of the combination with the separately administered U.S.-licensed vaccines.

Study 011 was a large scale safety study with the objective being to evaluate common and less common adverse events. The study was amended after initial enrollment as was mentioned earlier today, to include a control arm that received a separately administered U.S.-licensed vaccines. The study was

conducted in Germany on a 3, 4, 5 month schedule.

It should be noted here that there was no sera drawn to evaluate immunogenicity in this study.

This slide depicts the study arms in study 011. Groups 1 through 4 received the combination vaccine with Hib vaccine from various manufacturers. And as was mentioned, the original intent was to evaluate the safety with these four different Hib vaccines.

Infants in group 5 received separately administered vaccines, Infanrix, Hib, and OPV. As was noted earlier today, group 5 did not receive hepatitis B during the study period.

Also, as was mentioned earlier, the arms of the groups receiving the combination was significantly higher, 4,696 compared with the group receiving separate injections, 776.

This slide depicts the incidence of local reactions in the groups receiving the combinations, compared with the separately administered vaccines, by looking at the site of injection at the DTPa hepatitis B IPV compared with the Infanrix given alone site.

And I'm -- with the vaccines but not in combination. This was measured in three days, following the vaccination for each dose, and for any

dose of vaccine. The two columns in the middle present the data on the incidence of redness and swelling in the pooled groups receiving the combination, compared with the groups receiving separate vaccines.

Instead of P-values the last column presents the difference between the groups, and the confidence interval on the difference. The difference is statistically significant if the lower bound on the 90 percent confidence interval is greater than zero.

In this study increased incidence of redness and swelling was observed for groups receiving the combination, compared with the infants receiving separately administered Infanrix.

Following doses 2, 3, and for any dose the difference between the combination and Infanrix were statistically significant. Of note grade 3 local symptoms defined as swelling or redness greater than 20 millimeters did not appear increased in the combination recipients.

This slide presents the incidence of fever greater than 38 degrees after each dose, and after any dose. An increased incidence of fever greater than 38 degrees centigrade was observed in the combination with recipients with a difference between the

combination in a separately administered vaccine, statistically significant after each dose, and after any dose of the vaccine when compared with the separately administered vaccines.

For example, following dose one, 25 percent of infants receiving the combination experienced fever greater than 38 degrees centigrade, compared with 13 percent in the group receiving separately administered vaccines.

And for any dose the incidence of fever was 43 percent versus 26 percent in the separately administered vaccines.

To determine whether this increased rate of fever was for low grade fever or higher fever, we further evaluated the incidence of fever in addition to 38 degrees we looked at fever greater than 38.6 degrees or 101.5 degrees fahrenheit, and fever greater than 39.5 centigrade, or 103.2 degrees fahrenheit.

The incidence of fever greater than 38.6 degrees also increased with a difference of 4.7 percent, reaching statistical significance. The incidence of grade 3 fever, greater than 39.5 degrees was not significantly different in the groups receiving the combination, as compared with the control.

I will move on now to study 015, which I discussed earlier, with respect to immunogenicity. This slide reviews the study groups and the data I will present will concentrate, again, on groups one and four.

Note that in the study groups one and two received two injections, and group three and four received three injections, generally, each visit.

This slide presents the incidence of local swelling in the three days following vaccination, similar to the pattern observed in study 011, where the combination was associated with increased redness and swelling, compared with a separate DTPa site.

The incidence of redness and swelling was increased in the group receiving the combination, compared with the group receiving separately administered U.S.-licensed vaccines. Although this difference did not reach statistically significance.

The incidence of redness and swelling greater than 20 millimeters was higher in the group receiving the combination. However, again, this difference did not reach statistical significance.

I think it should be noted that this study was not powered for safety but for immunogenicity, so therefore the finding of no statistical significance